Etofenprox

Insecticide for Use as Wood Preservative

Dossier According to Directive 98/8/EC

Document III-A

Section A1 Applicant

Annex Point IIA-1

Official use only

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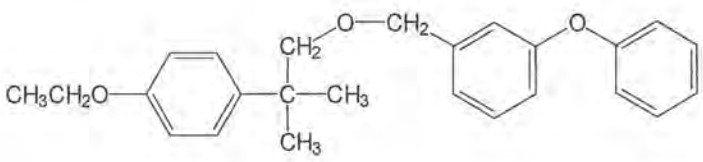
Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	June 2006
Materials and methods	not applicable
Conclusion	Adopt applicant's version
Reliability	not applicable
Acceptability	acceptable
Remarks	none
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Results and discussion	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant´s summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A2 Identity of Active Substance

Subsection (Annex Point)			Official use only
2.1	Common name (IIA2.1)	Etofenprox	
2.2	Chemical name (IIA2.2)	2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzyl ether [IUPAC] 1-[[2-(4-ethoxyphenyl)-2-methylpropoxy]methyl]-3-phenoxybenzene [CA]	x
2.3	Manufacturer's development code number(s) (IIA2.3)	MTI-500 (development code number given by the manufacturer of the a.i.) [redacted]01190-I (development code number given by the manufacturer of the formulated product)	
2.4	CAS No and EC numbers (IIA2.4)		
2.4.1	CAS-No	80844-07-1	
2.4.2	EC-No	407-980-2 [ELINCS]	
2.4.3	Other	471 [CIPAC]	
2.5	Molecular and structural formula, molecular mass (IIA2.5)		
2.5.1	Molecular formula	$C_{25}H_{28}O_3$	
2.5.2	Structural formula		
2.5.3	Molecular mass	376.49 g/mol	
2.6	Method of manufacture of the active substance (IIA2.1)	confidential information [redacted]	
2.7	Specification of the purity of the active substance, as appropriate (IIA2.7)	≥ 97.2 % w/w	

Section A2 Identity of Active Substance

Subsection (Annex Point)			Official use only
2.8	**Identity of impurities and additives, as appropriate (IIA2.8)**	confidential information [redacted]	
2.8.1	**Isomeric composition**	not applicable	
2.9	**The origin of the natural active substance or the precursor(s) of the active substance (IIA2.9)**	not applicable	

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*27.05.2005*
Materials and methods	*Agree with the applicant´s version*
Conclusion	*Agree with the applicant´s version*
Reliability	*1*
Acceptability	*Acceptable*
Remarks	2.2: CAS name: Benzene, 1-[[2-(4-ethoxyphenyl)-2-methylpropoxy]methyl]-3-phenoxy
	COMMENTS FROM...
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

Section A2.10
Annex Point IIA2.10

Exposure data in conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) amending Council Directive 67/548/EEC

Subsection			Official use only
2.10.1	**Human exposure towards active substance**	The human exposure assessment considers the production of the active substance and the product, workers treating wood with the product (primary exposure) and an exposure of persons who come into contact with treated wood (secondary exposure). While the workers are exposed to the formulated product, the general public is exposed to the active ingredient that can leach out of the wood, since the treated wood is sold only after it is completely dry. Human exposure in this section is calculated for the active substance etofenprox. The assessment of human exposure follows the recommendations of the Technical Notes for Guidance on Human Exposure to Biocidal Products (European Commission , 2002) and are reported in details in a separate report (Mirbach, 2004, section B 6.6).	X
2.10.1.1	**Production of the active substance**	General Note: As the active substance etofenprox is not produced in the European Union, European monitoring data are not available. Etofenprox is manufactured in industrial production plants by trained professionals using a multi-step batch process. The batch size is typically [redacted] are produced world-wide annually. Only a small fraction of the produced etofenprox is used in biocidal products marketed in Europe. Etofenprox is mainly used in plant protection products. Etofenprox does not have any properties that make it more hazardous than other chemicals used in chemical manufacturing plants. Exposure of worker to the active substance during manufacturing is very variable and depends strongly on the personal work hygiene of the individual worker. Therefore no attempt was made to estimate the exposure of workers during manufacturing of the active substance, but instead medical surveillance data were considered to indirectly asses the exposure. 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 in Japan (Yamazaki, 1992, section A 6.12.1.). The Ohmuta factory of Mitsui Toatsu Chemicals, Inc. produced [redacted] annum etofenprox technical during the period 1987 - 1992. 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. 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. Thus, it is concluded from this monitoring that there is no pattern of abnormalities in production operatives that suggest adverse health effects due to exposure to etofenprox.	
	i) Description of process	Confidential information [redacted]	X
	ii) Workplace description	See General Note.	
	iii) Inhalation exposure	Overall medical surveillance data were monitored (see General Note). Because of the low vapour pressure of etofenprox, the contribution of the inhalation to the overall exposure is small.	

Section A2.10
Annex Point IIA2.10

Exposure data in conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) amending Council Directive 67/548/EEC

Subsection			Official use only
	iv) Dermal exposure	Overall medical surveillance data were monitored (see General Note)	
2.10.1.2	**Production of the formulated product**	General Note:	
	i) Description of process	The biocidal product [redacted]01990-I is produced from etofenprox in a two step process. In the first step etofenprox is dissolved in a non-volatile, viscous organic solvent leading to a concentrate of 20% etofenprox in solvent. This concentrate [redacted] is then used to produce the product [redacted]01990-I which contains 0.1% etofenprox w/w in a mainly aqueous solution.	
	ii) Workplace description	The product is produced batch-wise in an automated liquid handling facility. The batch size and the frequency of the production are demand driven and thus variable. The amount of etofenprox used for the production of [redacted]01990-I is expected to be [redacted] The batch size in the first step can range from 10 to 1000 l concentrate, In the second step it could be 1 to 50 m^3 [redacted]01990-I. The active substance and the product are only handled by professionals with adequate training and protective equipment (gloves, boots, coverall).	
	iii) Inhalation exposure	Pure etofenprox has a melting point of 37.4 °C. Technical grade etofenprox is either an oily liquid or a sticky solid, depending on the temperature (Shimono, 2002a, section A 3.3.1/02). It has a very low probability to form inhalable airborne dust particles. The possibility of particle or aerosol formation is zero after dissolution of the etofenprox in the organic solvent. Inhalation of vaporised etofenprox could occur in a workplace, where open containers of neat etofenprox are handled or during cleaning and maintenance of equipment. The concentration in air is limited by vapour pressure and can be calculated from the following equation: $W = (P*V*M) / (R*T)$ where W is the concentration in air (g/m^3) P is the vapour pressure ($8.13*10^{-7}$ Pa, Tognucci, 2000) V is the volume of air (1 m^3) M is the molecular weight (376.5 g/mol) R is the gas constant (8.314 J/mol/K) T is the temperature (298 K) Using the values listed above, the saturation concentration is calculated to be 1.2×10^{-7} g/m^3. Assuming that the production takes place in a ventilated work area, the concentration is reduced to 1 % of the saturation concentration, i.e. 1.2×10^{-9} g/m^3. Assuming an inhalation rate of 1.25 m^3/h, a work day of 10 hours and an adult of 60 kg, this would lead to a inhalation exposure of $2.6 * 10^{-10}$ mg etofenprox/kg bw/day	X
	iv) Dermal exposure	Direct dermal contact with etofenprox is not foreseen. However, incidental contact is possible during transfer of the substance to the mixing vessel and during cleaning and disposal of the containers. Only hands could be incidentally exposed, when the gloves used are contaminated on the inside. In the absence of other guidance the indicative exposure values are taken from the model for dipping application. The TNsG on human exposure give indicative values of	X

Section A2.10 **Exposure data in conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) amending Council Directive 67/548/EEC**

Annex Point IIA2.10

Subsection		Official use only
	25.7 mg/min (worst case) and 12.7 mg/min (normal use, 75th percentile) for exposure of hands inside gloves. Assuming that the duration of the dermal exposure is 30 min/day, the dermal exposure is estimated to be 771 mg/day (worst case) and 381 mg/day (normal use). The highest exposure is during the first dilution step, i.e. during the production of the intermediate formulated product [redacted] which contains 20% w/w etofenprox. Dermal exposure is calculated assuming a worker of 60 kg bodyweight. In a Tier 1 approach, dermal penetration is assumed to be 100%. The tier 2 approach considers a dermal penetration of 13 %, as shown in a study on dermal absorption of etofenprox [redacted] 1999, section A 6.2/06). - Worst case, dermal penetration of 100%: 2.57 mg a.s./kg bw/day - Reasonable worst case, dermal penetration 13 %: 0.33 mg a.s./kg bw/day - Normal use, dermal penetration of 13%: 0.17 mg a.s./kg bw/day In the next production steps the product is diluted further, therefore the exposure to the active substance etofenprox will be lower than in the case scenario discussed above. The dermal exposure is incidental and not a consequence of normal work practice; it occurs only occasionally, when a new batch is produced, and it may involve different persons for each batch.	
2.10.1.3 Intended use(s) of the formulated product		
1. Professional Users		
(i) Description of application process	Etofenprox is used as insecticidal active ingredient in a wood preservative. Wood is treated industrially in sealed or partially sealed vessels by vacuum pressure and dipping treatment. A typical industrial work cycle consists of loading, treating, unloading and removal of the timber to storage. It is assumed that fresh and treated wood is moved using lift trucks. However, operators are closely involved with handling restraining straps, treatment machinery and other activities connected with loading and unloading. Therefore, the number of cycles is more critical for the exposure calculation than the duration of a cycle.	
(ii) Workplace description	Anticipated controls for all treatment types: gloves, coverall, foot protection, trained professionals Mixing and loading: The product [redacted]01990-I is supplied in 200 l drums, or 1000 l tanks. Incidental exposure can occur in connecting and disconnecting transfer lines by contact with product inside protective gloves and while taking off protective gloves. If exposure occurs, it is to the concentrate containing 0.1% etofenprox. It is assumed that mixing and loading of the application solution happens once a day. Vacuum pressure treatment: 2 cycles/day of 4 hours each (actual exposure only during handling of the treated timber) Dipping treatment: 3 cycles/day of 30 minutes (use classes 1&2) or 4	

Section A2.10
Annex Point IIA2.10

Exposure data in conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) amending Council Directive 67/548/EEC

Subsection		Official use only
	hours (use class 3) immersion per batch (actual exposure only during loading and unloading Post application: Professional post-application exposure relates to system maintenance. In this case the workers come into contact with the diluted application solution, not with the formulated product itself.	
(iii) Inhalation exposure	Although inhalation exposure will normally not occur during industrial use, it was considered in the risk assessment for vacuum pressure treatment. Inhalation uptake at primary worker exposure for each scenario as calculated in the human risk assessment (Mirbach 2004) is based on the TNsG on Human Exposure (European Commission 2002) and summarised in the following table (all values given in mg a.s./day). Generally four scenarios were distinguished: (a) Worst case without personal protective equipment (PPE), based on highest value in the TNsG on Human Exposure (b) Reasonable worst case with personal protective equipment (PPE) (c) Foreseeable misuse without protective equipment (PPE), 3x normal rate (d) Normal use with personal protective equipment (PPE), 75th percentile in TNsG on Human Exposure	X

Treatment	Scenario			
	(a)	(b)	(c)	(d)
Vacuum pressure	0.00080	0.00080	0.0024	0.00019
Dipping*	0.0	0.0	0.0	0.0

* No inhalation exposure

(iv) Dermal exposure	Primary worker exposure is mainly dermal. Workers are exposed through direct contact with the partially wet surface of the treated objects and through contact with ancillary equipment such as restraining straps. For the dermal exposure assessment, the same scenarios were considered as described for the inhalation exposure. Dermal uptake at primary worker exposure for each scenario as calculated in the human risk assessment (Mirbach 2004) is based on the TNsG on Human Exposure (European Commission 2002) and summarised in the following table (all values given in mg a.s./day)	X

Treatment	Scenario			
	(a)	(b)	(c)	(d)
Vacuum pressure	24.30	1.35	57.80	0.18
Dipping	9.57	0.51	25.60	0.28

2. Non-professional Users including the general public	The product is for professional use only. Secondary exposure as a consequence of professional use of the product is discussed in 2.10.1.4	
(i) via inhalational contact	Non-professional use is not considered	

Section A2.10
Annex Point IIA2.10

Exposure data in conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) amending Council Directive 67/548/EEC

Subsection			Official use only
	(ii) via skin contact	Non-professional use is not considered	
	(iii) via drinking water	Non-professional use is not considered	
	(iv) via food	Non-professional use is not considered	
	(v) indirect via environment	Non-professional use is not considered	
2.10.1.4	**Secondary Exposure**	The scenarios to be considered for secondary exposure are described in the TNsG on human exposure, Part 3, Appendix 7.1.1 (European Commission 2002) Secondary exposure is assumed to be to the active substance only, since treated wood is only used after it is completely dry. A tiered approach is used to estimate the exposure. In Tier 1 calculations (worst case), the maximum theoretically possible exposure is calculated. Tier 2 estimates represent the maximum exposure in a realistic scenario.	
	(i) acute inhalation of dust by an adult during sanding of wood	Tier 1: The worst case is based on the assumption that a wooden post is sanded by an adult worker (60 kg body weight) without protective equipment. The sanding generates a dust concentration in air of 5 mg/m^3. The post was dipping treated at a rate of 40 g product/m^2 wood (= 40 mg a.s./m^2) and all of the active substance is located in the outer 1 cm layer. Exposure is via inhalation only at a rate of 1.25 m^3/hour, for 6 hours per day as a single event. Tier 2: Not calculated since Tier 1 shows very low exposure.	X

	Inhalation	Dermal	Oral
Tier 1	3.13×10^{-6}	-	-
Tier 2	3.13×10^{-6}	-	-

(in mg a.s./kg bw /day)

(ii) acute dermal uptake by child	The product is used for industrial applications only and the treated wood is only used after it is completely dry. It is assumed that children are not present in the working area and are not acutely exposed by contact with treated timber while wet.	
(iii) acute oral ingestion by infant by chewing wood	Tier 1: The worst case is based on the assumption that an infant of 10 kg chews an off-cut of 4 cm * 4 cm * 1 cm. It is assumed that the child extracts 100 % of the active substance present in the off-cut. Exposure is via the oral route in a single event. Tier 2: The oral uptake via saliva is limited by the water solubility of the active substance (0.0225 mg/l). Assuming that an infant produces 0.2 l saliva per day the maximum ingestion is 0.0225 mg/l. * 0.2 l/day = 0.004 mg/day.	X

	Inhalation	Dermal	Oral
Tier 1	-	-	0.0064
Tier 2	-	-	0.00064

Section A2.10
Annex Point IIA2.10

Exposure data in conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) amending Council Directive 67/548/EEC

Subsection		Official use only

(in mg a.s./kg bw /day)

(iv) chronic inhalation of volatile residues indoors by adult

Tier 1: The realistic worst case is based on the assumption that the air of a room is completely saturated with active substance (100 % saturated vapour concentration, SVC). Exposure of an adult (60 kg body weight) is via inhalation only for 18 hours per day continuously.

Tier 2: It is assumed that the wood is installed indoors in a moderately ventilated room and that 1 % of SVC is reached.

	Inhalation	Dermal	Oral
Tier 1	4.6×10^{-5}	-	-
Tier 2	4.6×10^{-7}	-	-

(in mg a.s./kg bw /day)

(v) chronic dermal uptake by child playing on playground structure outdoors

Tier 1: The realistic worst case is based on the assumption that a child of 15 kg body weight plays outdoors on a playground structure. Exposure is dermal via the hand assuming a hand area of 200 cm^2, 100 % of hand contaminated and 100 % dermal uptake, continuously. X

Tier 2: It is assumed that only 20 % of the hand surface is contaminated and that the dermal penetration is 13 % [redacted] 1999).

	Inhalation	Dermal	Oral
Tier 1	-	0.053	-
Tier 2	-	0.0014	-

(in mg a.s./kg bw /day)

(vi) chronic dermal and ingestion uptake by infant playing on weathered structure and mouthing.

Tier 1: The realistic worst case is based on the assumption that an infant (10 kg body weight) plays on a weathered playground structure that was dipping treated with 40 g product / m^2 wood (= 40 mg a.s./m^2 wood). Exposure is dermal via the hand, assuming a hand area of 200 cm^2, 100 % of hand contaminated and 100 % dermal uptake. These are the same assumption as in point 5.6. In addition, oral ingestion of a surface deposit on 50 cm^2 wood is considered. It is assumed that the child extracts all of the active substance from the wood. X

Tier 2: It is assumed that only 20 % of the hand surface is contaminated and that the dermal penetration is 13 % [redacted] 1999). The oral uptake is limited by the water solubility of the active substance (0.0225 mg/l). Assuming that an infant produces 0.2 l saliva per day the maximum ingestion is 0.004 mg/day.

	Inhalation	Dermal	Oral
Tier 1	-	0.080	0.020
Tier 2	-	0.0021	0.0004

(in mg a.s./kg bw /day)

Section A2.10
Annex Point IIA2.10

Exposure data in conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) amending Council Directive 67/548/EEC

Subsection		**Official use only**
2.10.2 Environmental exposure towards active substance		
2.10.2.1 Production		
(i) Releases into water	No data available (a.i. not produced within the EU but in Japan)	
(ii) Releases into air	No data available (a.i. not produced within the EU but in Japan)	
(iii) Waste disposal	No data available (a.i. not produced within the EU but in Japan)	
2.10.2.2 Intended use(s)		
Affected compartments:		
- air	Yes, from the stage of wood treatment.	
- surface water	Yes - from the stage of wood treatment, via emissions to a facility drain and then sewage treatment plant (for both types of treatments) - from the stage of wood storage, via emissions through runoff after leaching from treated wood exposed to rainfall (for both types of treatments) - from the stage of wood in-service via emissions to a sewage treatment plant (noise barrier scenario only)	
- sediment	Yes, as for surface water	
- soil	Yes - from the stage of wood treatment, via emissions to a facility drain and then sewage treatment plant and finally application of the STP sludge to agricultural fields (for both types of treatments) - from the stage of wood storage, via emissions from treated wood exposed to rainfall (for both types of treatments) - from the stage of wood in-service via emissions to a sewage treatment plant and application of sludge application to agricultural fields (noise barrier scenario only) via emissions to the soil adjacent to the wood in service from leaching of the wood in-service exposed to rainfall (house and noise barrier scenarios)	
- groundwater	Yes, from leaching through contaminated soil - agricultural soil, from treatment stage and from wood in-service stage - industrial soil (i.e. soil under storage area) Note: concentrations in groundwater resulting from the contamination of the soil adjacent to the wood in-service was not considered, as this is a very local scale.	

Section A2.10 Annex Point IIA2.10	Exposure data in conformity with Annex VIIA to Council Directive 92/32/EEC (OJ No L, 05.06.1992, p. 1) amending Council Directive 67/548/EEC

Subsection		Official use only
Predicted concentration in the affected compartment(s)	Many values were calculated for each compartment, considering several time spans, taking or not into account removal processes (Tier 1 and Tier 2 PEC values, considering different standard receiving water bodies, etc. It is, therefore, difficult to summarise all the PEC values in just a few lines in this summary. Please refer to the Dossier Document II-B for the full overview.	

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*27.05.2005*
Materials and methods	*Agree with the applicants version*
Conclusion	-
Reliability	*2*
Acceptability	*Acceptable with revisions for data calculation (see remarks)*
Remarks	***2.10.1 Human exposure towards active substance*** As already mentioned the treated wood is sold only after it is completely dry and only industrial uses are intended. Therefore the general public is exposed to the active ingredient by emissions from treated wood (e.g. dermal uptake via direct contact) and while wood processing (e.g. sanding wood), *2.10.1.1 Production of the active substance* *i) Description of process:* A detailed description of the different stages of the production process is given in a separate report document (Document III, Section A2.6) *2.10.1.2 Production of the formulated product* *iii) Inhalation exposure:* typing error: Inhalation exposure should be specified as $2.6*10^{-10}$ g etofenprox/kg bw/day *iv) Dermal exposure* *General Notes:* - In model 1 for dipping application (due to of only 5 data points) indicative exposures are based upon maximum values, according to this normal use is inapplicable. - The maximum dermal absorption should be 13.8 %, as shown in Document III, Section A6.2/06. Since the dermal absorption is increased, the reasonable worst case is 0.35 mg a.s./kg/bw/day. *2.10.1.3 Intended use(s) of the formulated product* *General Notes:* - The 95th percentile value should be taken to reflect the anticipated exposure through normal use. - The maximum dermal absorption should be 13.8 %, as shown in Document III, Section A6.2/06. - Uptake of the active substance through the skin was determined experimentally, but no product data are available. Therefore the calculation should consider both, 100% uptake and 13.8% dermal absorption based on the data for the active substance. - In model 1 for dipping application (due to of only 5 data points) indicative exposures are based upon maximum values, according to this normal use is inapplicable.

Hence the following workplace data seem more appropriate:

(iii) Inhalation exposure

Treatment	Scenario			
	(a)	(b)	(c)	(d)
Vacuum pressure	0.003	0.003	0.007	0.002
Dipping*	0.0	0.0	0.0	0.0

* No inhalation exposure

(iv) Dermal exposure

Treatment	Scenario			
	(a)	(b)	(c)	(d)
Vacuum pressure	24.5	10.38 1.43*	20.3	3.23 0.45*
Dipping	9.57	3.93 0.54*	28.72	n.a.

* *Calculation was performed using a 13.8% dermal absorption based on the data for the active substance*

n.a. 95th percentile not applicable

2.10.1.4 Secondary Exposure

General Notes:

- Incorrect calculations in regard to active substance in the outer layer of the wood. The assumed volume of wooden post should is 0.004 m^3 (4 cm x 4 cm x 2.5 cm) but all of the active substance is located in the outer 1 cm layer (i.e. 0.003m^3).
- The maximum dermal absorption should be 13.8 %, as shown in Document III, Section A6.2/06.

Therefore, the secondary exposure should be specified as follows:

(i) acute inhalation of dust by an adult during sanding of wood

	Inhalation	Dermal	Oral
Tier 1	$4.17*10^{-6}$	-	-
Tier 2	$\leq 4.17*10^{-6}$	-	-

(iii) acute oral ingestion by infant by chewing wood

	Inhalation	Dermal	Oral
Tier 1	-	-	0.0053
Tier 2	-	-	0.0005

(v) chronic dermal uptake by child playing on playground structure outdoors

	Inhalation	Dermal	Oral
Tier 1	-	0.053	-
Tier 2	-	0.0015	-

(vi) chronic dermal and ingestion uptake by infant playing on weathered structure and mouthing.

	Inhalation	Dermal	Oral
Tier 1	-	0.080	0.017
Tier 2	-	0.0022	0.0005

	COMMENTS FROM...
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

Table A2.10: Workplace exposure / Inhalation exposure (based on the TNsGs on Human exposure, European Commission 2002)

Exposure scenario	**Workplace operation**	**PPE**	**Year(s) of measurement**	**Number of measurements**	**Type of measurements**	**Exposure concentration mg a.s./kg bw/day**
Production of active substance	Emptying, filling, weighing	Gloves, coveralls, boots, goggles	5 years between 1987 and 1992	21 male staff	medical surveillance	no work related health effects observed
Production of the formulated product	Connection of transfer lines, maintenance	Gloves, coveralls, boots, goggles	n.a.	n.a.	estimation, based on the TNsG on human exposure	a) 0.35 b) -
Application of the product: Vacuum – pressure process	Mixing and loading, handling of treated wood, maintenance of equipment	Gloves, coveralls, boots, goggles	HSE Surveys 1996 to 1998 on 56 timber treatment sites, as described in TNsG on human exposure	29 to 45	no details reported	a) 0.024 b) 0.0075
Application of the product: Dipping process	Mixing and loading, handling of treated wood, maintenance of equipment	Gloves, coveralls, boots, goggles	HSE Surveys 1999, as described in TNsG on human exposure	5	no details reported	a) 0.0090 b) -

a) Reasonable worst case, based on highest value of HSE survey, 12 % penetration through PPE, 13.8 % penetration through skin

b) Normal use case, based on 95th percentile of HSE survey, 12 % penetration through PPE, 13.8 % penetration through skin

Section A3 Physical and Chemical Properties of Active Substance

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
3.1 Melting point, boiling point, relative density (IIA-III.3.1)								
3.1.1 Melting point	OECD 102; EEC A.1; JMAFF; (capillary tester)	Pure etofenprox, >99% purity, batch MR-9301	Melting point = 37.4°C ± 0.1°C (i.e. 310.6K ± 0.1K)	none	Y	1	Tognucci A. 1999	
3.1.2 Boiling point	OECD 103; EEC A.2; JMAFF; (Differential thermal calori-meter/capillary tester)	Pure etofenprox, >99% purity, batch MR-9301	Boiling point not determinable, degradation at about 200°C	none	Y	1	Tognucci A. 1998a	
3.1.3 Bulk density/ relative density	OECD 109; EEC A.3; JMAFF; (gas compari-son pycno-meter)	Pure etofenprox, >99% purity, batch MR-9301	Density = 1.172 g/cm^3 at 20.7°C ± 0.1°C	none	Y	1	Tognucci A. 1998b	
3.2 Vapour pressure (IIA-III.3.2)	OECD 104; EEC A.4; (gas saturation method)	Pure etofenprox, >99% purity, batch MR-9301	Vapour pressure: at 80°C = 2.16 x 10^{-3} Pa at 90°C = 7.01 x 10^{-3} Pa at 25°C = 8.13 x 10^{-7} Pa	Determination of the vapour pressure at 80°C and twice at 90°C; extrapolation of the value at 25°C by linear regression.	Y	1	Tognucci A. 2000	

Section A3 Physical and Chemical Properties of Active Substance

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
3.2.1 Henry´s Law Constant (Pt. I-A3.2)	calculation	Pure etofenprox, >99% purity, batch MR-9301	calculated: 0.0136 Pa x m^3/mol	none	Y	1	Tognucci A. 2000	
3.3 Appearance (IIA-III.3.3)								
3.3.1 Physical state	not specified	Pure etofenprox, 99.8% purity, batch 90S-01	Physical state: solid (crystalline)	none	N	1	Shimono S. 1999a	X
	not specified	Manufactured etofenprox, 99.3% purity, batch 54023	Physical state: liquid (oil)	none	N	1	Shimono S. 2002a	X
3.3.2 Colour	JIS Z 8723; JIS Z 8102	Pure etofenprox, 99.8% purity, batch 90S-01	Colour: white	none	N	1	Shimono S. 1999b	
	JIS Z 8723; JIS Z 8102	Manufactured etofenprox, 99.3% purity, batch 54023	Colour: amber	none	N	1	Shimono S. 2002b	
3.3.3 Odour	not specified	Pure etofenprox, 99.8% purity, batch 90S-01	Odour: slight aromatic odour	none	N	1	Shimono S. 1999c	
	not specified	Manufactured etofenprox, 99.3% purity, batch 54023	Odour: aromatic odour	none	N	1	Shimono S. 2002c	

Section A3 Physical and Chemical Properties of Active Substance

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
3.4 Absorption spectra (IIA-III.3.4)								
UV/VIS IR NMR MS	OECD 101; 79/831/EEC; JMAFF	Pure **etofenprox**, >99% purity, batch MR-9301	- 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.	none	Y	1	Tognucci A. 1998c	
UV/VIS	OECD 101; 94/37/EEC	4'-OH, 96% purity, batch 043-011222-1	- UV/VIS absorption spectrum: similar in acid, alkaline and neutral solution; absorption maxima at 215-222 nm.	none	Y	1	Matsumoto T. 2002a	X
UV/VIS	OECD 101; 94/37/EEC	PENA, 99.8% purity, batch 043-011119-1	- UV/VIS absorption spectrum: similar in acid, alkaline and neutral solution; absorption maxima at 221-222 nm.	none	Y	1	Matsumoto T. 2002b	X
UV/VIS IR NMR MS		Impurities		Identity of impurities is confidential [redacted]				

Section A3 Physical and Chemical Properties of Active Substance

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
3.5 Solubility in water (IIA-III.3.5)								
Water solubility 1	OECD 105; 92/96/EEC; EPA OPPTS 830.7840	[2-^{14}C-propyl]-**etofenprox**, >98% radiochemical purity, 576.09 MBq/mmol specific radioactivity, batch MRH/MTC 276/37	Solubility in - 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	none	Y	1	Kunz Ch. 2000 Mirbach M. 2004a	X
Water solubility 2	OECD 105; EEC A.6; EPA OPPTS 830.7840/60	[^{14}C]-alpha-CO, 99.7% radiochemical purity, 5.19 MBq/mg specific radioactivity, batch CP-2491-1	Solubility in - bidistilled water: 42.5 µg/l (measured at 20 ± 0.5°C) - buffer at pH 4 and pH 9: not possible to determine due to significant degradation of the test substance	none	Y	1	McCorquodale G.Y. 2002a	X
Water solubility 3	OECD 105; EEC A.6; (column elution method)	4'-OH, 96% purity, batch 043-011222-1	Solubility in purified water: 217 µg/l	none	Y	1	Matsumoto T. 2002c	X
Water solubility 4	OECD 105; EEC A.6; (flask method)	PENA, 99.8% purity, batch 043-011119-1	Solubility in purified water: 1360 mg/l	none	Y	1	Matsumoto T. 2002d	X
3.6 Dissociation constant (-)	not applicable (expert statement)	not applicable (expert statement)	Etofenprox has no sites which can either be protonated or dissociate at pH 3 to 10	none			Schmiedel U. 1998	

Section A3 Physical and Chemical Properties of Active Substance

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
3.7 Solubility in organic solvents, including the effect of temperature on solubility (IIIA-III.1)	OECD 105; JMAFF;	Manufactured etofenprox, >98% purity, batch 55027	Solubility in g/l (at 20°C ± 1°C): Methanol: 49 Ethanol: 98 Acetone: 877 Ethylacetate: 837 Hexane: 667 Heptane: 621 Xylene: 856 Toluene: 862 Dichloromethane: 924 Solubility estimated to increase by ca. 4.9%/ °C	none	Y	1	Tognucci A. 1998d Mirbach M. 2004a	
3.8 Stability in organic solvents used in b.p. and identity of relevant breakdown products (IIIA-III.2)				Justification submitted			Document III.A3_08	

Section A3 Physical and Chemical Properties of Active Substance

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
3.9 Partition coefficient n-octanol/water (IIA-III.3.6)								
log Pow 1	OECD 107 and 117; EEC A8 JMAFF; (HPLC method)	Pure **etofenprox**, >99% purity, batch MR-9301	Log Pow = 6.9 Log Pow estimated to increase by ca. 1%/ °C	none	Y	1	Tognucci A. 1998e Mirbach M. 2004a	
log Pow 2	OECD 117; (HPLC method)	[^{14}C]-alpha-CO, 99.7% radiochemical purity, 5.19 MBq/mg specific radioactivity, batch CP-2491-1	Log P_{OW} = 6.5	none	Y	1	McCorquodale G.Y. 2002b	X
log Pow 3	OECD 117; EEC A.8; (HPLC method)	4'-OH, 96% purity, batch 043-011222-1	Log P_{OW} = 5.3	none	Y	1	Matsumoto T. 2002e	X
log Pow 4	OECD 117; EEC A.8; (HPLC method)	PENA, 99.8% purity, batch 043-011119-1	Log P_{OW} = 2.4	none	Y	1	Matsumoto T. 2002f	X

Section A3 Physical and Chemical Properties of Active Substance

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
3.10 Thermal stability, identity of relevant breakdown products (IIA-III.3.7)	OECD 113 JMAFF	Pure etofenprox, >99% purity, batch MR-9301	Temperature range: 25°C to 150°C: reproducible endothermic peaks and a fused sample residue indicate most probably the melting of the test article	none	Y	1	Tognucci A 1998f	X
3.11 Flammability, including auto-flammability and identity of combustion products (IIA-III.3.8)	EEC A.10	Manufactured etofenprox, 97.1% purity, batch 91-195	not flammable	none	Y	1	Dublaski A. 1991a	X
	EEC A.16	Manufactured etofenprox, 97.1% purity, batch 91-195	no self-ignition up to the melting point	none	Y	1	Dublaski A. 1991b	X
3.12 Flash-point (IIA-III.3.9)	EEC A.9 OPPTS 830.6315 (closed cup equilibrium method)	Manufactured etofenprox, 99.3% purity, batch 54023	no flash recorded at temperatures up to 110°C	none	Y	1	Bates M. 2001a	
3.13 Surface tension (IIA-III.3.10)	EEC A.5	Manufactured etofenprox, >97.1% purity, batch 91-195	Surface tension = 68.12 mN/m (90% aqueous solution at 20.1°C)	none	Y	1	Dublaski A. 1991c	
3.14 Viscosity (-)				not required (etofenprox is a solid)				

Section A3 Physical and Chemical Properties of Active Substance

Subsection (Annex Point)	Method	Purity/ Specification	Results Give also data on test pressure, temperature, pH and concentration range if necessary	Remarks/ Justification	GLP (Y/N)	Reliability	Reference	Official use only
3.15 Explosive properties (IIA-III.3.11)	EEC A.14; OPPTS 830.6316	Manufactured etofenprox, 99.3% purity, batch 54023	not explosive	none	Y	1	Bates M. 2001b	
3.16 Oxidizing properties (IIA-III.3.12)	EEC A.17	Manufactured etofenprox, 99.3% purity, batch 54023	not oxidizing	none	Y	1	Bates M. 2001c	
3.17 Reactivity towards container material (IIA-III.3.13)			Stable in container	Statement from manufacturer provided			Ohnuma K. 2004	X

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*27.05.2005*
Materials and methods	*3.3.1 Physical state:* As specified in detail in Mirbach, 2006, the thermodynamically stable state of etofenprox is crystalline solid. However, there exists a metastable state as supercooled liquid. Eventually the supercooled liquid will become very viscous (paste-like) and solidifies in an amorphous state (yellowish wax like solid). As an alternative, the liquid etofenprox may crystallise and form white microscopic crystals. Which of the processes occurs depends on factors like the cooling rate, the presence of seed crystals, the agitation of the liquid etc. *3.5 Solubility in water and 3.7 Solubility in organic solvents, including the effect of temperature on solubility* The report Mirbach M 2004a does not describe any new results from experimental work and, accordingly, the principles of Good Laboratory Practice do not apply. The present report describes calculated values for the temperature dependence of the solubility of Etofenprox in water and organic solvents and its partition coefficient octanol/water. *3.5 Solubility in water* For both water solubility 1 and 2 the column elution method was used. *3.10 Thermal stability, identity of relevant breakdown products* The temperature of the reproducible endothermic peaks is 42°C for the pre-test and 40.6°C for the main test. *3.11 Flammability, including auto-flammability and identity of combustion products* Tests A.12 and A.13 were not carried out since experience in use indicates that negative results would be obtained: No ignition in contact with water is expected, since the biocidal product contains 74.1% water and is stable. No spontaneous ignition after contact with air is expected, since the solid substance was used in tests (e.g. A.10, A.16) and did not ignite spontaneously. Performance of test A.15 is not possible due to the physical state of etofenprox. (See point 3.3.1) *3.17 Reactivity towards container material* The containers are made from mild steel (i.e. low carbon steel) plate, tinned for corrosion protection. On the inside, they are treated with a zinc phosphate based anti-corrosive.
Conclusion	*Agree with the applicant´s version with the amendments given above*
Reliability	*Agree with the applicant´s version with the amendments given above*
Acceptability	*Acceptable*
Remarks	*3.4, 3.5, 3.9:* 4'-OH, PENA, and [^{14}C]-alpha-CO are metabolites of etofenprox.

	COMMENTS FROM...
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

Section A3.8 Annex Point IIIA-III.2 — Stability in organic solvents used in b.p. and identity of relevant breakdown products

JUSTIFICATION FOR NON-SUBMISSION OF DATA

Official use only

Other existing data [ ] **Technically not feasible [ ]** **Scientifically unjustified [X]**

Limited exposure [ ] **Other justification [ ]**

Detailed justification:

[redacted]PM is used as the sole solvent in [redacted]01990-I. Total content of [redacted] is 5% (4.6% in the formulation of [redacted]01990-I, 0.4% is contained in [redacted].

Etofenprox is added to [redacted]01990-I as [redacted] a formulation containing 20% Etofenprox and < 80% [redacted] The following claims are given in the MSDS of [redacted]

- no thermal decomposition if used according to specifications (recommended storage temperature: 15-25°C; storage class 10)
- no dangerous reactions known
- no dangerous decomposition products known

A storage stability trial was conducted with [redacted]01990-I (Warncke, 2004; Section B3.7). It was shown that etofenprox was stable in [redacted] 01990-I after storage for 2 weeks at 54°C.

Undertaking of intended data submission [ ] not applicable

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	27.05.2005
Evaluation of applicant's justification	*The justification is acceptable according to TGD on data requirements, chapter 3A, point 3.8*
Conclusion	*Agree with applicant's version*
Remarks	-

Evaluation by Competent Authorities	
	COMMENTS FROM...
Date	
Evaluation of applicant's justification	
Conclusion	
Remarks	

Section A4 (4.2)
Annex Point IIA-IV.4.2

Analytical Methods for Detection and Identification
(a) Soil

Official use only

1 REFERENCE

1.1	**Reference**	Wolf S. (2003a): Validation of the residue analytical method for MTI-500 and α-CO in soil; RCC Ltd, Environmental Chemistry & Pharmanalytics Division, Itingen, Switzerland; unpublished report no. 811607 (September 24, 2003) Dates of work: April 24, 2003 – June 14, 2003
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted] Mitsui Chemicals Agro, Inc.
1.2.2	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing [a.s. / b.p.] for the purpose of its [entry into Annex I/IA / authorisation]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes Residue Analytical Method, Guideline 96/46/EC, July 16, 1996 SANCO/825/00 rev. 6, June 20, 2000 SANCO/3029/99 rev. 4, July 11, 2000 – working document
2.2	**GLP**	Yes
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Preliminary treatment**	
3.1.1	Enrichment	• Extraction: - analytical samples taken from sieved soil were weighed and dried to determine the water content in the sample - soil sample was soaked 3 hours in acetone, then shaken for 60 min on mechanical shaker - extract was filtered through Celite, filtrate cake was washed with acetone - combined extracts were evaporated until complete removal of acetone
3.1.2	Cleanup	• Hexane-water partition: - crude extract was dissolved in hexane (100 ml) and 5% sodium chloride solution (250 ml) - after shaking for 10 min, phases were separated by use of a separating funnel - aqueous phase was again mixed with hexane (50 ml), then again separation of phases - combined hexane phases were filtered through anhydrous sodium sulphate, the solvent was evaporated to dryness, and residue was dissolved in hexane • Determination of Etofenprox residues: - cleanup of residue by alumina column chromatography: an alumina column was prepared using aluminum oxide active neutral (Merck 1.01077), and the extract was added to the column. The column was washed with hexane/toluene mixture

Section A4 (4.2) **Analytical Methods for Detection and Identification**
Annex Point IIA-IV.4.2 **(a) Soil**

		(9+1, v/v), and etofenprox was eluted from the column with hexane/ethyl ether mixture (7+3, v/v). • Determination of α-CO residues: - cleanup of residue by silica gel column chromatography: a silica gel column was prepared using silica gel 60 (0.063-0.20 mm; Merck 1.07734), and the extract was added to the column. The column was washed and α-CO was eluted from the column with hexane/ethyl ether mixture (100:3, v/v). - cleanup of residue by florisil column chromatography: a column was prepared using florisil (0.15-0.25/60-100; Merck 1.12994), and the extract was added to the column. The column was washed with hexane, and α-CO was eluted from the column with hexane/ethyl ether mixture (85+15, v/v). The solvent was removed and the residue was dissolved in acetone/dodecane (1+1, v/v)
3.2	**Detection**	
3.2.1	Separation method	Gas chromatograph: Hewlett Packard 6890 (Agilent) Column: HP-5-MS, 30 m x 0.25 mm (0.25 µm) Pre-column:2 m x 0.32 mm deactivated fused silica Carrier gas: Helium, flow: 105 kpa, constant pressure Temperatures: Injector: 270°C Oven: 200°C initial time: 2 min rate: 10°C/min to 280°C for 7 min rate: 50°C/min to 320°C for 15 min Injection: 3 µl splitless
3.2.2	Detector	Detector: MS 5973; ChemStation Ver. B.01.00, Hewlett Packard, USA Ionization mode: EI, Scan mode: SIM m/z: 163 (for peak quantification) SIM m/z: 376 (for etofenprox peak identification) SIM m/z: 390 (for α-CO peak identification) Scan time: 2.86 s MS conditions: Electron energy: 70 eV; Ion source temperature: 230°C Transfer line temperature: 300°C; quadrupole temperature: 150°C Retention times: etofenprox: about 15 min; α-CO: about 15.6 min
3.2.3	Standard(s)	MTI-500 (=etofenprox): external standard α-CO: external standard
3.2.4	Interfering substance(s)	none
3.3	**Linearity**	
3.3.1	Calibration range	0.02 to 2.0 µg/ml for etofenprox 0.05 to 2.0 µg/ml for α-CO
3.3.2	Number of measurements	2
3.3.3	Linearity	r^2 = 0.995 to 1.000

Section A4 (4.2)
Annex Point IIA-IV.4.2

Analytical Methods for Detection and Identification
(a) Soil

3.4	**Specifity: interfering substances**	There was no interference with other substances observed at the retention times of etofenprox and α-CO above 30% of the limit of quantification as well as above the limit of detection	
3.5	**Recovery rates at different levels**	see table below	
3.5.1	Relative standard deviation	see 3.5 ; SD = standard deviation	X
3.6	**Limit of determination**	0.01 mg/kg	X
3.7	**Precision**		
3.7.1	Repeatability	see 3.5	
3.7.2	Independent laboratory validation	Not performed for soil. A confirmatory method is included in the report	

Matrix	Fort. level [mg/kg]	Recovery rate [%] mean	Recovery rate [%] range	SD [%]	Rep.
Soil	0.01 E	100.6	94.5 - 108.9	5.5	5
"	0.1 E	88.5	81.1 - 94.9	5.5	5
"	0.01 α	102.5	90.5 - 108.7	7.2	5
"	0.1 α	86.2	70.7 - 92.3	8.8	5

E = etofenprox; α = α-CO

4 APPLICANT'S SUMMARY AND CONCLUSION

4.1	**Materials and methods**	Soil samples were extracted with acetone. After filtration and evaporation of acetone, etofenprox and α-CO was partitioned from the remaining aqueous solution into hexane. To determine the residues of etofenprox the crude extract was cleaned up by Alumina column chromatography. To determine the residues of α-CO the crude extract was cleaned up by silica gel and florisil column chromatography. The concentration of etofenprox and α-CO in the extract was determined by GC/MS. For a summary of the analytical methods and results in tabular form see also Document II-A (effects assessment), Table 1.4.
4.2	**Conclusion**	The analytical method was valid for analysis of etofenprox and its metabolite α-CO in soil in a concentration range of 0.01 to 0.10 mg/kg.
4.2.1	Reliability	1
4.2.2	Deficiencies	No

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*27.08.2005*
Materials and methods	*3.5.1 Relative standard deviation* Standard deviations (SD) are reported instead of relative standard deviations (RSD). Please refer to the Dossier Document II-A for corresponding relative standard deviations. *3.6 Limit of determination* Wolf S. (2003a) specifies the limit of detection at about 0.002 µg/kg.
Conclusion	Agree with the applicant´s version
Reliability	1
Acceptability	Acceptable
Remarks	-
	COMMENTS FROM...
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

Section A4 (4.2) Analytical Methods for Detection and Identification

Annex Point IIA-IV.4.2 **(b) Air**

Official use only

1 REFERENCE

1.1	**Reference**	Wolf S. (2003b): Validation of the residue analytical method for MTI-500 and α-CO in air; RCC Ltd, Environmental Chemistry & Pharmanalytics Division, Itingen, Switzerland; unpublished report no. 811620 (October 15, 2003) Dates of work: August 28, 2003 – September 21, 2003
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted] Mitsui Chemicals Agro, Inc.
1.2.2	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing [a.s. / b.p.] for the purpose of its [entry into Annex I/IA / authorisation]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes Residue Analytical Method, Guideline 96/46/EC, July 16, 1996 SANCO/825/00 rev. 6, June 20, 2000 SANCO/3029/99 rev. 4, July 11, 2000 – working document
2.2	**GLP**	Yes
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Preliminary treatment**	
3.1.1	Enrichment	• Air sampling: - Tenax tubes were opened on both ends and spiked on the front end with fortification solutions of etofenprox and α-CO, respectively. Air was drawn through the adsorbent (Tenax, SKC 226-35-03) with a portable air pump (Gilian AirCon2). Two temperature/humidity conditions were used 20°C/58% and 37°C/81%. The flow rate was 1 litre/min for 6 hours.
3.1.2	Cleanup	• Extraction: - the front and the back parts of the Tenax tubes were extracted separately with acetone. The acetone was filtred through a 0.45-µm PTFE filter. - This solution was analysed for Etofenprox and α-CO by GC-MS.
3.2	**Detection**	
3.2.1	Separation method	Gas chromatograph: Hewlett Packard 6890 (Agilent) Column: HP-5-MS, 30 m x 0.25 mm (0.25 µm) Pre-column:2 m x 0.32 mm deactivated fused silica Carrier gas: Helium, flow: 1.8 ml/min Temperatures: Injector: 270°C Oven: 50 °C initial time: 0 min rate: 50°C/min to 200°C for 2min rate: 10°C/min to 280°C for 7 min rate: 50°C/min to 320°C for 15 min Injection: 1 µl splitless
3.2.2	Detector	Detector: HP 5972 series

Section A4 (4.2) **Analytical Methods for Detection and Identification**
Annex Point IIA-IV.4.2 **(b) Air**

		Ionization mode: EI, Electron energy: 70 eV Ion source temperature: 230°C Transfer line temperature: 300°C Quadrupole temperature: 150°C Scan mode: SIM m/z: 163 (for peak quantification) SIM m/z: 376 (for etofenprox peak identification) SIM m/z: 390 (for α-CO peak identification) Scan time: 2.86 s Retention times: etofenprox: about 12.1 min; α-CO: about 15.6 min	
3.2.3	Standard(s)	MTI-500 (=etofenprox): external standard α-CO: external standard	
3.2.4	Interfering substance(s)	none	
3.3	**Linearity**		
3.3.1	Calibration range	0.01 to 1.0 µg/ml for etofenprox 0.01 or 0.02 to 2.0 µg/ml for α-CO	X
3.3.2	Number of measurements	5	
3.3.3	Linearity	r^2 = 0.992 to 0.998	
3.4	**Specifity: interfering substances**	There was no interference with other substances observed at the retention times of etofenprox and α-CO above 30% of the limit of quantification as well as above the limit of detection	
3.5	**Recovery rates at different levels**	see table below	X
3.5.1	Relative standard deviation	see 3.5 ; SD = standard deviation	
3.6	**Limit of determination**	1.0 µg/m³.	X
3.7	**Precision**		
3.7.1	Repeatability	see 3.5	
3.7.2	Independent laboratory validation	There was no independent laboratory validation for air, but a confirmatory method was included in the report..	

Matrix	Fort. level	Recovery rate [%]		RSD [%]	Repli-cates
		mean	range		
Air, 20°C	1.0 µg/m³	98.4	75.0-108.3	13.5	5
Air, 20°C	10.0 µg/m³	85.1	71.4-106.8	13.6	5
Air, 37°C	1.0 µg/m³	103.7	99.4-109.2	4.1	5
Air, 37°C	10.0 µg/m³	104.5	98.1-107.2	3.7	5
Air, 20°C	1.0 µg/m³	89.9	72.1-104.3	13.0	5
Air, 20°C	10.0 µg/m³	84.8	75.7-108.3	13.5	5
Air, 37°C	1.0 µg/m³	105.2	99.4-108.8	3.6	5
Air, 37°C	10.0 µg/m³	105.8	101.5-107.9	2.5	5

E = etofenprox; α = α-CO

Section A4 (4.2)
Annex Point IIA-IV.4.2

Analytical Methods for Detection and Identification
(b) Air

4 APPLICANT'S SUMMARY AND CONCLUSION

4.1	**Materials and methods**	Tenax adsorption tubes were spiked with etofenprox and α-CO, respectively. Air was drawn through the tubes at a selected rated for a predetermined time. The front and back parts of the adsorbent were analysed for etofenprox and α-CO. For a summary of the analytical methods and results in tabular form see also Document II-A (effects assessment), Table 1.4.
4.2	**Conclusion**	The analytical method was valid for analysis of etofenprox and its metabolite α-CO in air in a concentration range of 1 to 10 µg/m^3.
4.2.1	Reliability	1
4.2.2	Deficiencies	No

<table>
<tr><th colspan="2">Evaluation by Competent Authorities</th></tr>
<tr><td></td><td>EVALUATION BY RAPPORTEUR MEMBER STATE</td></tr>
<tr><td>Date</td><td>27.08.05</td></tr>
<tr><td>Materials and methods</td><td>3.3.1 Calibration range
The calibration was performed using standards in the range of 0.01-1.0 µg/mL for both, MIT-500 and α-CO

3.5 Recovery rates at different levels
- The lines two to five of the table relate to etofenprox.
The lines six two to nine relate to α-CO.
- Wolf S. (2003b) specifies the relative standard deviations of the recoveries as follows:

<table>
<tr><th rowspan="2">Matrix</th><th rowspan="2">Fort. Level [µg/m³]</th><th colspan="2">Recovery rate [%]</th><th rowspan="2">RSD [%]</th><th rowspan="2">Repli-cates</th></tr>
<tr><th>mean</th><th>range</th></tr>
<tr><td>Air, 20°C</td><td>1.0 E</td><td>98.4</td><td>75.0-108.3</td><td>13.7</td><td>5</td></tr>
<tr><td>Air, 20°C</td><td>10.0 E</td><td>85.1</td><td>71.4-106.8</td><td>16.0</td><td>5</td></tr>
<tr><td>Air, 37°C</td><td>1.0 E</td><td>103.7</td><td>99.4-109.2</td><td>4.0</td><td>5</td></tr>
<tr><td>Air, 37°C</td><td>10.0 E</td><td>104.5</td><td>98.1-107.2</td><td>3.5</td><td>5</td></tr>
<tr><td>Air, 20°C</td><td>1.0 a</td><td>89.9</td><td>72.1-104.3</td><td>14.4</td><td>5</td></tr>
<tr><td>Air, 20°C</td><td>10.0 a</td><td>84.8</td><td>75.7-108.3</td><td>16.0</td><td>5</td></tr>
<tr><td>Air, 37°C</td><td>1.0 a</td><td>105.2</td><td>99.4-108.8</td><td>3.4</td><td>5</td></tr>
<tr><td>Air, 37°C</td><td>10.0 a</td><td>105.8</td><td>101.5-107.9</td><td>2.8</td><td>5</td></tr>
</table>

3.6 Limit of determination
Wolf S. (2003b) specifies the limit of detection at about 0.3 µg/kg.</td></tr>
<tr><td>Conclusion</td><td>Agree with the applicant´s version</td></tr>
<tr><td>Reliability</td><td>1</td></tr>
<tr><td>Acceptability</td><td>Acceptable</td></tr>
<tr><td>Remarks</td><td>-</td></tr>
<tr><td></td><td>COMMENTS FROM...</td></tr>
<tr><td>Date</td><td></td></tr>
<tr><td>Results and discussion</td><td></td></tr>
<tr><td>Conclusion</td><td></td></tr>
<tr><td>Reliability</td><td></td></tr>
<tr><td>Acceptability</td><td></td></tr>
<tr><td>Remarks</td><td></td></tr>
</table>

Section A4 (4.2) Analytical Methods for Detection and Identification

Annex Point IIA-IV.4.2 **(c) Water**

Official use only

1 REFERENCE

1.1	**Reference**	Wolf S. (2003c): Validation of the residue analytical method for MTI-500 and α-CO in drinking, ground and surface water; RCC Ltd, Environmental Chemistry & Pharmanalytics Division, Itingen, Switzerland; unpublished report no. 811618 (September 30, 2003) Dates of work: April 29, 2003 – July 02, 2003
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted]. Mitsui Chemicals Agro, Inc.
1.2.2	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing [a.s. / b.p.] for the purpose of its [entry into Annex I/IA / authorisation]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes Residue Analytical Method, Guideline 96/46/EC, July 16, 1996 SANCO/825/00 rev. 6, June 20, 2000 SANCO/3029/99 rev. 4, July 11, 2000 – working document
2.2	**GLP**	Yes
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Preliminary treatment**	
3.1.1	Enrichment	• Extraction: - water sample (1000 ml) and NaCl (50 g) were extracted twice with hexane (100 ml, 50 ml). - combined hexane phases were filtered through anhydrous sodium sulphate and rinsed with dichloromethane. - combined organic solvent was evaporated to dryness, residue was re-dissolved in hexane.
3.1.2	Cleanup	• Determination of Etofenprox residues: - clean-up of residue by alumina column chromatography: an alumina column was prepared using aluminum oxide active neutral (Merck 1.01077), and the extract was added to the column. The column was washed with hexane/toluene mixture (9+1, v/v), and etofenprox was eluted from the column with hexane/ethyl ether mixture (7+3, v/v). - clean-up by florisil column: the column was prepared with florisil (0.15 – 0.25/60-100 Merck 1.12994) and sodium sulphate. The sample from the alumina clean-up was added to the column, washed with hexane and eluted with hexane/ether (9+1, v/v). The solvent was removed and the residue dissolved in dodecane. • Determination of α-CO residues: - clean-up of residue by silica gel column chromatography: a silica gel column was prepared using silica gel 60 (0.063-0.20 mm;

Section A4 (4.2) **Analytical Methods for Detection and Identification**
Annex Point IIA-IV.4.2 **(c) Water**

		Merck 1.07734), and the extract was added to the column. The column was washed and α-CO was eluted from the column with hexane/ethyl ether (100+3, v/v). - clean-up by florisil column: the column was prepared with florisil (0.15 – 0.25/60-100 Merck 1.12994) and sodium sulphate. The sample from the alumina clean-up was added to the column, washed with hexane and eluted with hexane/ether (85+15, v/v). The solvent was removed and the residue dissolved in dodecane.
3.2	**Detection**	
3.2.1	Separation method	Gas chromatograph: Hewlett Packard 6890 (Agilent) Column: HP-5-MS, 30 m x 0.25 mm (0.25 µm) Pre-column:2 m x 0.32 mm deactivated fused silica Carrier gas: Helium, flow: 105 kpa, constant pressure Temperatures: Injector: 270°C Oven: 200°C initial time: 2 min rate: 10°C/min to 280°C for 7 min rate: 50°C/min to 320°C for 15 min Injection: 3 µl splitless
3.2.2	Detector	Detector: MS 5973; ChemStation Ver. B.01.00, Hewlett Packard, USA Ionization mode: EI, Scan mode: SIM m/z: 163 (for peak quantification) SIM m/z: 376 (for etofenprox peak identification) SIM m/z: 390 (for α-CO peak identification) Scan time: 2.86 s MS conditions: Electron energy: 70 eV; Ion source temperature: 230°C Transfer line temperature: 300°C; quadrupole temperature: 150°C Retention times: etofenprox: about 14 - 15 min; α-CO: about 16 min
3.2.3	Standard(s)	MTI-500 (=etofenprox): external standard α-CO: external standard
3.2.4	Interfering substance(s)	none
3.3	**Linearity**	Non-entry field
3.3.1	Calibration range	0.001 to 0.5 µg/ml for etofenprox 0.001 - 0.005 to 0.5 µg/ml for α-CO
3.3.2	Number of measurements	5
3.3.3	Linearity	r^2 = 0.995 to 0.999

Section A4 (4.2)
Annex Point IIA-IV.4.2

Analytical Methods for Detection and Identification
(c) Water

3.4 Specifity: interfering substances

There was no interference with other substances observed at the retention times of etofenprox and α-CO above 30% of the limit of quantification as well as above the limit of detection

3.5 Recovery rates at different levels

Matrix	Fort. level [µg/l]	Recovery rate [%] mean	Recovery rate [%] range	SD [%]	Repl.
Drinking water	0.05 E	98.9	79.0 - 110.4	13.1	5
"	0.5 E	91.2	81.2 – 100.5	8.8	5
"	0.05 α	93.5	87.6 – 102.1	6.2	5
"	0.5 α	100.6	95.2 – 104.7	4.7	5
Ground water	0.05 E	101.4	71.3 – 111.2	17.2	5
"	0.5 E	97.0	76.3 – 107.2	12.6	5
"	0.05 α	99.3	83.7 – 106.4	9.3	5
"	0.5 α	107.6	105.9 –109.0	1.3	5
Surface water	0.01E	77.9	71.7 – 85.3	5.5	5
"	0.1 E	83.6	70.0 – 103.4	17.4	5
"	0.01 α	87.6	73.0 – 109.8	19.5	5
"	0.1 α	93.1	81.9 – 109.6	13.5	5

E = etofenprox; α = α-CO

3.5.1 Relative standard deviation

see 3.5 ; SD = standard deviation

X

3.6 Limit of determination

Drinking water: 0.05 µg/L
Ground water: 0.05 µg/L
Surface water: 0.01 µg/L

3.7 Precision

3.7.1 Repeatability

see 3.5

3.7.2 Independent laboratory validation

not performed for water, but confirmatory method included in the report

Section A4 (4.2)
Annex Point IIA-IV.4.2

Analytical Methods for Detection and Identification
(c) Water

4 APPLICANT'S SUMMARY AND CONCLUSION

4.1	**Materials and methods**	Water samples were extracted with hexane. To determine the residues of etofenprox the crude extract was cleaned up by alumina column and Florisil column chromatography. To determine the residues of α-CO the crude extract was cleaned up by silica gel and florisil column chromatography. The concentration of etofenprox and α-CO in the extract was determined by GC/MS. For a summary of the analytical methods and results in tabular form see also Document II-A (effects assessment), Table 1.4.
4.2	**Conclusion**	The analytical method was valid for analysis of etofenprox and its metabolite α-CO in ground and drinking water in a concentration range of 0.05 to 0.5 µg/L and for surface water 0.01 to 0.1 µg/L.
4.2.1	Reliability	1
4.2.2	Deficiencies	No

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*27.08.2005*
Materials and methods	*3.5.1 Relative standard deviation* Standard deviations (SD) are reported instead of relative standard deviations (RSD). Please refer to the Dossier Document II-A for corresponding relative standard deviations. *3.6 Limit of determination* Wolf S. (2003c) specifies the limit of detection at about 0.002 µg/kg.
Conclusion	Agree with the applicant´s version
Reliability	1
Acceptability	Acceptable
Remarks	-
	COMMENTS FROM...
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

Section A4 (4.2)
Annex Point IIA-IV.4.2

Analytical Methods for Detection and Identification
(d) Animal body fluids and tissues

Official use only

1 REFERENCE

1.1	**Reference**	Wolf S. (2003e): Validation of the residue analytical method for MTI-500 and α-CO in meat (ruminant and chicken), milk, fat (ruminant) and egg; RCC Ltd, Environmental Chemistry & Pharmanalytics Division, Itingen, Switzerland; unpublished report no. 791254 (October 30, 2003) Dates of work: June 16, 2003 – September 11, 2003
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted]. Mitsui Chemicals Agro, Inc.
1.2.2	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing [a.s. / b.p.] for the purpose of its [entry into Annex I/IA / authorisation]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes Residue Analytical Method, Guideline 96/46/EC, July 16, 1996 SANCO/825/00 rev. 6, June 20, 2000 SANCO/3029/99 rev. 4, July 11, 2000 – working document Nachrichtenbl. Deut. Pflanzenschutzd., 52, 2000, 292 EPA OPPTS 860.1340
2.2	**GLP**	Yes
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Preliminary treatment**	Non-entry field
3.1.1	Enrichment	• Extraction, hexane – water partition: - 10 g meat (ruminant or chicken), fat(ruminant), egg (white or yolk) or 10 ml milk samples were extracted with acetone. After filtration and evaporation of the solvent, 5% sodium chloride solution was added (250 ml) and etofenprox and α-CO was partitioned twice from the aqueous solution into hexane (100 ml; 50 ml). The hexane phase was filtered through sodium sulphate and the organic solvent evaporated.
3.1.2	Cleanup	• Hexane-acetonitrile partition: - sample was dissolved in acetonitrile saturated hexane (50 ml) and hexane-saturated acetonitrile (40 ml). - mixture was shaken for 2min, and phases were separated by use of a separating funnel. - hexane phase was re-extracted with hexane-saturated acetonitrile. - from the combined acetonitrile phase the solvent was evaporated, and the residue dissolved in hexane. • Clean-up with silica gel column: - a silica gel column was prepared using silica gel 60 (0.063-0.20 mm; Merck 1.07734), and the extract was added to the column. The column was washed with hexane and the analytes eluted from the column with hexane/ethyl ether mixture (100+3, v/v).

Section A4 (4.2) **Analytical Methods for Detection and Identification**
Annex Point IIA-IV.4.2 **(d) Animal body fluids and tissues**

		• Clean-up with florisil column: - a column was prepared using florisil (0.15-0.25 mm, Merck 1.12994), and the extract was added to the column. The column was washed with hexane and the analytes eluted with hexane/ethyl ether mixture (90+10, v/v). The solvent was evaporated and the residue reconstituted in dodecane.
3.2	**Detection**	
3.2.1	Separation method	Gas chromatograph: Hewlett Packard 6890 (Agilent) Column: HP-5-MS, 30 m x 0.25 mm (0.25 µm) Pre-column:2 m x 0.32 mm deactivated fused silica Carrier gas: Helium, flow: 1.8 ml/min, constant flow Temperatures: Injector: 270°C Oven: 200°C initial time: 2 min rate: 10°C/min to 280°C for 7 min rate: 50°C/min to 320°C for 15 min Injection: 3 µl splitless
3.2.2	Detector	Detector: MS 5973; ChemStation Ver. B.01.00, Hewlett Packard, USA Ionization mode: EI, positive Scan mode: SIM m/z: 163 (for peak quantification) SIM m/z: 376 (for etofenprox peak identification) SIM m/z: 390 (for α-CO peak identification) Scan time: 2.86 s MS conditions: Electron energy: 70 eV; Ion source temperature: 230°C Transfer line temperature: 300°C; quadrupole temperature: 150°C Retention times: etofenprox: about 10 min; α-CO: about 11 min
3.2.3	Standard(s)	MTI-500 (=etofenprox): external standard α-CO: external standard
3.2.4	Interfering substance(s)	none
3.3	**Linearity**	
3.3.1	Calibration range	0.05 to 1.0 µg/ml
3.3.2	Number of measurements	10
3.3.3	Linearity	r^2 = 0.995 to 1.000
3.4	**Specifity: interfering substances**	There was no interference with other substances observed at the retention times of etofenprox and α-CO above 30% of the limit of quantification as well as above the limit of detection

Section A4 (4.2)
Annex Point IIA-IV.4.2

Analytical Methods for Detection and Identification
(d) Animal body fluids and tissues

3.5 Recovery rates at different levels

Matrix	Fort. level [mg/kg]	Recovery rate [%]		SD [%]	Repl.
		mean	range		
Meat (ruminant)	0.01 E	101.9	98.2 – 103.8	2.2	5
"	0.5 E	95.8	93.4 – 101.2	3.1	5
"	5.0 E	97.3	96.8 – 97.8	0.4	5
"	0.01 α	104.0	93.7 – 109.1	6.5	5
"	0.1 α	101.5	96.4 – 109.5	5.0	5
"	1.0 α	105.7	104.6–107.0	0.9	5
Meat (chicken)	0.01 E	103.0	98.1 – 108.9	4.2	5
"	0.5 E	97.5	92.0 – 105.3	5.7	5
"	5.0 E	100.2	95.9 – 107.0	4.4	5
"	0.01 α	104.4	102.3-105.8	1.4	5
"	0.1 α	89.6	82.7 – 101.8	8.0	5
"	1.0 α	99.1	90.5 – 103.2	5.1	5
Egg (yolk)	0.01 E	93.3	85.0 – 101.5	6.7	5
"	0.5 E	78.5	71.2 – 99.4	11.8	5
"	5.0 E	90.6	73.3 – 104.7	15.9	5
"	0.01α	104.4	99.9 – 106.9	2.7	5
"	0.1 α	83.3	74.5 – 107.3	13.5	5
"	1.0 α	74.5	71.8 – 76.8	1.9	5
Egg (white)	0.01 E	102.9	100.3–104.7	1.7	5
"	0.5 E	77.8	74.5 – 80.3	2.1	5
"	5.0 E	79.1	75.9 – 81.6	2.6	5
"	0.01 α	102.5	101.0-105.2	1.6	5
"	0.1 α	78.4	74.2 – 80.2	2.4	5
"	1.0 α	78.8	75.4 – 82.4	2.7	5
Milk *	0.01 E	78.9	72.8 – 84.3	5.2	5
"	0.5 E	94.0	91.6 – 95.1	1.4	5
"	5.0 E	92.8	91.5 – 93.8	1.0	5
"	0.01 α	75.2	70.5 – 82.0	5.4	5
"	0.1 a	106.3	101.3-108.6	3.3	5
"	1.0 α	97.6	95.9 – 98.6	1.1	5
Fat (ruminant)	0.01 E	102.2	97.5 – 106.2	4.2	5
"	0.5 E	96.6	95.2 – 97.3	1.8	5
"	5.0 E	89.6	86.9 – 95.4	3.5	5
"	0.01 α	99.8	99.4 – 100.2	0.4	5
"	0.1 α	91.2	90.9 – 91.4	0.2	5
"	1.0 α	90.5	87.7 – 98.8	4.7	5

E = etofenprox; α = α-CO

3.5.1 Relative standard deviation

see 3.5 ; SD = standard deviation

X

Section A4 (4.2)
Annex Point IIA-IV.4.2

Analytical Methods for Detection and Identification
(d) Animal body fluids and tissues

3.6 Limit of determination

0.01 mg/kg

3.7 Precision

Non-entry field

3.7.1 Repeatability

see 3.5

3.7.2 Independent laboratory validation

Class T (2003b)

Matrix	Fort. level [mg/kg]	Recovery rate [%]	Range	RSD %	Rep.
Milk	0.01 E	94	91-103	5	5
"	0.10 E	91	79-100	11	5
"	0.01 α	91	83-103	10	5
"	0.10 α	87	75-99	12	5
Meat	0.01E	90	69-106	19	5
"	0.10 E	84	74-97	10	5
"	0.01 α	76	65-87	11	5
"	0.10 α	88	85-99	7	5
Egg	0.01 E	78	65-95	14	5
"	0.10 E	80	77-82	2	5
"	0.01 α	95	88-104	6	5
"	0.10 α	93	85-97	5	5
Fat	0.01 E	73	70-76	3	5
"	0.10 E	79	66-105	19	5
"	0.01 α	85	72-98	11	5
"	0.10 α	83	73-100	13	5

E = etofenprox; α = α-CO

4 APPLICANT'S SUMMARY AND CONCLUSION

4.1 Materials and methods

Ground meat and mixed egg samples were extracted with acetone and methanol, respectively. After filtration and evaporation of the solvent, etofenprox and α-CO was partitioned from the remaining aqueous solution into hexane. From milk samples, etofenprox and α-CO was partitioned into hexane:ethyl ether. With all crude extracts acetonitrile-hexane partitioning was carried out in order to remove the fat. To determine the residues of etofenprox the crude extract was cleaned up by Alumina column chromatography. To determine the residues of α-CO the crude extract was cleaned up by silica gel and florisil column chromatography. The concentration of etofenprox and α-CO in the extract was determined by GC/MS.

For a summary of the analytical methods and results in tabular form see also Document II-A (effects assessment), Table 1.4.

4.2 Conclusion

The analytical method was valid for analysis of etofenprox and its metabolite α-CO in animal matrices in a concentration range of 0.01 to 1.0 mg/kg.

The validity of the method was confirmed by an independent laboratory.

4.2.1 Reliability

1

4.2.2 Deficiencies

No

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*27.08.2005*
Materials and methods	*3.3.1 Calibration range* The calibration was performed using standards in the range of 1.01 – 1.2 µg/ l for both, MTI-500 and α-CO *3.5.1 Relative standard deviation* Standard deviations (SD) are reported instead of relative standard deviations (RSD). Please refer to the Dossier Document II-A for corresponding relative standard deviations.
Conclusion	*Agree with the applicant´s version*
Reliability	*1*
Acceptability	*Acceptable*
Remarks	
	COMMENTS FROM...
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

Section A4 (4.3)
Annex Point IIIA-IV.1

Analytical Methods for Detection and Identification
Food / feedstuffs

Official use only

1 REFERENCE

1.1	**Reference**	Wolf S. (2001): Validation of the residue analytical method for MTI-500 and α-CO in oil seed rape; RCC Ltd, Environmental Chemistry & Pharmanalytics Division, Itingen, Switzerland; unpublished report no. 789390 (May 14, 2001) Dates of work: January 04, 2001 – April 07, 2001
1.2	**Data protection**	Yes
1.2.1	Data owner	[redacted] Mitsui Chemicals Agro, Inc.
1.2.2	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing [a.s. / b.p.] for the purpose of its [entry into Annex I/IA / authorisation]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes Residue Analytical Method, Guideline 96/46/EC, July 16, 1996 SANCO/825/00 rev. 6, June 20, 2000 SANCO/3029/99 rev. 4, July 11, 2000 – working document EPA OPPTS 860.1340
2.2	**GLP**	Yes
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Preliminary treatment**	
3.1.1	Enrichment	Samples were extracted with acetone. Extracts were filtered through Celite by suction and acetone was evaporated. The residue from the extraction was dissolved in hexane and extracted with water. The water was re-extracted with hexane. The organic phase was evaporated and the residue reconstituted in hexane. The hexane solution was extracted with water and acetonitrile. Acetonitrile extracts were then diluted with water and etofenprox and α-CO were partitioned into hexane. To determine the residues of etofenprox the crude extract was cleaned up by Alumina column chromatography (extract from cucumber was additionally cleaned up by florisil column chromatography). To determine the residues of α-CO the crude extract was cleaned up by silica gel and florisil column chromatography.
3.1.2	Cleanup	Included in 3.1.2
3.2	**Detection**	
3.2.1	Separation method	Gas chromatograph: Hewlett Packard 6890 Auto sampler : Hewlett Packard 7683 Column: HP-5-MS, 30 m x 0.25 mm (0.25 µm) Carrier gas: Helium, flow: 1.8 ml/min (15 psi) constant pressure (50°C)

Section A4 (4.3)
Annex Point IIIA-IV.1

Analytical Methods for Detection and Identification
Food / feedstuffs

		Temperatures: Injector: 270°C Oven: 50°C initial time: 0 min rate: 50°C/min to 200°C for 2 min rate: 10°C/min to 280°C for 7 min rate: 50°C/min to 320°C for 0min (OSR) Injection: 1 µl splitless
3.2.2	Detector	Detector: MS 5973; ChemStation Ver. B.01.00, Hewlett Packard, USA Ionization mode: EI, positive Scan mode: SIM m/z: 163 (for peak quantification) SIM m/z: 376 (for etofenprox peak identification) SIM m/z: 390 (for α-CO peak identification) Scan time: 2.86 s MS conditions: Electron energy: 70 eV; Ion source temperature: 230°C Transfer line temperature: 300°C; quadrupole temperature: 150°C Retention times: etofenprox: about 15.0-17.0 min; α-CO: about 16.4-19.0 min
3.2.3	Standard(s)	MTI-500 (=etofenprox): external standard α-CO: external standard
3.2.4	Interfering substance(s)	none
3.3	**Linearity**	
3.3.1	Calibration range	0.05 to 2.0 µg/ml
3.3.2	Number of measurements	2
3.3.3	Linearity	$r^2 = 0.999$ for both measurements
3.4	**Specifity: interfering substances**	The method allows the determination of etofenprox and α-CO in cabbage, oil seed rape, cucumber, grapes, peaches and apples. There was no interference with other substances observed at the retention times of etofenprox and α-CO above 30% of the limit of quantification as well as above the limit of detection

3.5 Recovery rates at different levels

Fortification level [mg/kg]	Recovery rate [%] mean	Recovery rate [%] range	RSD [%]	Replicates
etofenprox 0.01	93.3	81.5 - 110.5	12.8	5
etofenprox 0.10	94.9	90.6 - 100.5	4.7	5
etofenprox 2.00	77.5	72.0 - 84.0	6.8	5
α-CO 0.01	103.9	99.4 - 107.8	3.1	5
α-CO 0.10	91.6	79.8 - 99.3	7.9	5

3.5.1	Relative standard deviation	see 3.5
3.6	**Limit of determination**	0.01 mg/kg
3.7	**Precision**	

Section A4 (4.3)
Annex Point IIIA-IV.1

Analytical Methods for Detection and Identification
Food / feedstuffs

3.7.1 Repeatability — see 3.5

3.7.2 Independent laboratory validation
Class T (2003a)

Fortification level [mg/kg]	Recovery rate [%] mean	Recovery rate [%] range	RSD [%]	Repli-cates
etofenprox 0.01	81	76 - 89	6	5
etofenprox 0.10	81	68 – 93	13	5
α-CO 0.01	89	85 – 96	6	5
α-CO 0.10	88	74 – 101	13	5

4 APPLICANT'S SUMMARY AND CONCLUSION

4.1 Materials and methods

Samples were extracted with acetone. Extracts were filtered through Celite by suction and acetone was evaporated. The residue from the extraction was dissolved in hexane and extracted with water. The water was re-extracted with hexane. The organic phase was evaporated and the residue reconstituted in hexane. The hexane solution was extracted with water and acetonitrile. Acetonitrile extracts were then diluted with water and etofenprox and α-CO were partitioned into hexane. (For cabbage, peaches and apples the extraction with acetonitrile was omitted)

To determine the residues of etofenprox the crude extract was cleaned up by Alumina column chromatography (extract from cucumber was additionally cleaned up by florisil column chromatography). To determine the residues of α-CO the crude extract was cleaned up by silica gel and florisil column chromatography. The concentrations of etofenprox and α-CO in the extract were determined by GC/MS.

For a summary of the analytical methods and results in tabular form see also Document II-A (effects assessment), Table 1.4.

4.2 Conclusion

The analytica lmethod was valid for analysis of etofenproxand its metabolite α-CO in crop matrices in a concentration range of 0.01 to 2.0 mg/kg.

The validityof the method was confirmed by an independent laboratory.

4.2.1 Reliability — 1

4.2.2 Deficiencies — No

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*27.08.2005*
Materials and methods	Agree with the applicant´s version
Conclusion	Agree with the applicant´s version
Reliability	1
Acceptability	Acceptable
Remarks	-
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

Section A5 Effectiveness against target organisms and intended uses

Subsection (Annex Point)			Official use only
5.1	**Function (IIA-V.5.1)**	Insecticide	
5.2	**Organism(s) to be controlled and products, organisms or objects to be protected (IIA-V.5.2)**	in relation to use in a wood preservative biocidal product:	
5.2.1	**Organism(s) to be controlled (IIA-V.5.2)**	Efficacy against all major wood destroying insects, e.g. larvae of house longhorn beetle (*Hylotrupes bajulus*) and subterranean termites such as *Reticulitermes santonensis*. Organisms to be controlled exist in all parts of the Community with the exeption of termites in wide areas of middle and northern Europe.	
5.2.2	**Products, organisms or objects to be protected (IIA-V.5.2)**	All kinds of wood, partical board and ply wood	
5.3	**Effects on target organisms, and likely concentration at which the active substance will be used (IIA-V.5.3)**		
5.3.1	**Effects on target organisms (IIA-V.5.3)**	Etofenprox is the active ingredient providing the insecticidal activity of the wood preservative [redacted]01990-I, with contact and stomach action. For results of efficacy tests with the active ingredient etofenprox refer to the summary table on the last page of this section.	
5.3.2	**Likely concentrations at which the A.S. will be used (IIA5.3)**	0.1 % up to 0.2 % of etofenprox in those areas of the wood that have to be protected against insecticidal attack.	
	Dip treatment, use classes 1 and 2	0.3 g a.i./m^2 wood	
	Dip treatment, use class 3	0.4 g a.i./m^2 wood	
	Pressure process, use class 3	2.5 g a.i./m^3 wood	
5.4	**Mode of action (including time delay) (IIA-V.5.4)**		

Section A5 Effectiveness against target organisms and intended uses

Subsection (Annex Point)			Official use only
5.4.1	**Mode of action**	Contact and stomach action: Etofenprox seems to act on the insect nerve system by disturbing the normal neurotransmittance. Voltage clamp experiments with a crayfish giant axon showed that etofenprox decreased the peak sodium current and induced a large residual current during a step depolarization. It also induced a large and prolonged tail current after a step repolarization of the membrane (K. Nishimura et al., 1985, Pesticide Biochemistry and Physiology 25, 387-395 – see copy of the publication in the Document IVA.5.4). It appears that etofenprox interferes with sodium channels on insect nerve axons.	
5.4.2	**Time delay**	Rapid knockdown and death within several hours after the contact or intake	
5.5	**Field of use envisaged (IIA-V.5.5)**		
	MG02: Preservatives	Product type PT08: wood preservative, indoor and outdoor use (use classes 1 – 3).	
5.6	**User (IIA-V.5.6)**		
	Industrial and professional		
	Industrial	Wood protection by pre-treatment in industrial premises, e.g. vacuum pressure treatment and dipping treatment.	
	Professional	Professional use not envisaged.	
	General public	Use by the general public not envisaged.	
5.7	**Information on the occurrence or possible occurrence of the development of resistance and appropriate management strategies (IIA-V.5.7)**		
5.7.1	**Development of resistance**	No significant resistance against etofenprox has been found so far. Because of the wide alternation of generations (e.g. house longhorn beetle) no formation of resistance has to be expected.	
5.7.2	**Management strategies**	Application of wood preservatives generally takes place above the lethal level, therefore no formation of resistance within the alternation of generations is possible.	

Section A5 Effectiveness against target organisms and intended uses

Subsection (Annex Point)			Official use only
5.8	**Likely tonnage to be placed on the market per year (IIA-V.5.8)**	Estimated overall total market volume for Etofenprox in wood preservatives within EU: about [redacted] including imported quantities. Other biocidal uses are estimated to be at about [redacted] Market volume for Etofenprox as active substance of plant protection products is estimated to become [redacted] after Annex I listing according to 91/414/EC in Germany (estimation for Germany).	

Section A5.3: Summary table of experimental data on the effectiveness of the active substance against target organisms at different fields of use envisaged, where applicable.

Function	**Field of use envisaged**	**Test substance**	**Test organism(s)**	**Test method**	**Test conditions**	**Test results: effects, mode of action, resistance**	**Reference*)**
Insecticide	08	etofenprox	Termites (*Reticulitermes santonensis*)	EN 117 (08/90) Determination of toxic values – without accelerated ageing procedure	Impregnation of pine wood by pressure treatment. Preservative retention: 5.1 – 51.7 g / m^3	Toxic value between 15.8 and 30.7 g etofenprox/m^3 wood resp. 0.003% and 0.006%	Schumacher,P., Fennert, E.-M. (2003a) 3.2/03/8417/01
Insecticide	08	etofenprox	Termites (*Reticulitermes santonensis*)	EN 117 (08/90) after EN 84 (05/97) Determination of toxic values after leaching procedure (14 days)	Impregnation of pine wood by pressure treatment. Preservative retention: 10.4 – 105 g / m^3	Toxic value between 83.8 and 105 g etofenprox/m^3 wood resp. 0.016% and 0.02%	Schumacher,P., Fennert, E.-M. (2003b) 3.2/03/8417/02
Insecticide	08	etofenprox	Larvae of House longhorn beetle (*Hylotrupes bajulus*)	EN 47 (08/90) Determination of toxic values – without accelerated ageing procedure	Impregnation of pine wood by pressure treatment. Preservative retention: 10.5 – 63.6 g / m^3	Toxic value between 10.5 and 21.1 g etofenprox/m^3 wood resp. 0.002% and 0.004%	Schumacher,P., Fennert, E.-M. (2003c) 3.2/03/8417/03
Insecticide	08	etofenprox	Larvae of House longhorn beetle (*Hylotrupes bajulus*)	EN 47 (08/90) after EN 84 (05/97) Determination of toxic values after leaching procedure (14 days)	Impregnation of pine wood by pressure treatment. Preservative retention: 10.5 – 84.3 g / m^3	Toxic value between 42.2 and 50.9 g etofenprox/m^3 wood resp. 0.008% and 0.012%	Schumacher,P., Fennert, E.-M. (2003d) 3.2/03/8417/04

)* References: see next page

Report No.	Reference
3.2/03/8417/01	Schumacher P., Fennert E.-M. (2003a) Determination of toxic values against *Reticulitermes santonensis* De Feytaud according to EN 117 (08/90) without accelerated ageing procedure – test material [redacted]01190-I; Material Testing Institute Brandenburg, Department 3 wood and wood protection, Germany; unpublished report, May 27, 2003
3.2/03/8417/02	Schumacher P., Fennert E.-M. (2003b) 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 [redacted]01190-I; Material Testing Institute Brandenburg, Department 3 wood and wood protection, Germany; unpublished report, July 07, 2003
3.2/03/8417/03	Schumacher P., Fennert E.-M. (2003c) Determination of toxic values against larvae of *Hylotrupes bajulus* (L) according to EN 47 (08/90) without accelerated ageing procedure – test material [redacted]01190-I; Material Testing Institute Brandenburg, Department 3 wood and wood protection, Germany; unpublished report, July 08, 2003
3.2/03/8417/04	Schumacher P., Fennert E.-M. (2003d) Determination of toxic values against larvae of *Hylotrupes bajulus* (L) according to EN 47 (08/90) after leaching procedure to EN 84 – test material [redacted]01190-I; Material Testing Institute Brandenburg, Department 3 wood and wood protection, Germany; unpublished report, August 21, 2003

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*2005-08-02*
Materials and methods	*Agree with the applicant's version*
Conclusion	*Agree with the applicant's version*
Reliability	*1*
Acceptability	*acceptable*
Remarks	
	COMMENTS FROM ...
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

Section A5.2/01 Efficacy Data

Annex Point IIA-V.5.2 **Termites (*Reticulitermes santonensis* De Feytaud)**

			Official use only
		1 REFERENCE	
1.1	**Reference**	Schumacher P., Fennert E.-M. (2003a) Determination of toxic values against *Reticulitermes santonensis* De Feytaud according to EN 117 (08/90) – without accelerated ageing procedure; Material Testing Institute Brandenburg, Department 3 wood and wood protection, Germany; unpublished report no. 3.2/03/8417/01 (May 27, 2003) Dates of experimental work: February 2003 – May 2003	
1.2	**Data protection**	Yes	
1.2.1	Data owner	[redacted]	
1.2.2	Criteria for data protection	Data submitted to the MS after May 13, 2000 on existing a.s. for the purpose of its entry into Annex I.	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	EN 117 (August 1990)	
2.2	**GLP**	No	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Etofenprox ([redacted]01190-I)	
3.1.1	Lot/Batch number	No information in the report.	
3.1.2	Specification	As given in section 2	
3.1.3	Description	No information in the report.	
3.1.4	Purity	No information in the report.	
3.1.5	Stability	No information in the report.	
3.1.6	Further relevant properties	Solubility in water: 22.5 µg/L at 20 ± 0.5°C Vapour pressure: 8.13 x 10^{-7} Pa at 25°C Stability in water: hydrolytically stable at pH 4, 7 and 9	
3.1.7	Method of analysis	No analyses were performed	
3.2	**Preparation of TS solution for poorly soluble or volatile test substances**	Ethanol was used as solvent/vehicle	
3.3	**Reference substance**	No	
3.3.1	Method of analysis for reference substance	Not applicable	
3.4	**Testing procedure**		
3.4.1	Test organism	Termites (*Reticulitermes santonensis* De Feytaud), laboratory culture	
3.4.2	Test system	Impregnated wood blocks were exposed to test organisms; wood species: pine (*Pinus sylvestris* L.)	

Section A5.2/01 **Efficacy Data**
Annex Point IIA-V.5.2 **Termites (*Reticulitermes santonensis* De Feytaud)**

3.4.3	Application of TS	Vacuum pressure treatment (wood impregnation); date of treatment: February 12, 2003
3.4.4	Concentrations tested	0, 0.001, 0.003, 0.006, 0.008, 0.01% (w/w) calculated average retention of test substance: 0, 5.1, 15.8, 30.7, 41.6, 51.7 g/m^3
3.4.5	Test conditions	Duration of conditioning period after impregnation: 28 days Ageing test was not carried out.
3.4.6	Duration of the test / Exposure time	Installation of test blocks: March 20, 2003 Removal of test blocks: May 15, 2003 Exposure of the wood to the test organisms: 8 weeks
3.4.7	Number of replicates performed	3 replicates (test wood blocks) per treatment
3.4.8	Controls	Yes: (a) untreated blocks, (b) blocks treated with ethanol without test substance
3.5	**Examination**	
3.5.1	Effect investigated	Mortality, damage on test blocks
3.5.2	Method for recording / scoring of the effect	Counting, visual evaluation of test blocks
3.5.3	Intervals of examination	Once at the end of exposure, when test blocks were removed
3.5.4	Statistics	No statistics applied
3.5.5	Post monitoring of the test organism	No

4 RESULTS

4.1	**Efficacy**	
4.1.1	Dose/Efficacy curve	Not applicable
4.1.2	Begin and duration of effects	Not applicable
4.1.3	Observed effects in the post monitoring phase	Not applicable
4.2	**Effects against organisms or objects to be protected**	Mortality of termites, reduced damage of test blocks
4.3	**Other effects**	none
4.4	**Efficacy of the reference substance**	Toxic value: 15.8 – 30.7 g/m^3 (corresponding to 0.003 – 0.006% w/w)
4.5	**Tabular and/or graphical presentation of the summarised results**	see Table A5_2_01-1

Section A5.2/01 **Efficacy Data**
Annex Point IIA-V.5.2 **Termites (*Reticulitermes santonensis* De Feytaud)**

4.6	**Efficacy limiting factors**	
4.6.1	Occurrences of resistances	Not observed
4.6.2	Other limiting factors	None reported

5 RELEVANCE OF THE RESULTS COMPARED TO FIELD CONDITIONS

5.1	**Reasons for laboratory testing**	The laboratory efficacy test was performed according to the guideline EN 117 (1990) and EN 84 (1997)
5.2	**Intended actual scale of biocide application**	Not applicable, test was performed with the active ingredient etofenprox
5.3	**Relevance compared to field conditions**	
5.3.1	Application method	The application method in the laboratory test is comparable with the planned industrial application method. However, the test was performed with the active ingredient etofenprox
5.3.2	Test organism	Test organism is identical with the target organism of the intended use for the biocidal product
5.3.3	Observed effect	The observed effect in the laboratory test shows the efficacy of etofenprox as active ingredient in the wood preservative [redacted]01990-I for protection against wood destroying termites.
5.4	**Relevance for read-across**	Relevance for read across is limited because the test was performed with the active ingredient etofenprox. However, the test proves the efficacy of the insecticidal active ingredient in the wood preservative [redacted] 01990-I when applied under realistic conditions (vacuum pressure impregnation)

6 APPLICANT'S SUMMARY AND CONCLUSION

6.1	**Materials and methods**	Pine (*Pinus sylvestris*) wood blocks were treated (vacuum pressure impregnation) with etofenprox, ethanol was used as solvent/vehicle. After a conditioning period of 28 days, treated and control (ethanol treatment, untreated) wood blocks were exposed for 8 weeks to termites (*Reticulitermes santonensis*). Efficacy was investigated by assessment of the mortality of the test organisms and by visual evaluation of the test blocks.
6.2	**Reliability**	The test results are reliable and relevant for an efficacy assessment of the active ingredient etofenprox.

Section A5.2/01 Efficacy Data

Annex Point IIA-V.5.2 **Termites (*Reticulitermes santonensis* De Feytaud)**

6.3	**Assessment of efficacy, data analysis and interpretation**	Threshold of toxicity: 15.8 – 30.7 g/m^3 (0.003 – 0.006% respectively, based on mass percentage; w/w) Threshold of toxicity of a wood preservative is expressed according to EN 117 as: - the lowest concentration which protects the wood, i.e. the concentration at which none of the test specimens shows a degree of termite attack above level 1 (only traces of gnawing allowed), - the next lower concentration in series at which the wood is no longer sufficiently protected, i.e. the concentration at which at least one test specimen shows an attack of level 2 (slight attack) or more severe.
6.4	**Conclusion**	Laboratory test can be considered as valid to assess the efficacy of etofenprox as insecticide for wood preservation. Test was conducted according to guideline EN 117 (no deviations). A good effectiveness against temites (*Reticulitermes santonensis*) was attested for [redacted]01190-I (etofenprox).
6.5	**Proposed efficacy specification**	See point 6.3

Table A5_2_01-1: Retention of test substance per test block, number of surviving termites and visual examination of test blocks after 8 weeks exposure period.

Concentration of test substance (% w/w)	**Replicate**	**Solution retention per test block** (g/block)	**Retention of test substance per test block** (g/m^3)	**Amount of surviving termites**		**Visual evaluation of test blocks ***
				Workers (%)	**Soldiers (S), Nymphs (N)** (number of S/N)	
0 (ethanol control)	1	9.471	0	65	1/3	4
	2	9.630	0	16	0/0	1
	3	9.814	0	64	0/2	4
	average		0			
0.001	1	9.707	5.06	67	1/2	4
	2	9.777	5.11	0	0/0	2
	3	9.730	5.07	61	2/2	4
	average		5.08			
0.003	1	9.907	15.50	48	2/2	4
	2	10.406	16.28	20	3/2	4
	3	10.027	15.63	39	1/2	4
	average		15.80			
0.006	1	9.724	30.40	0	0/0	1
	2	9.873	30.66	0	0/0	1
	3	9.902	30.99	0	0/0	1
	average		30.68			
0.008	1	9.948	41.95	0	0/0	1
	2	9.892	41.28	0	0/0	1
	3	9.973	41.60	0	0/0	1
	average		41.61			
0.01	1	9.933	51.28	0	0/0	1
	2	9.967	52.02	0	0/0	1
	3	9.889	51.37	0	0/0	1
	average		51.74			
0 (untreated control)	1	–	–	70	1/2	4
	2	–	–	66	2/2	4
	3	–	–	78	2/2	4
	average					

*) 0 = no attack
1 = traces of gnawing
2 = slight attack
3 = medium attack
4 = heavy attack

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*2005-08-02*
Materials and methods	*Agree with the applicant's version*
Conclusion	*Agree with the applicant's version*
Reliability	*1*
Acceptability	*acceptable*
Remarks	
	COMMENTS FROM...
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

Section A5.2/02 Efficacy Data

Annex Point IIA-V.5.2 **Termites (*Reticulitermes santonensis* De Feytaud)**

			Official use only
		1 REFERENCE	
1.1	**Reference**	Schumacher P., Fennert E.-M. (2003b) Determination of toxic values against *Reticulitermes santonensis* De Feytaud according to EN 117 (08/90) – after leaching procedure according to EN 84 (05/97); Material Testing Institute Brandenburg, Department 3 wood and wood protection, Germany; unpublished report no. 3.2/03/8417/02 (July 07, 2003) Dates of experimental work: Februar 2003 – May 2003	
1.2	**Data protection**	Yes	
1.2.1	Data owner	[redacted]	
1.2.2	Criteria for data protection	Data submitted to the MS after May 13, 2000 on existing a.s. for the purpose of its entry into Annex I.	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	EN 117 (August 1990) EN 84 (May 1997)	
2.2	**GLP**	No	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Etofenprox ([redacted]01190-I)	
3.1.1	Lot/Batch number	No information in the report.	
3.1.2	Specification	As given in section 2	
3.1.3	Description	No information in the report.	
3.1.4	Purity	No information in the report.	
3.1.5	Stability	No information in the report.	
3.1.6	Further relevant properties	Solubility in water: 22.5 µg/L at 20 ± 0.5°C Vapour pressure: 8.13×10^{-7} Pa at 25°C Stability in water: hydrolytically stable at pH 4, 7 and 9	
3.1.7	Method of analysis	No analyses were performed	
3.2	**Preparation of TS solution for poorly soluble or volatile test substances**	Ethanol was used as solvent/vehicle	
3.3	**Reference substance**	No	
3.3.1	Method of analysis for reference substance	Not applicable	
3.4	**Testing procedure**		
3.4.1	Test organism	Termites (*Reticulitermes santonensis* De Feytaud), laboratory culture	

Section A5.2/02 **Efficacy Data**
Annex Point IIA-V.5.2 **Termites (*Reticulitermes santonensis* De Feytaud)**

3.4.2	Test system	Impregnated wood blocks were exposed to test organisms; wood species: pine (*Pinus sylvestris* L.)
3.4.3	Application of TS	Vacuum pressure treatment (wood impregnation); date of treatment: February 18, 2003
3.4.4	Concentrations tested	0, 0.002, 0.006, 0.01, 0.016, 0.02% (w/w) retention of test substance: 0, 10.4, 31.1, 51.1, 83.8, 105.0 g/m^3
3.4.5	Test conditions	Duration of conditioning period after impregnation: 28 days Ageing test was carried out, according to EN 84; period of leaching: March 24, 2003 – April 07, 2003
3.4.6	Duration of the test / Exposure time	Installation of test blocks: April 25, 2003 Removal of test blocks: June 20, 2003 Exposure of the wood to the test organisms: 8 weeks
3.4.7	Number of replicates performed	3 replicates (test wood blocks) per treatment
3.4.8	Controls	Yes: (a) untreated blocks, (b) blocks treated with ethanol without test substance
3.5	**Examination**	
3.5.1	Effect investigated	Mortality, damage on woody test blocks
3.5.2	Method for recording / scoring of the effect	Counting, visual evaluation of test blocks
3.5.3	Intervals of examination	Once at the end of exposure, when test blocks were removed
3.5.4	Statistics	No statistics applied
3.5.5	Post monitoring of the test organism	No
		4 RESULTS
4.1	**Efficacy**	
4.1.1	Dose/Efficacy curve	Not applicable
4.1.2	Begin and duration of effects	Not applicable
4.1.3	Observed effects in the post monitoring phase	Not applicable
4.2	**Effects against organisms or objects to be protected**	Mortality of termites, reduced damage of test blocks
4.3	**Other effects**	none
4.4	**Efficacy of the reference substance**	Toxic value: 83.8 – 105.0 g/m^3 (corresponding to 0.016 – 0.02% w/w)

Section A5.2/02 **Efficacy Data**
Annex Point IIA-V.5.2 **Termites (*Reticulitermes santonensis* De Feytaud)**

4.5	**Tabular and/or graphical presentation of the summarised results**	→ see Table A5_2_02-1
4.6	**Efficacy limiting factors**	
4.6.1	Occurrences of resistances	Not observed
4.6.2	Other limiting factors	None reported

5 RELEVANCE OF THE RESULTS COMPARED TO FIELD CONDITIONS

5.1	**Reasons for laboratory testing**	The laboratory efficacy test was performed according to the guideline EN 117 (1990) and EN 84 (1997)
5.2	**Intended actual scale of biocide application**	Not applicable, test was performed with the active ingredient etofenprox
5.3	**Relevance compared to field conditions**	
5.3.1	Application method	The application method in the laboratory test is comparable with the planned industrial application method. However, the test was performed with the active ingredient etofenprox
5.3.2	Test organism	Test organism is identical with the target organism of the intended use for the biocidal product
5.3.3	Observed effect	The observed effect in the laboratory test shows the efficacy of etofenprox as active ingredient in the wood preservative [redacted]01990-I for protection against wood destroying termites.
5.4	**Relevance for read-across**	Relevance for read across is limited because the test was performed with the active ingredient etofenprox. However, the test proves the efficacy of the insecticidal active ingredient in the wood preservative [redacted] 01990-I when applied under realistic conditions (vacuum pressure impregnation)

6 APPLICANT'S SUMMARY AND CONCLUSION

6.1	**Materials and methods**	Pine (*Pinus sylvestris*) wood blocks were treated (vacuum pressure impregnation) with etofenprox, ethanol was used as solvent/carrier. After a conditioning period of 28 days, wood blocks were treated according to EN 84 to simulate ageing by leaching. Treated and control (ethanol treatment, untreated) wood blocks were then exposed for 8 weeks to termites (*Reticulitermes santonensis*). Efficacy was investigated by assessment of the mortality of the test organisms and by visual evaluation of the test blocks.
6.2	**Reliability**	The test results are reliable and relevant for an efficacy assessment of the active ingredient etofenprox.

Section A5.2/02 Efficacy Data

Annex Point IIA-V.5.2 **Termites (*Reticulitermes santonensis* De Feytaud)**

6.3	**Assessment of efficacy, data analysis and interpretation**	Threshold of toxicity after leaching procedure: 83.8 – 105.0 g/m^3 (0.016 – 0.02% respectively, based on mass percentage; w/w) Threshold of toxicity of a wood preservative is expressed according to EN 117 as: - the lowest concentration which protects the wood, i.e. the concentration at which none of the test specimens shows a degree of termite attack above level 1 (only traces of gnawing allowed), - the next lower concentration in series at which the wood is no longer sufficiently protected, i.e. the concentration at which at least one test specimen shows an attack of level 2 (slight attack) or more severe.
6.4	**Conclusion**	Laboratory test can be considered as valid to assess the efficacy of etofenprox as insecticide for wood preservation. Test was conducted according to guidelines EN 117 and EN 84 (no deviations). A good effectiveness against temites (*Reticulitermes santonensis*) was attested for [redacted]01190-I (etofenprox).
6.5	**Proposed efficacy specification**	See point 6.3

Table A5_2_02-1: Retention of test substance per test block, number of surviving termites and visual examination of test blocks after 8 weeks exposure.

Concentration of test substance (% w/w)	**Replicate**	**Solution retention per test block** (g/block)	**Retention of test substance per test block** (g/m^3)	**Amount of surviving termites**		**Visual evaluation of test blocks ***
				Workers (%)	**Soldiers (S), Nymphs (N)** (number of S/N)	
0 (ethanol control)	1	9.976	0	18	0/0	2
	2	9.556	0	67	2/3	4
	3	9.514	0	68	2/3	4
	average		0			
0.002	1	10.018	10.52	41	2/3	4
	2	9.984	10.49	42	2/3	4
	3	9.840	10.30	35	2/3	3
	average		10.4			
0.006	1	10.005	31.43	0	0/0	1
	2	9.800	30.59	3	½	1
	3	10.004	31.30	43	2/3	4
	average		31.1			
0.01	1	9.300	48.69	0	0/0	1
	2	9.995	51.84	2	0/2	2
	3	10.106	52.77	0	0/0	2
	average		51.1			
0.016	1	9.202	77.61	1	0/3	2
	2	10.114	84.72	0	0/1	1
	3	10.636	88.96	1	0/2	0
	average		83.8			
0.02	1	9.963	104.71	0	0/0	0
	2	9.933	104.06	0	0/0	1
	3	10.148	106.37	0	0/0	0
	average		105.0			
0 (untreated control)	1	–	–	68	1/3	4
	2	–	–	70	2/3	4
	3	–	–	69	2/4	4
	average					

*) 0 = no attack
1 = traces of gnawing
2 = slight attack
3 = medium attack
4 = heavy attack

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*2005-08-02*
Materials and methods	*Agree with the applicant's version*
Conclusion	*Agree with the applicant's version*
Reliability	*1*
Acceptability	*acceptable*
Remarks	
	COMMENTS FROM...
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

Section A5.2/03 Efficacy Data

Annex Point IIA-V.5.2 **House longhorn beetle (*Hylotrupes bajulus* L.)**

			Official use only
		1 REFERENCE	
1.1	**Reference**	Schumacher P., Fennert E.-M. (2003c) Determination of the toxic values against larvae of *Hylotrupes bajulus* (L) according to EN 47 (08/90) – without accelerated ageing procedure; Material Testing Institute Brandenburg, Department 3 wood and wood protection, Germany; unpublished report no. 3.2/03/8417/03 (July 08, 2003) Dates of experimental work: March 2003 – June 2003	
1.2	**Data protection**	Yes	
1.2.1	Data owner	[redacted]	
1.2.2	Criteria for data protection	Data submitted to the MS after May 13, 2000 on existing a.s. for the purpose of its entry into Annex I.	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	EN 47 (August 1990)	
2.2	**GLP**	No	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Etofenprox ([redacted]01190-I)	
3.1.1	Lot/Batch number	No information in the report.	
3.1.2	Specification	As given in section 2	
3.1.3	Description	No information in the report.	
3.1.4	Purity	No information in the report.	
3.1.5	Stability	No information in the report.	
3.1.6	Further relevant properties	Solubility in water: 22.5 µg/L at 20 ± 0.5°C Vapour pressure: 8.13 x 10^{-7} Pa at 25°C Stability in water: hydrolytically stable at pH 4, 7 and 9	
3.1.7	Method of analysis	No analyses were performed	
3.2	**Preparation of TS solution for poorly soluble or volatile test substances**	Ethanol was used as solvent/vehicle	
3.3	**Reference substance**	No	
3.3.1	Method of analysis for reference substance	Not applicable	
3.4	**Testing procedure**		
3.4.1	Test organism	Larvae of the house longhorn beetle (*Hylotrupes bajulus* L.), laboratory culture	

Section A5.2/03 **Efficacy Data**
Annex Point IIA-V.5.2 **House longhorn beetle (*Hylotrupes bajulus* L.)**

3.4.2	Test system	Impregnated wood blocks were exposed to test organisms; wood species: pine (*Pinus sylvestris* L.)
3.4.3	Application of TS	Vacuum pressure treatment (wood impregnation); date of treatment: March 06, 2003
3.4.4	Concentrations tested	0, 0.002, 0.004, 0.008, 0.01, 0.012% (w/w) retention of test substance: 0, 10.5, 21.1, 42.1, 53.1, 63.6 g/m^3
3.4.5	Test conditions	Duration of conditioning period after impregnation: 28 days Ageing test was not carried out.
3.4.6	Duration of the test / Exposure time	Installation of test blocks: April 01, 2003 Removal of test blocks: June 24, 2003 Exposure of the wood to the test organisms: 12 weeks
3.4.7	Number of replicates performed	5 replicates (test wood blocks) per test substance concentration
3.4.8	Controls	Yes: (a) untreated blocks, (b) blocks treated with ethanol without test substance
3.5	**Examination**	
3.5.1	Effect investigated	Mortality of the larvae
3.5.2	Method for recording / scoring of the effect	Counting (split up of test blocks)
3.5.3	Intervals of examination	Once at the end of exposure, when test blocks were removed
3.5.4	Statistics	No statistics applied
3.5.5	Post monitoring of the test organism	No
		4 RESULTS
4.1	**Efficacy**	
4.1.1	Dose/Efficacy curve	Not applicable
4.1.2	Begin and duration of effects	Not applicable
4.1.3	Observed effects in the post monitoring phase	Not applicable
4.2	**Effects against organisms or objects to be protected**	Mortality of larvae
4.3	**Other effects**	none
4.4	**Efficacy of the reference substance**	Toxic value: 10.5 – 21.1 g/m^3 (corresponding to 0.002 – 0.004% w/w)

Section A5.2/03 **Efficacy Data**
Annex Point IIA-V.5.2 **House longhorn beetle (*Hylotrupes bajulus* L.)**

4.5	**Tabular and/or graphical presentation of the summarised results**	→ see Table A5_2_03-1
4.6	**Efficacy limiting factors**	
4.6.1	Occurrences of resistances	Not observed
4.6.2	Other limiting factors	None reported

5 RELEVANCE OF THE RESULTS COMPARED TO FIELD CONDITIONS

5.1	**Reasons for laboratory testing**	The laboratory efficacy test was performed according to the guideline EN 47
5.2	**Intended actual scale of biocide application**	Not applicable, test was performed with the active ingredient etofenprox
5.3	**Relevance compared to field conditions**	
5.3.1	Application method	The application method in the laboratory test is comparable with the planned industrial application method. However, the test was performed with the active ingredient etofenprox
5.3.2	Test organism	Test organism is identical with the target organism of the intended use for the biocidal product
5.3.3	Observed effect	The observed effect in the laboratory test shows the efficacy of etofenprox as active ingredient in the wood preservative [redacted]01990-I for protection against wood destroying larvae of the house longhorn beetle.
5.4	**Relevance for read-across**	Relevance for read across is limited because the test was performed with the active ingredient etofenprox. However, the test proves the efficacy of the insecticidal active ingredient in the wood preservative [redacted] 01990-I when applied under realistic conditions (vacuum pressure impregnation)

6 APPLICANT'S SUMMARY AND CONCLUSION

6.1	**Materials and methods**	Pine (*Pinus sylvestris*) wood blocks were treated (vacuum pressure impregnation) with etofenprox, ethanol was used as solvent/vehicle. After a conditioning period of 28 days, treated and control (ethanol treatment, untreated) wood blocks were exposed for 12 weeks to larvae of the house longhorn beetle (*Hylotrupes bajulus*). Efficacy was investigated by assessment of the mortality of the test organisms.
6.2	**Reliability**	The test results are reliable and relevant for an efficacy assessment of the active ingredient etofenprox.

Section A5.2/03 Efficacy Data

Annex Point IIA-V.5.2 **House longhorn beetle (*Hylotrupes bajulus* L.)**

6.3	**Assessment of efficacy, data analysis and interpretation**	Threshold of toxicity: 10.5 – 21.1 g/m^3 (0.002 – 0.004% respectively, based on mass percentage; w/w) The threshold of toxicity is expressed according to EN 47 as: - the lowest concentration at which no adults emerge and at which, at the end of the test, all larvae are dead, - the next lower concentration in series at which some adults emerge, or at the end of the test, live larvae are found.
6.4	**Conclusion**	Laboratory test can be considered as valid to assess the efficacy of etofenprox as insecticide for wood preservation. Test was conducted according to guidelines EN 47 (no deviations). A good effectiveness against larvae of house longhorn beetle (*Hylotrupes bajulus*) was attested for [redacted]01190-1 (etofenprox).
6.5	**Proposed efficacy specification**	See point 6.3

Table A5_2_03-1: Retention of test substance per test block, and number of surviving and dead larvae of the house longhorn beetle after 12 weeks exposure to the test blocks.

Concentration of test substance (% w/w)	**Retention of test solution per test block**			**Retention of test substance per test block**	**Number of larvae**			
	Min. (g)	**Average** (g)	**Max.** (g)	**Average** (g/m^3)	**Dead, not gnawed**	**Dead, gnawed**	**Alive**	**Not recovered**
0 (ethanol control	10.4	10.28	10.60	–	0	2	28	0
0.002	9.63	9.96	10.30	10.46	6	5	19	0
0.004	9.80	10.02	10.19	21.06	22	8	0	0
0.008	9.82	10.04	10.22	42.11	28	2	0	0
0.01	9.93	10.12	10.40	53.14	26	3	0	1
0.012	9.77	10.09	10.48	63.62	30	0	0	0
Untreated control	–	–	–	–	0	1	29	0

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*2005-08-02*
Materials and methods	*Agree with the applicant's version*
Conclusion	*Agree with the applicant's version*
Reliability	*1*
Acceptability	*acceptable*
Remarks	
	COMMENTS FROM...
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

Section A5.2/04 Efficacy Data

Annex Point IIA-V.5.2 **House longhorn beetle (*Hylotrupes bajulus* L.)**

			Official use only
		1 REFERENCE	
1.1	**Reference**	Schumacher P., Fennert E.-M. (2003d) Determination of the toxic values against larvae of *Hylotrupes bajulus* (L) according to EN 47 (08/90) – after leaching procedure to EN 84 (05/97); Material Testing Institute Brandenburg, Department 3 wood and wood protection, Germany; unpublished report no. 3.2/03/8417/04 (July 08, 2003) Dates of experimental work: March 2003 – June 2003	
1.2	**Data protection**	Yes	
1.2.1	Data owner	[redacted]	
1.2.2	Criteria for data protection	Data submitted to the MS after May 13, 2000 on existing a.s. for the purpose of its entry into Annex I.	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	EN 47 (August 1990) EN 84 (May 1997)	
2.2	**GLP**	No	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Etofenprox ([redacted]01190-I)	
3.1.1	Lot/Batch number	No information in the report.	
3.1.2	Specification	As given in section 2	
3.1.3	Description	No information in the report.	
3.1.4	Purity	No information in the report.	
3.1.5	Stability	No information in the report.	
3.1.6	Further relevant properties	Solubility in water: 22.5 µg/L at 20 ± 0.5°C Vapour pressure: 8.13 x 10^{-7} Pa at 25°C Stability in water: hydrolytically stable at pH 4, 7 and 9	
3.1.7	Method of analysis	No analyses were performed	
3.2	**Preparation of TS solution for poorly soluble or volatile test substances**	Ethanol was used as solvent/vehicle	
3.3	**Reference substance**	No	
3.3.1	Method of analysis for reference substance	Not applicable	
3.4	**Testing procedure**		
3.4.1	Test organism	Larvae of the house longhorn beetle (*Hylotrupes bajulus* L.), laboratory culture	

Section A5.2/04 Efficacy Data
Annex Point IIA-V.5.2 **House longhorn beetle (*Hylotrupes bajulus* L.)**

3.4.2	Test system	Impregnated wood blocks were exposed to test organisms; wood species: pine (*Pinus sylvestris* L.)
3.4.3	Application of TS	Vacuum pressure treatment (wood impregnation); date of treatment: March 21, 2003
3.4.4	Concentrations tested	0, 0.002, 0.004, 0.008, 0.012, 0.016% (w/w) retention of test substance: 0, 10.5, 20.6, 42.2, 50.9, 84.3 g/m^3
3.4.5	Test conditions	Duration of conditioning period after impregnation: 28 days Ageing test was carried out according to EN 84; period of leaching: April 22, 2003 – May 06, 2003
3.4.6	Duration of the test / Exposure time	Installation of test blocks: May 21, 2003 Removal of test blocks: August 13, 2003 Exposure of the wood to the test organisms: 12 weeks
3.4.7	Number of replicates performed	5 replicates (test wood blocks) per test substance concentration
3.4.8	Controls	Yes: blocks treated with ethanol without test substance
3.5	**Examination**	
3.5.1	Effect investigated	Mortality of the larvae
3.5.2	Method for recording / scoring of the effect	Counting (split up of test blocks)
3.5.3	Intervals of examination	Once at the end of exposure, when test blocks were removed
3.5.4	Statistics	No statistics applied
3.5.5	Post monitoring of the test organism	No
		4 RESULTS
4.1	**Efficacy**	
4.1.1	Dose/Efficacy curve	Not applicable
4.1.2	Begin and duration of effects	Not applicable
4.1.3	Observed effects in the post monitoring phase	Not applicable
4.2	**Effects against organisms or objects to be protected**	Mortality of larvae
4.3	**Other effects**	none
4.4	**Efficacy of the reference substance**	Toxic value: 42.2 – 50.9 g/m^3 (corresponding to 0.008– 0.012% w/w)

Section A5.2/04 **Efficacy Data**
Annex Point IIA-V.5.2 **House longhorn beetle (*Hylotrupes bajulus* L.)**

4.5	**Tabular and/or graphical presentation of the summarised results**	→ see Table A5_2_04-1
4.6	**Efficacy limiting factors**	
4.6.1	Occurrences of resistances	Not observed
4.6.2	Other limiting factors	None reported

5 RELEVANCE OF THE RESULTS COMPARED TO FIELD CONDITIONS

5.1	**Reasons for laboratory testing**	The laboratory efficacy test was performed according to the guidelines EN 47 and EN 84
5.2	**Intended actual scale of biocide application**	Not applicable, test was performed with the active ingredient etofenprox
5.3	**Relevance compared to field conditions**	
5.3.1	Application method	The application method in the laboratory test is comparable with the planned industrial application method. However, the test was performed with the active ingredient etofenprox
5.3.2	Test organism	Test organism is identical with the target organism of the intended use for the biocidal product
5.3.3	Observed effect	The observed effect in the laboratory test shows the efficacy of etofenprox as active ingredient in the wood preservative [redacted]01990-I for protection against wood destroying larvae of the house longhorn beetle.
5.4	**Relevance for read-across**	Relevance for read across is limited because the test was performed with the active ingredient etofenprox. However, the test proves the efficacy of the insecticidal active ingredient in the wood preservative [redacted] 01990-I when applied under realistic conditions (vacuum pressure impregnation)

6 APPLICANT'S SUMMARY AND CONCLUSION

6.1	**Materials and methods**	Pine (*Pinus sylvestris*) wood blocks were treated (vacuum pressure impregnation) with etofenprox, ethanol was used as solvent/vehicle. After a conditioning period of 28 days, wood blocks were treated according to EN 84 to simulate ageing by leaching. Treated and control (ethanol treatment) wood blocks were then exposed for 12 weeks to larvae of the house longhorn beetle (*Hylotrupes bajulus*). Efficacy was investigated by assessment of the mortality of the test organisms.
6.2	**Reliability**	The test results are reliable and relevant for an efficacy assessment of the active ingredient etofenprox.

Section A5.2/04 Efficacy Data

Annex Point IIA-V.5.2 **House longhorn beetle (*Hylotrupes bajulus* L.)**

6.3	**Assessment of efficacy, data analysis and interpretation**	Toxic value after leaching procedure: 42.2 – 50.9 g/m^3 (0.008 – 0.012% respectively, based on mass percentage; w/w) Threshold of toxicity: 42.2 – 50.9 g/m^3 (0.008 – 0.012% respectively, based on mass percentage; w/w) The threshold of toxicity is expressed according to EN 47 as: - the lowest concentration at which no adults emerge and at which, at the end of the test, all larvae are dead, - the next lower concentration in series at which some adults emerge, or at the end of the test, live larvae are found.
6.4	**Conclusion**	Laboratory test can be considered as valid to assess the efficacy of etofenprox as insecticide for wood preservation. Test was conducted according to guidelines EN 47 and EN 84 (no deviations). A good effectiveness against larvae of house longhorn beetle (*Hylotrupes bajulus*) was attested for [redacted]01190-I (etofenprox).
6.5	**Proposed efficacy specification**	See point 6.3

Table A5_2_04-1: Retention of test substance per test block, and number of surviving and dead larvae of the house longhorn beetle after 12 weeks exposure to the test blocks.

Concentration of test substance (% w/w)	**Retention of test solution per test block**			**Retention of test substance per test block**	**Number of larvae**			
	Min. (g)	**Average** (g)	**Max.** (g)	**Average** (g/m^3)	**Dead, not gnawed**	**Dead, gnawed**	**Alive**	**Not recovered**
0 (ethanol control) [b]	9.77	10.00	10.22	–	1	0	29	0
0.002 [b]	9.83	10.03	10.23	10.52	8	21	1	0
0.004 [b]	9.62	9.86	10.09	20.58	26	3	1	0
0.008 [b]	9.96	10.10	10.17	42.20	18	10	2	0
0.012 [b]	9.78	9.85	9.98	50.87	30	0	0	0
0.016 [a]	10.3	10.08	9.98	84.31	11	0	1	0
0.016 [b]	10.3	10.08	9.98	84.31	18	0	0	0

[a] assessment after 4 weeks (2 blocks of the highest treatment)
[b] assessment after 12 weeks (highest treatment: 3 blocks assessed)

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*2005-08-02*
Materials and methods	*Agree with the applicant's version*
Conclusion	*Agree with the applicant's version*
Reliability	*1*
Acceptability	*acceptable*
Remarks	
	COMMENTS FROM...
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

LKC UK Ltd.

Section A6.1.1 Acute Toxicity

Annex Point IIA-VI.6.1.1

Oral

Rat, limit test

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (2003a): Acute oral toxicity study of Etofenprox in rats; Gotemba Laboratory, [redacted] unpublished report no. B-5039 (February 05, 2003). Dates of work: November 05, 2002 - November 19, 2002.	
1.2	**Data protection**	Yes	
1.2.1	Data owner	[redacted] Mitsui Chemicals Agro, Inc.	
1.2.2	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I.	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes OECD guideline no. 420 (1992) ≡ 92/69/EEC method B.1 bis; US-EPA OPPTS 870.1100; Japan MAFF, 12 NohSan, no. 8147.	
2.2	**GLP**	Yes	
2.3	**Deviations**	Yes Deviations: no preliminary dose sighting was performed, since there was sufficient information available to establish a limit dose level without mortality. An additional group, treated with vehicle only, was used.	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Etofenprox	
3.1.1	Lot/Batch number	Batch no. 20024	
3.1.2	Specification	Deviating from specification given in section 2 as follows	X
3.1.2.1	Description	Clear liquid.	
3.1.2.2	Purity	99.0%	
3.1.2.3	Stability	No information in the report.	

Section A6.1.1 Acute Toxicity

Annex Point IIA-VI.6.1.1 **Oral**
Rat, limit test

3.2	**Test Animals**	
3.2.1	Species	Rat
3.2.2	Strain	Sprague-Dawley-derived rats (Crj:CD(SD)IGS strain.
3.2.3	Source	[redacted]
3.2.4	Sex	male and female.
3.2.5	Age/weight at study initiation	7-week old, weight range 164 - 197g.
3.2.6	Number of animals per group	5 males and 5 females rat per group.
3.2.7	Control animals	Yes
3.3	**Administration/ Exposure**	**Oral**
3.3.1	Postexposure period	14 days
3.3.2	Type	Gavage
3.3.3	Concentration	Test group: 2000 mg/kg bw Control group: 0 mg/kg bw
3.3.4	Vehicle	Corn oil
3.3.5	Concentration in vehicle	Test group: 200 mg/mL Control group: 0 mg/mL
3.3.6	Total volume applied	10 mL of the test suspension/kg bw
3.3.7	Controls	Vehicle
3.4	**Examinations**	Morbidity/mortality, clinical signs, body weight, necropsy, *post mortem* examination of the external surfaces and the major organs and tissues of the cranial, thoracic and abdominal cavities.
3.5	**Method of determination of LD_{50}**	Estimated based on the absence of mortality.
3.6	**Further remarks**	Body weight data were analysed statistically using the F-test to estimate variance, followed by Student's t-test at the 95% level of confidence.

Section A6.1.1 **Acute Toxicity**

Annex Point IIA-VI.6.1.1 **Oral**

Rat, limit test

4 RESULTS AND DISCUSSION

4.1	**Mortality**	No deaths occurred in either males or females treated with etofenprox at 0 or 2000mg/kg.
4.2	**Clinical signs**	No effects
4.3	**Pathology**	No effects
4.4	**Body weight**	No statically significant ($p > 0.05$) differences between the treated and control groups with respect to body weight gain, but both sexes treated with etofenprox showed slightly suppressed weight gain during the 24 hours following treatment (see Table A6_01_1_01). Thereafter, weight gain was comparable to the controls.
4.5	**LD_{50}**	The acute oral LD_{50} of etofenprox in the rat was estimated to be > 2000mg/kg in both sexes, based on the absence of mortality at this dose level.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Test guidelines: OECD guideline no. 420 (1992) ≡ 92/69/EEC method B.1 bis; US-EPA OPPTS 870.1100; Japan MAFF, 12 NohSan, no. 8147. No relevant deviations from test guidelines. Description of method: limit test plus one control group, 5 males and 5 females per group, oral gavage, etofenprox administered as suspension in corn oil, 14-day observation period.
5.2	**Results and discussion**	Rat, etofenprox: oral LD_{50} > 2000mg/kg in both sexes.
5.3	**Conclusion**	
5.3.1	Reliability	1
5.3.2	Deficiencies	No

Table A6_01_1_01. Mortality and group mean body weights.

Dose level (mg/kg)	Sex	No. dying / no. tested	Group mean body weight (g) on day:				
			0	1	3	7	14
0	Male	0 / 5	189	215	241	281	343
	Female	0 / 5	169	188	199	214	245
2000	Male	0 / 5	189	209	235	276	344
	Female	0 / 5	169	184	201	213	242

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	27.05.2005
Materials and methods	**3.1.2. Specification** According to document A3 the physical state changes from white crystals to amber liquid with decreasing purity from 99,8 % to 99,3%. Within the 5 batch analysis a purity between 97,2 % and 99,6% is indicated. Within the present study the specification does not deviate to these indications.
Conclusion	Agree with applicant´s version
Reliability	1
Acceptability	acceptable
Remarks	-
	COMMENTS FROM...
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

LKC UK Ltd.

Section A6.1.2 Acute Toxicity

Annex Point IIA-VI.6.1.2

Dermal

Rat, limit test

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (2003b): Acute dermal toxicity study of Etofenprox in rats; Gotemba Laboratory, [redacted] unpublished report no. B-5040 (February 05, 2003). Dates of work: November 05, 2002 - November 19, 2002.	
1.2	**Data protection**	Yes	
1.2.1	Data owner	[redacted] Mitsui Chemicals Agro, Inc.	
1.2.2	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I.	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes OECD guideline no. 402 (1987) ≡ 92/69/EEC method B.3; US-EPA OPPTS 870.1200 (1998); Japan MAFF, 12 NohSan, no. 8147.	
2.2	**GLP**	Yes	
2.3	**Deviations**	Yes Deviations: an additional group, treated with vehicle only, was used for comparative purposes.	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Etofenprox	
3.1.1	Lot/Batch number	Batch no. 20024	
3.1.2	Specification	Deviating from specification given in section 2 as follows	X
3.1.2.1	Description	Clear liquid	
3.1.2.2	Purity	99.0%	
3.1.2.3	Stability	No information in the report	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Sprague-Dawley-derived rats (Crj:CD(SD)IGS strain.	
3.2.3	Source	[redacted]	
3.2.4	Sex	male and female	
3.2.5	Age/weight at study initiation	7-week old, weight range 167 – 240 g	
3.2.6	Number of animals per group	5 males and 5 females rat per group	
3.2.7	Control animals	Yes	

Section A6.1.2 Acute Toxicity

Annex Point IIA-VI.6.1.2

Dermal

Rat, limit test

3.3	**Administration/ Exposure**	**Dermal**
3.3.1	Postexposure period	14 days
3.3.2	Concentrations	Test group: 2000 mg/kg bw Control group: 0 mg/kg bw
3.3.3	Area covered	Approximately 10 % of body surface (6 x 5 cm).
3.3.4	Occlusion	Semiocclusive
3.3.5	Vehicle	Distilled water used to moisture test article.
3.3.6	Concentration in vehicle	Not applicable
3.3.7	Total volume applied	Test group: 1.85 mL/kg bw Control group: 0 mL/kg bw
3.3.8	Duration of exposure	24 h
3.3.9	Removal of test substance	Warm water.
3.3.10	Controls	Dressing only.
3.4	**Examinations**	Morbidity/mortality, clinical signs, body weight, necropsy, *post mortem* examination of the external surfaces and the major organs and tissues of the cranial, thoracic and abdominal cavities.
3.5	**Method of determination of LD_{50}**	Estimated based on the absence of mortality.
3.6	**Further remarks**	Body weight data were analysed statistically using the F-test to estimate variance, followed by Student's t-test at the 95% level of confidence.
		4 RESULTS AND DISCUSSION
4.1	**Mortality**	No deaths occurred in either males or females treated with etofenprox at 0 or 2000mg/kg.
4.2	**Clinical signs**	There was no evidence of dermal irritation at the application sites.
4.3	**Pathology**	No effects
4.4	**Body weight**	There were no statically significant ($p > 0.05$) differences between the treated and control groups with respect to body weight gain, but both sexes treated with etofenprox and the controls showed slightly suppressed weight gain during the 24 hours following treatment (Table A6_01_2_01). Thereafter, weight gain was comparable between the groups.
4.5	**LD_{50}**	The acute dermal LD_{50} of etofenprox in the rat was estimated to be > 2000mg/kg in both sexes, based on the absence of mortality at this dose level.

Section A6.1.2 Acute Toxicity

Annex Point IIA-VI.6.1.2

Dermal

Rat, limit test

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Test guidelines: OECD guideline no. 402 (1987) ≡ 92/69/EEC method B.3; US-EPA OPPTS 870.1200 (1998); Japan MAFF, 12 NohSan, no. 8147.

No relevant deviations from test guidelines.

Description of method: limit test plus one control group, 5 males and 5 females per group, semiocclusive dermal application to dorsal skin, etofenprox moistured with distilled water, 14-day observation period.

5.2 Results and discussion

Rat, etofenprox: dermal LD_{50} > 2000mg/kg in both sexes.

5.3 Conclusion

5.3.1 Reliability: 1

5.3.2 Deficiencies: No

Table A6_01_2_01. Mortality and group mean body weights.

Dose level (mg/kg)	Sex	No. dying / no. tested	Group mean body weight (g) on day:				
			0	1	3	7	14
0	Male	0 / 5	230	230	258	298	367
	Female	0 / 5	174	171	185	201	230
2000	Male	0 / 5	230	229	254	297	361
	Female	0 / 5	173	172	183	199	226

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	27.05.2005
Materials and methods	**3.1.2. Specification** According to document A3 the physical state changes from white crystals to amber liquid with decreasing purity from 99,8 % to 99,3%. Within the 5 batch analysis a purity between 97,2 % and 99,6% is indicated. Within the present study the specification does not deviate to these indications.
Conclusion	Agree with applicant´s version
Reliability	1
Acceptability	acceptable
Remarks	-
	COMMENTS FROM...
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

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Section A6.1.3 Acute Toxicity

Annex Point IIA-VI.6.1.3

Inhalation

Rat, limit test

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (1983): MTI-500 acute inhalation toxicity in rats, 4 hour exposure; [redacted] unpublished report no. MTC 60/821079 (April 19, 1983). Dates of work: not specified in the report.	
1.2	**Data protection**	Yes	
1.2.1	Data owner	[redacted] Mitsui Chemicals Agro, Inc.	
1.2.2	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I.	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes 92/69/EEC (method B.3)	
2.2	**GLP**	Yes	
2.3	**Deviations**	Yes Deviations: a limit test was performed, but included air and solvent control groups; relative humidity in the exposure chamber was not monitored; nominal exposure concentration was not reported.	X
		3 MATERIALS AND METHODS	
3.1	**Test material**	Etofenprox	
3.1.1	Lot/Batch number	Batch no. ST-101	
3.1.2	Specification	Deviating from specification given in section 2 as follows	X
3.1.2.1	Description	Light brown solid	
3.1.2.2	Purity	96 %	
3.1.2.3	Stability	No information provided in the report.	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Wistar	
3.2.3	Source	[redacted]	
3.2.4	Sex	Male and female	
3.2.5	Age/weight at study initiation	Young adult, weight range 194 - 216g	
3.2.6	Number of animals per group	5 males and 5 females per group	
3.2.7	Control animals	Yes	

Section A6.1.3 Acute Toxicity

Annex Point IIA-VI.6.1.3 **Inhalation**

Rat, limit test

3.3	**Administration/ Exposure**	**Inhalation**
3.3.1	Postexposure period	14 days
3.3.2	Concentrations	The exposure concentration of etofenprox was measured analytically by HPLC in 5 air samples withdrawn 30 minutes after the start of exposure and at approximate hourly intervals thereafter. The samples were drawn through a glass fibre filter at a rate of 5L/minute. The volume withdrawn was measured with a wet type gas meter. analytical concentration 5.88 mg/L.
3.3.3	Particle size	The particle size distribution of the atmosphere was determined on 2 occasions during exposure by drawing atmosphere at a flow rate of 10L/minute through a 3-stage impinger (< 2.0µm, 2.0 - 5.5µm and > 5.5µm) with mixed solvent as trapping agent in each stage. Mean particle size (% of sample): > 5.5µm: 4.7 2.0 - 5.5µm: 18.4 0.5 - 2.0µm: 75.2 < 0.5µm: 1.7
3.3.4	Type or preparation of particles	The exposure equipment comprised a venturi atomizing jet connected, via a glass elutriator, to a square section perspex exposure chamber with a pyramidal top with a continuous airflow system. The equipment was subjected to a 12-minute equilibration period prior to the introduction of animals. Exposure chamber temperature was measured at 30-minute intervals and air flow was continuously monitored throughout the exposure period. Values for exposure chamber parameters are shown in Table A6_1_3-1.
3.3.5	Type of exposure	Whole body
3.3.6	Vehicle	Acetone
3.3.7	Concentration in vehicle	Solution: 10% acetone and 90% etofenprox (by weight)
3.3.8	Duration of exposure	4 h
3.3.9	Controls	2 control groups: 1) air only 2) 10% acetone in air
3.4	**Examinations**	Clinical observations, individual body weight, food and water consumption. Necropsy and *post mortem* examination of major organs and tissues. The lungs were dissected free of contiguous tissues, weighed, and lung weights relative to body weight were calculated. The lungs, infused with fixative, and samples of liver and kidneys, were preserved for subsequent histopathological evaluation.
3.5	**Method of determination of LD_{50}**	Estimated based on the absence of mortality.
3.6	**Further remarks**	None

Section A6.1.3 **Acute Toxicity**

Annex Point IIA-VI.6.1.3 **Inhalation**

Rat, limit test

4 RESULTS AND DISCUSSION

4.1	**Mortalities**	There were no deaths during the study.
4.2	**Clinical signs**	All animals exposed to etofenprox showed abnormal body posture during exposure, accompanied in some animals by partially or fully closed eyelids and abnormal respiratory movements. The animals exposed to acetone in air were hypoactive during exposure. Approximately one hour post-exposure, etofenprox -treated animals were lethargic and showed an oily appearance of the fur. No further treatment-related clinical signs were evident within 72 hours of exposure although some female animals showed hair loss and transient hyperactivity.
4.3	**Pathology**	There was no effect of treatment with etofenprox on absolute and relative lung weights (Table A6_1_3-2). There were no gross lesions at necropsy that could be unequivocally ascribed to etofenprox exposure, although a single male showed a black area on the liver. There were no treatment-related histopathological findings in the lungs, liver and kidneys of any animal.
4.4	**Body weight**	There was a treatment-related, transient weight loss in males exposed to etofenprox for one day following exposure (Table A6_1_3-3). Thereafter, weight gain was comparable to the controls. A slightly reduced post-exposure weight gain of females treated with etofenprox was considered to be incidental to treatment since the mean body weight was diverging from the controls during the pre-exposure period. Females in the acetone group showed transiently reduced weight gain for one day following exposure.
4.5	**Food and water consumption**	The food consumption of males and females exposed to etofenprox was transiently reduced by up to 27% for one or 2 days post-exposure, respectively. Thereafter food consumption was unaffected by treatment. The effect on male food consumption was accompanied by a 14.3% reduction in water consumption on the day following exposure. The food and water consumption of the acetone-treated group were unaffected by exposure.
4.6	**LD_{50}**	The acute 4-hour LC_{50} of respirable etofenprox in male and female rats was established as > 5.88mg/L, based on the absence of mortality at this concentration.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Test guidelines: 92/69/EEC (method B.3). No relevant deviations from test guidelines. Description of method: limit test plus control groups, 5 males and 5 females per group, inhalation, 4-hour whole body exposure to aerosol (etofenprox in acetone), 14-day observation period.
5.2	**Results and discussion**	Rat, etofenprox: inhalation LD_{50} > 5.9 g/m^3 of air, in both sexes.
5.3	**Conclusion**	
5.3.1	Reliability	1
5.3.2	Deficiencies	No

Section A6.1.3 **Acute Toxicity**

Annex Point IIA-VI.6.1.3 **Inhalation**

Rat, limit test

Table A6_1_3-1. Mean measured exposure parameters.

Chamber parameter	Control (air) group	Control (acetone) group	Test (etofenprox in 10% acetone) group
Volume	130L	130L	130L
Air flow rate	30L/min	30L/min	30L/min
Material injection rate	-	0.15mL/min	1.1mL/min
Mean temperature	24.9°C	24.8°C	23.8°C
Mean etofenprox concentration	0	0	5.88mg/L
Mean particle size (% of sample): > 5.5µm 2.0 - 5.5µm 0.5 - 2.0µm < 0.5µm	- - - - -	- - - - -	 4.7 18.4 75.2 1.7
Proportion particles < 5.5µm	-	-	95.3%

Table A6_1_3-2 Summary of absolute and relative lung weights.

Treatment (mg/L)	Sex	Group mean value:		
		Day 14 body weight (g)	Lung weight (g)	Lung/body weight ratio
0 (air)	Male	325	1.40	0.43
0 (acetone)		331	1.45	0.44
5.88		328	1.43	0.43
0 (air)	Female	247	1.21	0.49
0 (acetone)		256	1.27	0.49
5.88		234	1.14	0.49

Table A6_1_3-3. Summary of group mean body weights.

Treatment (mg/L)	Sex	Group mean body weight (g) on day:					
		- 5	- 1	0 (pre)	1	7	14
0 (air)	Male	165	203	211	219	271	325
0 (acetone)		163	203	210	220	274	331
5.88		162	201	210	207	267	328
0 (air)	Female	183	201	208	216	234	247
0 (acetone)		185	207	211	211	236	256
5.88		181	198	201	202	219	234

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	27.05.2005
Materials and methods	**2.3 Deviations** typing error: … included air and air/solvent control groups… **3.1.2. Specification** According to document A3 the physical state changes from white crystals to amber liquid with decreasing purity from 99,8 % to 99,3%. Within the 5 batch analysis a purity between 97,2 % and 99,6% is indicated. ST-101 contained the same main impurities as later production batches (e.g. 5 batch analysis) at comparable percentages. The concentration of etofenprox is with 96% lower than in the 5 batch analysis. Therefore the specification within in the present study does not relevantly deviate to these indications.
Conclusion	Agree with applicant's version
Reliability	1
Acceptability	Acceptable
Remarks	-
	COMMENTS FROM...
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

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Section A6.1.4.e Acute Eye Irritation

Annex Point IIA-VI.6.1.4 **Rabbit**

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted](1985b); MTI-500 primary ophthalmic stimulation test in rabbits; [redacted] unpublished report no. [redacted]H-85-55; October 24, 1985 + amendment dated October 28, 1991 Dates of work: August 26, 1985 - August 29, 1985	
1.2	**Data protection**	Yes	
1.2.1	Data owner	[redacted] Mitsui Chemicals Agro, Inc.	
1.2.2	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes 92/69/EEC (method B.5)	
2.2	**GLP**	Yes	
2.3	**Deviations**	Yes Deviations: 6 rabbits instead of 3 (92/69/EEC, B.5) were used since this is a regulatory requirement in the US. The deviation does not affect the validity of the study.	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Etofenprox	
3.1.1	Lot/Batch number	Batch no. ST-103	
3.1.2	Specification	Deviating from specification given in section 2 as follows	X
3.1.2.1	Description	Light yellow solid	
3.1.2.2	Purity	96.3%	
3.1.2.3	Stability	No information provided in the report.	
3.2	**Test Animals**		
3.2.1	Species	Rabbit	
3.2.2	Strain	Not specified (Japanese white rabbits)	X
3.2.3	Source	[redacted]	
3.2.4	Sex	Male	
3.2.5	Age/weight at study initiation	Age not specified, body weight 2.24 to 3.01 kg	
3.2.6	Number of animals per group	6	
3.2.7	Control animals	No (left eye of each test animal remained untreated to serve as reference control)	

Section A6.1.4.e Acute Eye Irritation

Annex Point IIA-VI.6.1.4 **Rabbit**

3.3	**Administration/ Exposure**	
3.3.1	Preparation of test substance	The etofenprox was instilled after melting in a waterbath.
3.3.2	Amount of active substance instilled	0.1mL etofenprox was introduced into the right conjunctival sac.
3.3.3	Observation period	72h after instillation
3.4	**Examinations**	
3.4.1	Ophthalmoscopic examination	Yes Examination for ocular irritation reactions in the cornea, iris and conjunctivae
3.4.1.1	Scoring system	Irritation reactions were graded and scored according to the grading system specified in 92/69/EEC (method B.5), and then photographed.
3.4.1.2	Examination time points	1, 24, 48 and 72 hours after instillation
3.4.2	Other investigations	The animals were killed after the 72-hour observation, the region around the treated eye was examined macroscopically and the treated eye was excised and retained in fixative.
3.5	**Further remarks**	None

4 RESULTS AND DISCUSSION

4.1	**Clinical signs**	No effects
4.2	**Average score**	see Tables A6_01_4E-1 and A6_01_4E-2
4.2.1	Cornea	0 (group mean score 24-72 hr)
4.2.2	Iris	0 (group mean score 24-72 hr)
4.2.3	Conjunctiva	
4.2.3.1	Erythema	0.44 (group mean score 24-72 hr)
4.2.3.2	Edema	0 (group mean score 24-72 hr)
4.3	**Reversibility**	Yes Transient minimal conjunctival erythema in some animals up to 48 hours after application (reversed after 72 hours)
4.4	**Other**	There were no relevant observations on the site of application at necropsy.
4.5	**Overall result**	The individual and group mean irritation scores do not meet the criteria for classification as irritating to the eyes. not irritant to the eye.

Section A6.1.4.e Acute Eye Irritation

Annex Point IIA-VI.6.1.4 **Rabbit**

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Test guideline: 92/69/EEC (method B.5)

No relevant deviations from test guidelines.

Description of method: 6 male rabbits, instillation of 0.1mL etofenprox into the right conjunctival sa, left eye untreated to serve as control, 72-hour observation period.

5.2 Results and discussion

Etofenprox is not irritant to the eye.

5.3 Conclusion

5.3.1 Reliability 1

5.3.2 Deficiencies No

Table A6_01_4E-1. 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

Table A6_1_4E-2. Group mean irritation scores according to Commission Directive 93/21/EEC (Annex VI).

	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

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	27.05.2005
Materials and methods	**3.1.2. Specification** According to document A3 the physical state changes from white crystals to amber liquid with decreasing purity from 99,8 % to 99,3%. Within the 5 batch analysis a purity between 97,2 % and 99,6% is indicated. ST-103 contained the same main impurities as later production batches (e.g. 5 batch analysis) at comparable percentages. The concentration of etofenprox is with 96,3% lower than in the 5 batch analysis. Therefore the specification within in the present study does not relevantly deviate to these indications. **3.2.2. Strain** The study report specifies "species and lineage": Japanese White Rabbits
Conclusion	Agree with applicant's version
Reliability	1
Acceptability	Acceptable
Remarks	-
	COMMENTS FROM...
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

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Section A6.1.4s Acute Dermal Irritation

Annex Point IIA-VI.6.1.4 **Rabbit**

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (1985a); MTI-500 primary skin stimulation test in rabbits; [redacted] unpublished report no. [redacted] H-85-5; August 23, 1985 - amendment dated October 28, 1991 Dates of work: July 09, 1985 - July 23, 1985	
1.2	**Data protection**	Yes	
1.2.1	Data owner	[redacted] Mitsui Chemicals Agro, Inc.	
1.2.2	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes 92/69/EEC (method B.4)	
2.2	**GLP**	Yes	
2.3	**Deviations**	Yes Deviations: 6 rabbits instead of 3 (92/69/EEC, B.4) were used since this is a regulatory requirement in the US. The deviation does not affect the validity of the study.	
		3 MATERIALS AND METHODS	
3.1	**Test material**	*Etofenprox*	
3.1.1	Lot/Batch number	Batch no. ST-103	
3.1.2	Specification	Deviating from specification given in section 2 as follows	X
3.1.2.1	Description	Light yellow solid	
3.1.2.2	Purity	96.3%	
3.1.2.3	Stability	No information provided in the report.	
3.2	**Test Animals**		
3.2.1	Species	Rabbit	
3.2.2	Strain	Not specified (Japanese white rabbits)	X
3.2.3	Source	[redacted]	
3.2.4	Sex	Male	
3.2.5	Age/weight at study initiation	Age not specified, body weight 2.0 to 2.5 kg	
3.2.6	Number of animals per group	6	
3.2.7	Control animals	No	
3.3	**Administration/ Exposure**	**Dermal**	

Section A6.1.4s — Acute Dermal Irritation

Annex Point IIA-VI.6.1.4 — **Rabbit**

3.3.1	Application	
3.3.1.1	Preparation of test substance	Melted test substance was applied to the skin (undiluted).
3.3.1.2	Test site and Preparation of Test Site	Shaved and clipped area of dorsal skin (2.5 x 2.5cm) along the mid-line.
3.3.2	Occlusion	semiocclusive
3.3.3	Vehicle	None
3.3.4	Concentration in vehicle	Not applicable
3.3.5	Total volume applied	0.5 mL undiluted melted etofenprox/animal
3.3.6	Removal of test substance	warm water
3.3.7	Duration of exposure	4 h
3.3.8	Postexposure period	72 hours, extended to 11 days for animals showing any dermal reaction at the 72-hour observation.
3.3.9	Controls	None
3.4	**Examinations**	
3.4.1	Clinical signs	Yes
3.4.2	Dermal examination	Yes Skin reactions were evaluated approximately 30 minutes after patch removal, and subsequently at 24, 48 and 72 hours. Animals continuing to show any dermal reaction at the 72-hour observation were re-examined daily for a further 11 days. Erythema/eschar formation and edema at the application sites were recorded and graded according to the scale specified in Japan MAFF Notification 59, no. 4200 (equivalent to the scale specified in 92/69/EEC, method B.4). The animals were also examined for evidence of dermal corrosivity
3.4.2.1	scoring system	EU index scores were calculated by the reviewer based on Annex VI, Offic. J. Europ. Commun., no. L110A, 36: 45 - 86, 1993.
3.4.2.2	Examination time points	60min, /24h, 48h,72h or other
3.4.3	Other examinations	Body weight, necropsy and gross examination of the subcutaneous tissues at the application site. A sample of skin was preserved but not examined histologically.
3.5	**Further remarks**	None

4 RESULTS AND DISCUSSION

4.1	**Average score**	
4.1.1	Erythema	see Table A6_01_4S
4.1.2	Edema	see Table A6_01_4S

Section A6.1.4s
Annex Point IIA-VI.6.1.4

Acute Dermal Irritation
Rabbit

4.2	**Reversibility**	No
4.3	**Other examinations**	No gross findings at necropsy
4.4	**Overall result**	Etofenprox is non-irritant to skin based on the EU classification system, since neither the overall mean index score nor any individual score was greater than 2.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Test guideline: 92/69/EEC (method B.4) No relevant deviations from test guidelines. Description of method: 6 male rabbits, application of 0.5 mL melted etofenprox on dorsal skin (2.5 x 2.5 cm), semiocclusive, for 4 hours.
5.2	**Results and discussion**	Etofenprox is not irritant to the skin.
5.3	**Conclusion**	
5.3.1	Reliability	1
5.3.2	Deficiencies	No

Table A6_1-4S. Individual skin irritation and EU index scores.

Animal number	**Individual erythema / edema scores at:**				**EU index score***
	30 minutes	**24 hours**	**48 hours**	**72 hours**	
1	0 / 0	0 / 0	0 / 0	0 / 0	0.0
2	0 / 0	0 / 0	0 / 0	0 / 0	0.0
3	0 / 0	0 / 0	0 / 0	0 / 0	0.0
4	0 / 0	0 / 0	0 / 0	0 / 0	0.0
5	0 / 0	0 / 0	0 / 0	0 / 0	0.0
6	0 / 0	0 / 0	1 / 0	1 / 0	0.6
Total score (erythema + edema)	0	0	1	1	Mean (24 - 72 hrs) 0.1

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

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	27.05.2005
Materials and methods	**3.1.2. Specification** According to document A3 the physical state changes from white crystals to amber liquid with decreasing purity from 99,8 % to 99,3%. Within the 5 batch analysis a purity between 97,2 % and 99,6% is indicated. ST-103 contained the same main impurities as later production batches (e.g. 5 batch analysis) at comparable percentages. The concentration of etofenprox is with 96,3% lower than in the 5 batch analysis. Therefore the specification within in the present study does not relevantly deviate to these indications. **3.2.2. Strain** The study report specifies "species and lineage": Japanese White Rabbits
Conclusion	Agree with applicant's version
Reliability	1
Acceptability	acceptable
Remarks	-
	COMMENTS FROM...
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

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Section A6.1.5 Skin sensitisation

Annex Point IIA-VI.6.1.5 **Guinea pig, modified maximisation test**

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (1985); MTI-500 skin sensitization test in guinea pigs; [redacted] unpublished report no. not specified; October 31, 1985 + correction to translation dated October 21, 2003 Dates of work: September 08, 1985 - October 13, 1985	
1.2	**Data protection**	Yes	
1.2.1	Data owner	[redacted] Mitsui Chemicals Agro, Inc.	
1.2.2	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	No Method employed was equivalent to 92/69/EEC (method B.6) with some deviations	
2.2	**GLP**	Yes	
2.3	**Deviations**	Yes Deviations: one animal exceeded the upper body weight limit by 10g. The vehicle control group was challenged with vehicle only, rather than test material in vehicle. Challenge sites were also evaluated 72 hours after challenge. Topical challenge applications were applied to one flank only, and no vehicle challenge applications were made. The report does not specify if dermal reactions were scored following induction applications, although 10% sodium lauryl sulphate was applied 24 hours prior to topical induction.	X
		3 MATERIALS AND METHODS	
3.1	**Test material**	Etofenprox	
3.1.1	Lot/Batch number	Batch no. ST-103	
3.1.2	Specification	Deviating from specification given in section 2 as follows	X
3.1.2.1	Description	Light yellow solid	
3.1.2.2	Purity	Not specified	
3.1.2.3	Stability	No information in the report	
3.1.2.4	Preparation of test substance for application	a) <u>for induction:</u> etofenprox diluted in corn oil b) <u>for challenge:</u> etofenprox diluted in corn oil	
3.1.2.5	Pretest performed on irritant effects	Yes	

Section A6.1.5 Skin sensitisation

Annex Point IIA-VI.6.1.5 **Guinea pig, modified maximisation test**

3.2	**Test Animals**	
3.2.1	Species	Guinea pigs
3.2.2	Strain	English Hartley strain
3.2.3	Source	[redacted]
3.2.4	Sex	Male
3.2.5	Age/weight at study initiation	348 – 510 g
3.2.6	Number of animals per group	20
3.2.7	Control animals	Yes → - Vehicle control group (corn oil) - Positive control group (DNCB, i.e. dinitrochlorobenzene)
3.3	**Administration/ Exposure**	Study type: Adjuvant
3.3.1	Induction schedule	- Day 1: intradermal induction - Day 7, the test sites of all animals were treated with 10% sodium lauryl sulphate in petrolatum. - Day 8: topical induction (occlusive, for 48 hours)
3.3.2	Way of Induction	Intradermal and topical (occlusive)
3.3.3	Concentrations used for induction	- Intradermal induction: 3 injections of 0.05mL/site - 50% FCA in water - 20% etofenprox (or 0.125% DNCB) in corn oil - 20% etofenprox (or 0.125% DNCB) in 50% FCA Vehicle control group animals received vehicle only or vehicle in FCA for intradermal induction - Topical induction: 20% etofenprox in corn oil (or 2.5% DNCB in corn oil) at a volume of 0.5mL. The control group animals were similarly treated with corn oil only. See Table A6_1_5-1.
3.3.4	Concentration Freunds Complete Adjuvant (FCA)	50 % in water
3.3.5	Challenge schedule	Day 21
3.3.6	Concentrations used for challenge	20% etofenprox in corn oil (or 2.5% DNCB in corn oil). Vehicle control animals were challenged in a similar manner with corn oil only. See Table A6_1_5-1.
3.3.7	Rechallenge	No
3.3.8	Scoring schedule	24h, 48h and 72h after challenge or other
3.3.9	Removal of the test substance	24 h after challenge
3.3.10	Positive control substance	DNCB (dinitrochlorobenzene)

X

Section A6.1.5 Skin sensitisation

Annex Point IIA-VI.6.1.5 **Guinea pig, modified maximisation test**

3.4	**Examinations**	
3.4.1	Pilot study	No
3.5	**Further remarks**	- Following removal of the patches, the challenge sites were scored on a 4-point scale for dermal reactions (erythema and edema) 24, 48 and 72 hours after removal of the challenge dressings. - Clinical observations and morbidity/mortality checks were performed periodically and individual body weights were recorded at the start of the study and weekly thereafter. - Body weights were analysed using a t-test statistic. - All experimental animals were killed at the end of the study and the skin and subcutaneous tissues of the challenge sites, and major organs were examined macroscopically. The criterion for sensitization was the occurrence of skin reactions in test animals at a higher incidence and greater intensity than in the respective controls.
		4 RESULTS AND DISCUSSION
4.1	**Results of pilot studies**	not applicable
4.2	**Results of test**	
4.2.1	24h after challenge	The skin reaction scores for all vehicle control and etofenprox -treated groups were zero (no reaction) at the 24, 48 and 72-hour observation periods (Table A6_1_5-2). Consequently, the sensitization incidence in these groups was 0%. In contrast, all 20 animals treated with DNCB 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.
4.2.2	Other findings	- The body weight gains of the etofenprox and DNCB-treated groups were comparable to those of the control group throughout the study. - There were no abnormal findings at necropsy in any animals.
4.3	**Overall result**	Etofenprox is not a dermal sensitizer in the guinea pig maximization test. Based on a positive sensitization incidence of zero, which is below the 30% threshold of significance specified in Commission Directive 93/21/EEC, etofenprox does not require classification.

Section A6.1.5 Skin sensitisation

Annex Point IIA-VI.6.1.5 **Guinea pig, modified maximisation test**

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Test guidelines: equivalent to 92/69/EEC (method B.6)

Deviations from test guideline do not impact on the validity of the study.

Description of method: modified maximization test with 20 male Guinea pigs per group ,intradermal and topical induction on Day 1 and Day 8, respectively, challenge on Day 21, vehicle corn oil, positive control DNCB, scoring at 24, 48 and 72 hours after challenge.

5.2 Results and discussion

Etofenprox is not a dermal sensitizer

5.3 Conclusion

5.3.1 Reliability: 1

5.3.2 Deficiencies: No

Table A6_1_5-1. Schedule and concentrations for skin sensitisation test

Group description	Number of animals	Concentration applied (%)		
		Induction		Challenge
		(intradermal)	(topical)	(topical)
		Day 1	Day 8	Day 21
Etofenprox test group	20	20	20	20
Vehicle control group	20	0 (vehicle)	0 (vehicle)	0 (vehicle)
DNCB positive control group	20	0.125	2.5	2.5

Table A6_1_5-2. Summary of skin reactions following challenge.

Group	No. animals tested	Time after challenge (hours)	No. animals with skin reaction grade: 0	1	2	3	No. animals sensitized
Etofenprox	20	24	20	0	0	0	0
		48	20	0	0	0	
		72	20	0	0	0	
Vehicle control	20	24	20	0	0	0	0
		48	20	0	0	0	
		72	20	0	0	0	
DNCB control	20	24	0	19	1	0	20
		48	0	12	8	0	
		72	0	5	7	8	

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	27.05.2005
Materials and methods	**2.3. Deviations** The deviations are not considered to be critical. Since the results are negative the lacking negative controls for vehicle effects are of minor importance. **3.1.2. Specification** According to document A3 the physical state changes from white crystals to amber liquid with decreasing purity from 99,8 % to 99,3%. Within the 5 batch analysis a purity between 97,2 % and 99,6% is indicated. ST-103 contained the same main impurities as later production batches (e.g. 5 batch analysis) at comparable percentages. The concentration of etofenprox is with 96,3% lower than in the 5 batch analysis. Therefore the specification does not relevantly deviate to these indications. **3.3.10 Positive control substance** DNCB (dinitrochlorobenzene): The preferred positive control chemicals would have been hexyl cinnamic aldehyde or mercaptobenzothiazole or benzocaine (OECD guideline 406, paragraph 11and ECETOC Mo 29), but this does not interfere with the validity of the assay.
Conclusion	Agree with applicant's version
Reliability	1
Acceptability	acceptable
Remarks	-
	COMMENTS FROM...
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

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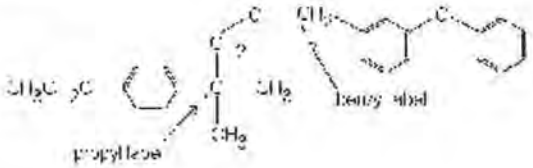
Section A6.2/01 Metabolism studies in mammals

Annex Point IIA-VI.6.2 **Rat**

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (1985a): The biokinetics and metabolism of ^{14}C-ethofenprox in the rat; [redacted] unpublished report no. [redacted]MTC 68/84610; August 01, 1985 (re-issued with amendments October 24, 1985). Dates of work: May 06, 1983 - November 30, 1983 (in life phase).	
1.2	**Data protection**	Yes	
1.2.1	Data owner	[redacted] Mitsui Chemicals Agro, Inc.	
1.2.2	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I.	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes OECD guideline no. 417 (1984)	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Etofenprox	
3.1.1	Lot/Batch number	Batch no. ST-103	
3.1.2	Specification	Deviating from specification given in section 2 as follows	X
3.1.3	Description	No information in the report	
3.1.4	Purity	Not specified in report	
3.1.5	Stability	No information in the report	
3.1.6	Radiolabelling	1:1 radioactivity mixture of [^{14}C]-etofenprox radiolabelled on either side of the ether linkage, [1-^{14}C-propyl]-etofenprox (specific activity 15.3Ci/mol, radiochemical purity >99% by TLC) and [α-^{14}C-benzyl]-etofenprox (specific activity 9.9Ci/mol, radiochemical purity 97% by TLC).	
			
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Sprague-Dawley derived rats (CD strain)	
3.2.3	Source	[redacted]	

Section A6.2/01 **Metabolism studies in mammals**
Annex Point IIA-VI.6.2 **Rat**

3.2.4	Sex	Male and female
3.2.5	Age/weight at study initiation	- Males and non-pregnant females: approximate weight 200g, 5 - 9 week old - Time-mated females: young adults, 236 - 254g body weight.
3.2.6	Number of animals per group	Depends on study element see Table A6_2_01-1.
3.2.7	Control animals	No
3.3	**Administration/ Exposure**	Oral
3.3.1	Type	Gavage
3.3.2	Number of doses	Depends on study element see Table A6_2_01-1.
3.3.3	Dose	Depends on study element see Table A6_2_01-1.
3.3.4	Total volume administered	2.5mL/kg
3.4	**Study elements**	- preliminary study (PRE) - excretion-retention (ER) - biliary excretion (BE) - pharmacokinetics (PK) - quantitative tissue distribution (QTD) -qualitative whole-body autoradiography (QWBA) - placental transfer (PT) - milk transfer (MT)

Section A6.2/01 **Metabolism studies in mammals**
Annex Point IIA-VI.6.2 **Rat**

3.5 Samples and observations

Types and timing of observations and samplings for each study element: see Table A6_2_01-1.

-PRE and RE: preliminary study and excretion-retention study animals were housed in individual metabolism cages for the separate collection of urine and feces, and expired air for preliminary study animals. The cages were rinsed with water after 5 days.

- BE: biliary excretion animals were restrained for the collection of bile into cooled vessels.

- PK: blood samples from plasma concentration animals were withdrawn from the tail vein into heparinised tubes and the cells separated by centrifugation.

- QWBA : qualitative whole body autoradiographs were obtained from 20µm sagittal sections at several levels between the kidneys and the spinal cord.

- QTD and PT: relative tissue concentrations of radioactivity were estimated by visual inspection. The minimum detectable levels of radioactivity in the autoradiographs were 1.0 - 2.7µg equivalents/g wet tissue, or 1.5 - 4.0µg equivalents/g wet tissue for placental transfer animals.

- MT: samples of pup stomach contents for milk transfer analysis were obtained according to the schedule in Table A6_2_01-1 by substitution of up to 3 pups/litter/time point. Naïve pups were introduced into the litters of treated dams and allowed to suckle for one hour before sacrifice and removal of stomach contents. A maternal blood sample was withdrawn at each sampling interval.

All samples were stored at -20°C until analysis. Feces and carcasses were extracted once by homogenisation with methanol, although some fecal samples were further extracted with ethyl acetate. Radioactivity was measured in both extract and residue. Samples of urine, bile, plasma, solvent extracts, expired air trapping fluid, cage washings and other liquid samples were mixed with special scintillant. Tissues, except fat and muscle, were finely minced. Groups of fetuses and placentae were homogenised. Samples of tissues, pup stomach contents, tissue homogenates, whole blood, and fecal and carcass residues were mixed with dry cellulose, combusted, absorbed on to Carbosorb and mixed with scintillant. Radioactivity was measured by liquid scintillation counting, generally for 4 minutes except for plasma and tissue samples that were counted for 10 minutes. Quench correction curves were prepared from radiochemical standards using the external standard channels ratio method. Sample radioactivity of less than twice the background level was considered to be below the level of accurate measurement.

Section A6.2/01 **Metabolism studies in mammals**
Annex Point IIA-VI.6.2 **Rat**

3.6 Analytics

Thin layer chromatography (TLC) was performed on pooled 24-hour interval concentrated fecal extracts, pooled 0 - 72-hour fecal extracts, concentrated bile samples incubated with β-glucuronidase/sulphatase enzyme, methanol-extracts of liver samples incubated with β-glucuronidase, and concentrated 0 - 8 and 8 - 24-hour pooled male urine samples incubated with β-glucuronidase/sulphatase enzyme. High performance liquid chromatography (HPLC) was performed on concentrated fat and pup stomach contents extracts, followed by liquid scintillation counting of the eluate fractions. Following preparative TLC on 0 - 48-hour fecal extracts, further clean-up was achieved using semi-preparative HPLC. The isolated metabolites were subjected to mass spectrometry by alternate electron impact / chemical ionisation conditions. Specific metabolite fractions were also subjected to nuclear magnetic resonance (NMR) analysis.

4 RESULTS AND DISCUSSION

4.1 Preliminary study (PRE)

See Table A6_2_01-2.

The preliminary study in 2 animals/sex animals demonstrated that the patterns of excretion were similar after a single oral administration of 30mg/kg [1-^{14}C-propyl]-etofenprox and [α-^{14}C-benzyl]-etofenprox. The excretion patterns were also comparable between the sexes. More than 90% of the administered dose was eliminated in feces and 7.1 - 10.6% in urine. No radioactivity was detected in the expired air traps with [α-^{14}C-benzyl]-etofenprox and only 0.3 and 0.1% administered dose with [1-^{14}C-propyl]-etofenprox in males and females, respectively. Therefore, expired air was not monitored in the main excretion experiment.

4.2 Excretion-retention (ER)

See Table A6_2_01-3.

The routes and rates of excretion of radioactivity after single oral doses of 30 and 180mg/kg were comparable between the sexes and between the dose levels. Fecal excretion was the main route of elimination and accounted for 86.4 - 90.4% administered dose in both sexes at both low and high dose levels. Most fecal elimination occurred within 72 hours of administration. Urinary elimination accounted for 6.3 - 10.7% administered dose in both sexes at low and high dose levels, most of which was eliminated within the first 24 hours after administration. Retention of radioactivity in the body 120 hours after administration was low in both sexes at low and high dose levels and amounted to 3.4 - 4.3% administered dose.

Section A6.2/01
Annex Point IIA-VI.6.2

Metabolism studies in mammals
Rat

4.3 Biliary excretion (BE)

See Table A6_2_01-4.

Biliary excretion at 30mg/kg amounted to 15.2 and 29.6% administered dose in males and females, respectively, whereas 9.9 and 10.3% was excreted in the bile of males and females at 180mg/kg. The rate of biliary excretion was greatest 3 - 15 hours after treatment in both sexes at 30 and 180mg/kg. Based on biliary excretion, the data suggest that the extent of oral absorption at 180mg/kg would be slightly lower than at 30mg/kg in intact animals. Fecal elimination, representing unabsorbed dose, was comparable in males at 30mg/kg and both sexes at 180mg/kg and amounted to 75.2 - 77.8% administered dose, but in females at 30mg/kg fecal elimination was slightly lower at 49.5%. Urinary elimination in both sexes at 30 and 180mg/kg was uniformly low and amounted to 1.3 - 3.3% administered dose. The data from bile duct cannulated animals indicated a greater degree of absorption than indicated by urinary excretion in the intact main study animals. Furthermore, a substantial proportion of the radioactivity in fecal extracts was associated with metabolites (Table A6_2_01-10). Thus, a minimum of 54.1 and 53.3% administered dose was orally absorbed at 30mg/kg and 45.8 and 38.1% dose at 180mg/kg, in males and females, respectively. Based on urinary elimination, carcass residues and fecal metabolites, the extent of oral absorption is likely to be approximately 64 - 68% dose at 30mg/kg and 48 - 58% dose at 180mg/kg. X

4.4 Pharmacokinetics (PK)

See Table A6_2_01-5.

Mean achieved peak plasma concentrations were 5.20 and 5.03µg equivalents/mL at 30mg/kg in males and females, respectively. The corresponding values at 180mg/kg were 17.3 and 16.4µg equivalents/mL, in males and females. Mean peak plasma concentrations occurred 5 hours (range 2 - 7 hours) after administration in males at 30mg/kg and in both sexes treated at 180mg/kg, and after 3 hours in females at 30mg/kg. Peak plasma concentrations declined rapidly until 24 hours and 48 hours after administration at 30 and 180mg/kg, respectively. Thereafter, a slower decline occurred at both dose levels until 192 and 216 hours after administration of 30 and 180mg/kg, respectively, at which times males at 30mg/kg and both sexes at 180mg/kg were below the levels of accurate measurement. In females at 30mg/kg, a mean residual level of 0.13µg equivalents/mL was apparent at 192 hours. The ratios of AUC values for a dose ratio of 6 were 3.3 and 3.8 in males and females, respectively.

See Table A6_2_01-6.

Highest tissue concentrations 120 hours after single doses of 30 or 180mg/kg occurred in the fat, and greatly exceeded the concentrations in the liver, kidneys and muscle. The tissue concentrations relative to dose level in the 4 tissues examined approximately reflected the 6-fold difference in the dose levels evaluated, since the relative concentrations varied between 4.2 (male kidneys) and 8.5 (female fat).

Section A6.2/01 **Metabolism studies in mammals**
Annex Point IIA-VI.6.2 **Rat**

4.5	**Quantitative tissue distribution (QTD)**	See Table A6_2_01-7. Following 7 daily oral doses, tissue concentrations were highest in all tissues of both sexes 4 hours after the last dose, at which time adrenal glands, fat, G. I. tract, kidneys, liver, lungs, pancreas, thymus, thyroid glands and ovaries showed higher concentrations than in plasma. Other than the G. I. tract with contents, the highest concentrations occurred in fat (94.2 / 101µg equivalents/g, in males / females), adrenal glands (41.4 / 43.4µg equivalents/g, in males / females), liver (30.5 / 22.3µg equivalents/g, in males / females), pancreas (25.1 / 30.8µg equivalents/g, in males / females), ovaries (23.9µg equivalents/g), and thyroid gland (18.7 / 12.9µg equivalents/g, in males / females). All other tissues showed maximum tissue concentrations at 4 hours ≤ 8.84µg equivalents/g. Tissue concentrations declined rapidly in all tissues except fat and pancreas, in which concentrations declined to 25.0 / 45.2µg equivalents/g, in male / female fat and 8.00 / 12.2µg equivalents/g, in male / female pancreas at 240 hours. Since whole body autoradiography showed pancreas concentrations to be lower than most other tissues, the high levels detected in the quantitative study are considered to be due to contamination of pancreas with contiguous fat. Most other tissues showed a rapid decline in concentration during the first 24 hours after the cessation of treatment followed by a slower decline to 240 hours. Tissues showing higher concentrations at 240 hours were adrenal glands (1.55 / 5.06µg equivalents/g, in males / females), G. I. tract with contents (2.98 / 5.07µg equivalents/g, in males / females), thyroid gland (<1.10 / <1.00µg equivalents/g, in males / females) and ovaries (4.55µg equivalents/g), at which time other tissue concentrations were ≤ 0.67µg equivalents/g. Comparison of liver, kidney, fat and muscle concentrations 120 hours after one dose (Table A6_2_01-6) or 7 daily doses showed that mean radioactivity concentrations were higher after 7 doses by a factor of 2.7 to 5.5, with the exception of female muscle in which the tissue concentration was 13-fold higher.
4.6	**Qualitative whole-body autoradiography (QWBA)**	The results of qualitative whole body autoradiography in male animals were generally consistent with the quantitative findings, with the exception of pancreas. Maximum tissue concentrations occurred 4 hours after the 7th dose and were highest in the G. I. tract, bile ducts and fat with slightly lower levels in the liver. Relatively low concentrations were evident in the other tissues, and specifically in the pancreas. Tissue concentrations declined in all tissues except fat at 24, 48 and 120 hours with the distribution pattern reflecting the excretion pattern of etofenprox and metabolites. After 240 hours, detectable radioactivity was confined to fat and the lower G. I. tract, although the concentration in fat had declined substantially from the 120-hour concentration.

Section A6.2/01 **Metabolism studies in mammals**

Annex Point IIA-VI.6.2 **Rat**

4.7	**Placental transfer (PT)**	See Table A6_2_01-8. The concentrations and rates of decline of radioactivity in the adrenal glands, kidneys, heart and liver of pregnant animals were comparable to those in non-pregnant females (Table A6_2_01-7). Tissue concentrations, including placentae and fetuses, were highest at 4 hours and declined in all tissues thereafter. The rate of decline in mammary gland was slower than in other tissues, and at 120 hours 32.4µg equivalents/g wet weight tissue remained, a tissue concentration similar to that of fat in non-pregnant females. The calculated half-life for mammary gland was 3.5 days assuming first order kinetics. The concentrations in placentae and fetuses at 4 hours were very low relative to plasma concentration and after 120 hours the concentrations were comparable to plasma concentration. Whole body autoradiography of pregnant animals confirmed the results of the quantitative study and the general distribution of radioactivity was comparable to that in male animals.
4.8	**Milk transfer (MT)**	See Table A6_2_01-9. Radioactivity was actively secreted into maternal milk during the treatment period but decreased markedly on cessation of treatment. Mean concentrations in pup stomach contents during treatment were in the range 47.9 to 72.3µg equivalents/g compared with mean maternal plasma concentrations in the range 2.2 to 3.4µg equivalents/mL giving concentration ratios > 20 during treatment. The concentration in pup stomach contents declined rapidly during the first 31 hours after the cessation of treatment. Thereafter, concentrations declined more slowly giving pup stomach contents / maternal plasma concentration ratios of between 4 and 5. Approximately 95% of radioactivity in pup stomach contents was identified as unchanged etofenprox.

Section A6.2/01 **Metabolism studies in mammals**
Annex Point IIA-VI.6.2 **Rat**

4.9 Analytics and radioactive components

See Table A6_2_01-10.

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 was not a significant metabolic process. The fecal extracts resolved into 2 major components and a number of minor components. Unchanged etofenprox was identified by electron impact and chemical ionisation MS as one of the 2 major components. Most unchanged etofenprox was excreted during the first 24 hours after administration and was considered to represent unabsorbed material. The other major component was subsequently resolved into 2 radioactive metabolites. Desethyletofenprox occurred at 19.5 - 25.1% dose, and was identified by electron impact and chemical ionisation MS. Etofenprox hydroxylated in the 4' position of the phenoxybenzyl moiety (7.2 - 13.8% dose) was identified by electron impact and chemical ionisation MS and NMR. None of the other components of fecal extracts was positively identified. Most of the radioactivity in bile was non-mobile on TLC, but enzymatic hydrolysis reduced non-mobility to 5 - 6%. The major radioactive metabolites released by hydrolysis and separated by TLC were desethyletofenprox and etofenprox hydroxylated in the 4' position of the phenoxybenzyl moiety. Four minor hydrolysed bile metabolites corresponded to the minor metabolites of feces. HPLC analysis of fat demonstrated that 94.6 / 93.2% of fat radioactivity corresponded to unchanged etofenprox with minor amounts of desethyletofenprox and etofenprox hydroxylated in the 4' position of the phenoxybenzyl moiety. The major components in liver extracts were unchanged etofenprox (22.5 / 30.3% in males / females) and desethyletofenprox (8.1 / 10.3% in males / females), and 43.3 / 24.1% in males / females non-mobile radioactivity which was considered to represent conjugates. The effect of enzyme hydrolysis was limited to reducing the proportion of non-mobile radioactivity to 31.6 / 18.1% in males / females and to increasing the proportion of desethyletofenprox to 16.4 / 24.8% in males / females. The 4'-hydroxlated derivative of etofenprox was not markedly affected by enzyme incubation of liver. Most of the radioactivity in urine was not mobile during TLC, but enzyme incubation released some non-mobile radioactivity to form 2 unknown metabolites accounting for 1.5 and 2.0% administered dose at 30mg/kg and 0.3 and 1.4% administered dose at 180mg/kg. Only minor amounts of the metabolites desethyletofenprox and the 4'-hydroxylated-ethoxyfenprox were evident in urine and the proportions did not markedly alter on enzyme incubation. There were no apparent sex-related differences in the metabolism of etofenprox in any of the matrices examined.

5 APPLICANT'S SUMMARY AND CONCLUSION

Section A6.2/01
Annex Point IIA-VI.6.2

Metabolism studies in mammals
Rat

5.1	**Materials and methods**	Test guidelines: OECD guideline no. 417 (1984) No deviations from test guidelines. Description of method: biokinetics and metabolism study of etofenprox in the rat, exposure by oral gavage, single dose or repeated doses during 7 or 14 days, use of radiolabelled etofenprox (1:1 mixture of two radiolabel positions), study included the following elements: preliminary study, excretion-retention, biliary excretion, pharmacokinetics, quantitative tissue distribution, qualitative whole-body autoradiography, placental transfer, milk transfer.	
5.2	**Results and discussion**	Low and high dose levels of etofenprox are extensively absorbed from the gastrointestinal tract of male and female rats. Excretion proceeds rapidly, predominantly via the feces, and is almost complete within 5 days of administration. Tissue distribution is extensive after multiple low doses but brain and eye levels are uniformly low relative to blood plasma concentration. Elimination proceeds rapidly from all tissues except body fat which shows a slower elimination with estimated half-lives of approximately 5 and 8.5 days in males and females, respectively. 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, but transfer to milk decreases markedly on cessation of dosing. Two major metabolites of etofenprox in total 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. These metabolites are subsequently eliminated in bile and urine as glucuronide or sulphate conjugates. With the exception of a slightly lower degree of oral absorption at high dose levels, the biokinetics of etofenprox are not influenced by dose level, dose regimen and sex.	X
5.3	**Conclusion**		
5.3.1	Reliability	1	
5.3.2	Deficiencies	No	

Table A6_2_01-1. Treatment schedule and sampling regime

Study element	Dose (mg/kg)	Number doses (1 dose/day)	Position of radiolabel	No. animals (M + F)	Sampling regime
PRE	30	1	1-^{14}C-propyl	1 + 1	Urine: 0 - 8, 8 - 24, 24 - 48, 48 - 72, 72 - 96, 96 - 120hr Feces: 24-hour intervals for 5 days Expired air: 0 - 48hr
	30	1	α-^{14}C-benzyl	1 + 1	
ER	30	1	1:1 mixture	5 + 5	Urine: 0 - 8, 8 - 24, 24 - 48, 48 - 72, 72 - 96, 96 - 120hr Feces: 24-hour intervals for 5 days Tissues: liver, kidneys, GI tract, muscle, fat
	180	1	1:1 mixture	5 + 5	
BE	30	1	1:1 mixture	3[a] + 3[a]	Bile: 3-hour intervals for 48 hours Urine: 0 - 24, 24 - 48hr Feces: 0 - 48hr Tissues: liver, GI tract
	180	1	1:1 mixture	3[a] + 3[a]	
PK	30	1	1:1 mixture	5 + 5	Blood: pre-dose, 0.25, 0.5, 1, 2, 3, 5, 7, 24, 48, 72, 96, 120, 144, 168, 192 (30mg/kg), 216hr (180mg/kg)
	180	1	1:1 mixture	5 + 5	
QTD	30	7	1:1 mixture	25 + 25	Sacrifice: 5M + 5F killed at 4, 24, 48, 120 and 240hr Tissues: blood, liver, kidneys, heart, lungs, fat, brain, eyes, gonads, spleen, pancreas, muscle, adrenals, thymus, thyroid, GI tract + contents
QWBA	30	7	1:1 mixture	5 + 0	Sacrifice: 1M killed at 4, 24, 48, 120 and 240hr after final dose
		1		1 + 0	Sacrifice: 1M killed at 24hr Qualitative whole body autoradiography
PT	30	7	1:1 mixture	0 + 10[b]	Sacrifice: 2F killed at 4, 24, 48, 72 and 120hr after final dose Tissues: blood, liver, kidneys, heart, adrenal glands, placentae, fetuses, mammary gland
				0 + 5[b]	Sacrifice: 1F killed at 4, 24, 48, 72 and 120hr for qualitative whole body autoradiography
MT	30	14	1:1 mixture	0 + 3[c] 0 + 4[d]	Sacrifice: 1-3 pups/dam 7hrs after 9th, 11th and 14th doses, and 1, 2, 3, 5 and 7 days after 14th dose Pup stomach contents for metabolite profiling Maternal plasma: 7hrs after 9th, 11th and 14th doses, and 1, 2, 3, 5 and 7 days after 14th dose

[a] restrained animals surgically prepared with bile duct cannulae; [b] pregnant females on day 10 of gestation at first dose; [c] pregnant females on day 18 of gestation at first dose; [d] untreated females at day 18 of gestation for provision of naïve pups; PRE preliminary study; ER excretion-retention; BE biliary excretion; PK pharmacokinetics; QTD quantitative tissue distribution; QWBA qualitative whole-body autoradiography; PT placental transfer; MT milk transfer

Table A6_2_01-2. Total excretion of radioactivity 120 hours[a] after a single oral dose of 30mg/kg [^{14}C]-etofenprox (preliminary study)

Matrix	% administered dose			
	[1-^{14}C-propyl]-etofenprox		[α-^{14}C-benzyl]-etofenprox	
	Male	Female	Male	Female
Urine	10.58	7.89	7.46	7.04
Cagewash	0.06	0.20	0.03	0.05
Feces	92.6	94.1	90.1	91.0
Expired air [a]	0.25	0.1	< 0.08	< 0.08
Total	103.5	102.3	97.6	98.1

[a] 0 - 48 hours only

Table A6_2_01-3. Mean excretion of radioactivity after a single oral dose of 30 or 180mg/kg [^{14}C]-etofenprox (main study).

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

[a] including contents

Table A6_2_01-4. Mean excretion of radioactivity after a single oral dose of 30 or 180mg/kg etofenprox in bile duct cannulated animals (biliary excretion study).

Matrix	Time (hrs post-dose)	% administered dose			
		30mg/kg		180mg/kg	
		Male	Female	Male	Female
Urine[a]	0 - 48	2.0	3.3	1.4	1.3
Bile	0 - 48	15.2	29.6	9.9	10.3
Feces	0 - 48	75.9	49.5	77.8	75.2
Carcass	48	2.8	5.7	3.0	1.5
Liver	48	0.05	0.2	0.2	0.04
G. I. tract[b]	48	1.5	9.1	3.3	14.4
Total	48	97.5	97.4	95.6	102.7

[a] including cagewash; [b] including contents

Table A6_2_01-5. Mean plasma concentration of radioactivity and AUC values after a single oral dose of 30 or 180mg/kg [^{14}C]-etofenprox (main study)

Time (hrs post-dose)	**Mean plasma concentration (µg equivalents/mL)**			
	30mg/kg		**180mg/kg**	
	Male	**Female**	**Male**	**Female**
0.25	0.27	0.27	0.29	0.33
0.5	0.94	0.89	1.55	1.30
1	2.69	2.46	4.50	3.61
2	4.78	4.66	11.9	9.19
3	5.13	5.03	15.5	14.0
5	5.20	4.40	17.3	16.4
7	4.63	3.50	15.6	13.6
24	0.63	0.45	2.33	3.22
48	0.20	0.16	0.65	0.81
72	0.09	0.09	0.36	0.48
96	0.06	0.08	0.21	0.34
120	0.06[a]	0.09	0.20	0.26
144	0.05[a]	0.15	0.18	0.24
168	< 0.05	0.06	0.19[a]	0.17
192	< 0.05	0.13	-	-
216	-	-	< 0.14	< 0.15
AUC (µg.hr/mL)	93	83	308	315

- not sampled; [a] mean calculated based on assumption that one value below limit of accurate detection was equal to the limit

Table A6_2_01-6. Mean tissue concentration of radioactivity 120 hours after a single oral dose of 30 or 180mg/kg [^{14}C]-etofenprox (pharmacokinetic study).

Tissue	**Mean tissue concentration (µg equivalents/g wet weight)**			
	30mg/kg		**180mg/kg**	
	Male	**Female**	**Male**	**Female**
Liver	0.34	0.33	1.50	1.71
Kidneys	0.13	0.16	0.55	0.84
Muscle	0.04[a]	0.05[a]	0.23	0.35
Fat	16.6	11.1	90.2	94.0

[a] mean calculated based on assumption that one value below limit of accurate detection was equal to the limit

Table A6_2_01-7. Mean tissue concentrations after 7 daily doses of 30mg/kg [^{14}C]-etofenprox (quantitative tissue distribution study).

Tissue	Mean tissue concentration (µg equivalents/g wet weight) at (hours after 7th dose):									
	Males					Females				
	4hr	24hr	48hr	120hr	240hr	4hr	24hr	48hr	120hr	240hr
Adrenals	41.4	13.1	5.21	2.94	1.55	43.4	13.0	12.0	5.13	5.06
Brain	2.77	0.23	0.19	0.10	0.06	2.17	0.30	0.20	0.12	0.09
Eyes	1.54	0.24	0.15[b]	0.09[b]	< 0.06	1.06	0.37	0.22	0.17	0.07[b]
Fat	94.2	81.1	78.4	45.0	25.0	101	88.7	86.3	61.0	45.2
G. I. tract[a]	271	53.0	17.3	9.28	2.98	443	146	38.7	10.5	5.07
Heart	5.00	0.58	0.43	0.24	0.12	4.79	0.88	0.54	0.32	0.18
Kidneys	8.84	1.72	1.31	0.39	0.22	8.71	2.95	1.50	0.83	0.58
Liver	30.5	6.39	3.20	1.45	0.53	22.3	5.33	3.11	1.59	0.55
Lungs	8.20	2.51	2.54	1.25	0.53	7.27	4.51	3.54	1.74	0.67
Muscle	3.50	0.56	2.02	0.21	0.46	2.60	0.64	0.92	0.67	0.52
Ovaries	-	-	-	-	-	23.9	14.4	9.92	5.63	4.55
Pancreas	25.1	22.4	25.0	11.9	8.00	30.8	18.2	15.6	10.8	12.2
Plasma	6.93	0.63	0.34	0.14	0.07	5.39	0.80	0.39	0.17	0.06
Spleen	2.66	0.65	0.84	0.28	0.16	3.14	1.38	1.37	0.53	0.39
Testes	2.79	0.50	0.35	0.26	0.16	-	-	-	-	-
Thymus	7.46	1.84	1.47	0.83	0.44	6.51	4.59	3.72	1.12	0.65
Thyroid	18.7	5.43	4.11	1.67[b]	< 1.10	12.9	8.89	4.72	2.78	< 1.00
Whole blood	4.31	0.44	0.24	0.12	0.07	3.34	0.50	0.25	0.12	0.06

[a] including contents; [b] mean calculated based on assumption that values below limit of accurate detection were equal to the limit

Table A6_2_01-8. Mean tissue concentrations of radioactivity in pregnant animals after 7 oral doses of 30mg/kg [^{14}C]-etofenprox (placental transfer study).

Tissue	Mean tissue concentration (µg equivalents/g wet weight) at (hours after 7th dose):				
	4	24	48	72	120
Adrenal glands	61.5	11.3	12.2	7.88	5.74
Kidneys	9.68	1.99	1.58	1.24	1.09
Heart	8.03	0.88	1.01	0.52	0.49
Liver	27.2	4.57	3.01	2.26	1.55
Mammary gland	87.4	61.9	56.5	43.2	32.4
Fetuses (group 1)	1.72	0.16	0.12	0.14	0.10
Fetuses (group 2)	1.61	0.17	0.19	0.15	0.14
Placentae (group 1)	4.61	0.62	0.37	0.27	0.17
Placentae (group 2)	4.81	0.59	0.37	0.27	0.17
Plasma (µg/mL)	7.05	0.87	0.36	0.25	0.10

Table A6_2_01-9. Mean concentrations of radioactivity in lactating animals and suckling pups after multiple oral doses of 30mg/kg [^{14}C]-etofenprox (milk transfer study).

No. of doses	**Sampling time (days + hours) after final dose**	**Mean concentration (µg equivalents/g or mL) in:**	
		Pup stomach contents	**Maternal plasma**
9	0 + 7	72.3	3.4
11	0 + 7	60.5	2.5
14	0 + 7	47.9	2.2
14	1 + 7	1.7	0.4
14	2 + 7	0.8	0.2
14	3 + 7	1.2	0.2
14	5 + 7	0.8	< 0.2
14	7 + 7	0.3	< 0.2

Table A6_2_01-10. Proportions of radioactive components in various matrices 72 hours[b] after oral administration of 30 or 180mg/kg [^{14}C]-etofenprox.

Matrix	**Component number**	**Proportions of radioactive components (% dose):**			
		30mg/kg		**180mg/kg**	
		Male	**Female**	**Male**	**Female**
Feces	1 (etofenprox)	6.6	14.0	22.6	29.0
	2	1.7	0.9	1.4	0.8
	-	0.2	0.4	0.5	0.4
	3A (DE)	19.5	25.1	23.2	20.6
	3B (4'-OH)	13.2	13.8	7.2	8.1
	4	2.1	1.6	0.5	0.3
	5	1.4	0.4	0.7	0.5
	6	2.3	1.0	0.9	0.2
	-	8.2	5.8	9.3	5.2
	-	5.5	4.3	2.1	2.0
	Total metabolites	54.1	53.3	45.8	38.1
Deconjugated bile[a]	2	7.2	6.3	-	-
	3A (DE), 3B (4'-OH)	70.8	68.9	-	-
	4	5.2	4.1	-	-
	5	2.7	1.4	-	-
	6	2.4	1.9	-	-
	7	1.5	1.0	-	-
	8	1.3	1.3	-	-
	-	*	0.3	-	-
	9	0.8	0.8	-	-
	-	*	2.1	-	-
	-	0.9	3.1	-	-
	-	2.1	2.8	-	-
	non-mobile	5.1	6.0	-	-
Fat[a]	1	94.6	93.2	-	-
	3A (DE), 3B (4'-OH)	2.5	2.5	-	-
	not eluted	2.8	4.3	-	-

* not detected (<0.3 - <0.5); [a] % radioactivity in sample; [b] 0 - 24 hour sample for urine

Table A6_2_01-10.continued: Proportions of radioactive components in various matrices 72 hours[b] after oral administration of 30 or 180mg/kg [^{14}C]-etofenprox.

Matrix	**Component number**	**Proportions of radioactive components (% dose):**			
		30mg/kg		**180mg/kg**	
		Male	**Female**	**Male**	**Female**
Liver [a]		Liver extract		Hydrolysed liver extract	
	-	0.2	0.3	0.1	0.2
	1	22.5	30.3	14.8	32.9
	3A	8.1	10.3	16.4	24.8
	3B	3.6	4.0	6.1	3.4
	4 - 8	1.9	1.4	6.2	1.6
	9	4.2	2.8	5.1	3.7
	-	0.4	0.7	0.4	1.5
	non-mobile	43.3	24.1	31.6	18.1
	not extracted	15.8	26.0	19.4	13.8
Urine [b]		Urine	Hydrolysed urine	Urine	Hydrolysed urine
	-		0.2	0.1	0.2
	3A (DE), 3B (4'-OH)		0.6	1.8	1.7
	-	0.6	0.2		0.2
	8		1.5	0.1	0.3
	9		2.0		1.4
	-	0.9	1.1	0.4	0.7
	non-mobile	7.3	3.2	3.6	1.6

* not detected (<0.3 - <0.5); [a] % radioactivity in sample; [b] 0 - 24 hour sample for urine

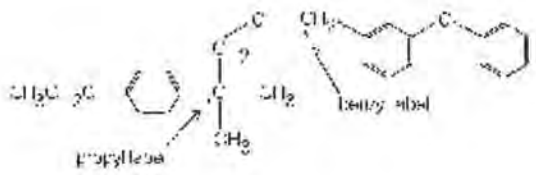
Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	27.05.2005
Materials and methods	**3.1.3 Description** and **3.1.4. Purity** ST-103 contained the same main impurities as later production batches (e.g. 5 batch analysis) at comparable percentages. The concentration of etofenprox is with 96,3 % lower than in the 5 batch analysis. However radiolabelled substance was added and the purity is considered less important for kinetic studies. Therefore the present study is acceptable also with regard to specification of the substance.
Conclusion	Agree with applicant's version
Reliability	1
Acceptability	acceptable
Remarks	**4.3. Bilary excretion** Based on these results the oral absorption factor is estimated as 65% of the applied dose with 30mg/kg bw. **5.2. Results and Discussion** Since elimination from body fat occurs with half-lives of approximately 5 and 8.5 days in males and females, respectively, etofenprox shows a potential for accumulation.
	COMMENTS FROM...
Date	
Results and discussion	
Conclusion	
Reliability	
Acceptability	
Remarks	

LKC UK Ltd.

Section A6.2/06 Percutaneous absorption (*in vivo* test)

Annex Point IIA-VI.6.2 **Rat**

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (1999); Dermal absorption of ^{14}C-Etofenprox in male rats (preliminary and definitive phases); [redacted] unpublished report no. [redacted] 6648-135; January 04, 1999. Dates of work: December 04, 1997 - January 10, 1998.	
1.2	**Data protection**	Yes	
1.2.1	Data owner	[redacted] Mitsui Chemicals Agro,	
1.2.2	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I.	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes OECD guideline no. 424 (1997); US-EPA FIFRA, 40 CFR 158, subdivision F, series 85-3; Japan MAFF, 59 NohSan notification no. 4200	X
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Etofenprox	
3.1.1	Lot/Batch number	Batch no. 9904	
3.1.2	Specification	Deviating from specification given in section 2 as follows	
3.1.3	Description	No information in the report	X
3.1.4	Purity	99.99%	
3.1.5	Stability	No information in the report	
3.1.6	Radiolabelling	^{14}C: batch no. MRH/MTC277/29, radiochemical purity > 99%, benzyl label only.	



3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Sprague-Dawley strain	

Section A6.2/06 Percutaneous absorption (*in vivo* test)

Annex Point IIA-VI.6.2 **Rat**

3.2.3	Source	[redacted]	
3.2.4	Sex	Male	
3.2.5	Age/weight at study initiation	body weight range 159 - 198g	
3.2.6	Number of animals per group	Preliminary test: one group of 4 rats Definitive study: 3 groups of 16 rats	
3.2.7	Control animals	Yes	
3.3	**Administration/ Exposure**	Dermal, non-occlusive	
3.3.1	Preparation of test site	Shaved and water-washed	
3.3.2	Concentration of test substance	5, 50 and 250µg/cm^2, equivalent to analytically-determined dose levels of 5, 59 and 184µg/cm^2 (0.061, 0.741 and 2.30mg/animal, respectively).	
3.3.3	Specific activity of test substance	9.91mCi/mmol	
3.3.4	Volume applied	100µL by even spreading across the entire area using glass spreaders	
3.3.5	Size of test site	12.5cm^2	
3.3.6	Exposure period	96 hours, with interim kills of 4 rats per group after 1, 10 and 24 hours exposure.	X
3.3.7	Samples	Urine and feces - Individual cumulative urine and feces from all animals killed at 1, 10 and 24 hours were collected from the start of treatment to necropsy, and at 24 hour intervals from the start of treatment for animals killed at 96 hours. - Residual urine in the bladder after necropsy was collected and added to the cumulative samples. Blood Skin The skin from the application site, together with the plastic enclosure, was excised and retained. Residual carcass Non-biological samples were also retained for analysis of radioactivity: - Glass spreader rinse (ca. 5mL acetonitrile (ACN)/water) and gauze wipes - Skin wash materials (2% soapy water, and absorbent materials in 100mL ACN) - Non-occlusive filter papers used to seal treatment chambers - Cage wash solution - Cage wipe gauze in ACN/water	
3.3.9	Observation	- morbidity/mortality: twice daily - clinical signs: daily - body weights: recorded at randomisation and prior to skin site preparation	

Section A6.2/06 **Percutaneous absorption (*in vivo* test)**

Annex Point IIA-VI.6.2 **Rat**

3.3.10	Analytics	Duplicate pre-dose and post-dose aliquots of the dosing suspensions were analysed for radioactivity levels, homogeneity and radiochemical purity. Stability was also determined pre-dose. Analyses were performed by liquid scintillation counting for 5 minutes or 100,000 counts, with automatic conversion to dpm, using the external standardisation technique and an instrument-stored quench curve generated from quenched standards. Radioanalysis procedures were validated by analysis of selected control blood, urine, feces and skin fortified with known amounts of etofenprox. The concentration of radioactivity was reported as not detectable (ND) when radioactivity in the sample was less than twice background.
3.3.11	Other information	The animals were anesthetised with ketamine and the application site skin was washed after 10 hours contact for all groups, except those killed after 1 hour which were washed immediately before necropsy. Animals were subjected to necropsy under halothane anesthesia and exsanguinated by cardiac puncture and 2 to 10mL blood collected into heparin.

4 RESULTS AND DISCUSSION

4.1	**Stability / Homogeneity**	2D-TLC confirmed the radiochemical purity of ^{14}C-etofenprox as > 98% and confirmed the stability of the pre-dose formulations for at least 24 hours. Homogeneity analyses revealed the dose suspensions to be homogeneous, but that the mean concentration of radioactivity at the highest concentration was 71.35% of the expected value due to adherence of test material to the glass vial. Since both the labelled and unlabelled material had been co-dissolved in ethyl ether prior to transfer to CMC, it was assumed that equal amounts of labelled and unlabelled material had adhered to the glass. Validation of the radioanalytical procedures gave a mean recovery value of 101% from several fortified matrices.
4.2	**Toxic effects, clinical signs**	There were no clinical signs of an adverse reaction to treatment in any of the groups, although one animal scheduled to be sacrificed at 96 hours was noted not to be breathing at the 10 hour skin wash. The animal was killed at the 10-hour time point and an animal scheduled to be killed at 10 hours was maintained for 96 hours.
4.3	**Dermal irritation**	No effects

Section A6.2/06 **Percutaneous absorption (*in vivo* test)**

Annex Point IIA-VI.6.2 **Rat**

4.4 Recovery of labelled compound

See Table A6_2_06-1.

The mean recoveries of radioactivity at all necropsy times were in the ranges 92.6 - 96.9%, 87.3 - 105% and 103 - 134% applied dose, in order of ascending applied dose. The overall mean recovery at 250µg/cm^2 was greater than expected at 122%, possibly as a result of the low concentration of radioactivity in the dose preparation and the subsequent use of a dose correction factor. The absorption data for this group were also normalized to account for greater than expected recovery, but the calculations produced only small decreases in the extent of direct absorption. The greatest overall (direct + indirect) dermal absorption (33.0% applied dose) occurred at 96 hours in the 250µg/cm^2 group.

4.5 Percutaneous absorption

Direct dermal absorption (Table A6_2_06-2)

Direst dermal absorption was very low after 1 hour at all applied concentrations (< 0.005 - 0.03% applied dose). Generally, the extent of direct dermal absorption at 10 - 96 hours was also low, but increased with the duration of the sampling time suggesting continuing movement of the indirectly absorbed etofenprox into the systemic circulation after the skin wash at 10 hours. During this period, direct dermal absorption was within the ranges 0.58 - 5.07%, 0.78 - 6.10% and 0.74 - 6.57% applied dose, in order of ascending applied concentration. Direct dermal absorption was highest (6.57%) at 96 hours in the 250µg/cm^2 group, but the extent of direct absorption was not markedly influenced by the applied dose. The extent of direct dermal absorption increased with increasing dermal contact time (1-hour *vs.* 10-hour contact times).

Indirect dermal absorption (Table A6_2_06-3).

The author defined indirect absorption as the sum of the direct absorption and the amount detected in/on the skin after washing. However, for clarity, the reviewer has defined, and presented the indirect absorption data, as the amount of radioactivity remaining in the washed application site skin only. The greatest amount of radioactivity (79.7 - 101% applied dose) was found in the skin washes in all treatment groupsIndirect absorption of etofenprox was substantially higher than direct absorption in all treatment groups and showed some correlation with applied dose since it was greatest in the group treated at 250µg/cm^2. Indirect absorption was greatest in animals killed after 10 or 24 hours, but declined at 96 hours in all treatment groups.

4.6 Urinary and fecal eliminatiom

In the animals killed at 96 hours, urinary elimination of radioactivity peaked in all groups at 0 - 24 hours and later, at 24 - 48 hours, in the feces. Thereafter, both urinary and fecal elimination of radioactivity declined in all groups (Table A6_2_06-4).