5.11 ETOFENPROX (184)

TOXICOLOGY

Etofenprox is the International Organization for Standardization (ISO)–approved name for 2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzyl ether (International Union of Pure and Applied Chemistry), with the Chemical Abstracts Service No. 80844-07-1.

Similar to pyrethroids, etofenprox acts on ion channels of the insect nervous system. It is used as an insecticide with contact and stomach action against many pests on a broad range of crops.

Etofenprox was evaluated previously by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) in 1993, when an acceptable daily intake (ADI) of 0–0.03 mg/kg body weight (bw) was established based on a carcinogenicity study in mice and using a 100-fold safety factor. It was reviewed at the present Meeting as part of the periodic review programme of the Codex Committee on Pesticide Residues. Since the last review by JMPR, the following new studies of etofenprox have been submitted: an absorption, distribution, metabolism and excretion study in male rats, acute oral and dermal toxicity studies in rats, a 4-week dermal toxicity study in rabbits, a 4-week dietary mechanistic study on thyroid function and hepatic microsomal enzyme induction in rats, a developmental toxicity study in rabbits, acute and subacute (90-day) neurotoxicity studies in rats, a developmental neurotoxicity study in rats and 4-week immunotoxicity studies in mice and rats. In addition, oral and dermal acute toxicity studies, a 13-week toxicity study and genotoxicity studies of a plant metabolite of etofenprox, 2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzoate (α-CO), were conducted.

All critical studies complied with good laboratory practice.

Biochemical aspects

In rats given a single oral dose of 1:1 [^{14}C]etofenprox mixtures labelled on either side of the ether linkage, absorption was rapid but incomplete, to the extent of approximately 64–68% of the dose at 30 mg/kg bw and 48–58% of the dose at 180 mg/kg bw. The time to reach maximum concentrations in plasma was 3–5 hours. Distribution to the tissues was extensive after 7 daily doses of 30 mg/kg bw, with tissue concentrations reaching their maxima 4 hours after the last dose. Highest concentrations were found in fat, adrenals, liver, ovaries and thyroid. Apart from the gastrointestinal tract, which contained much unabsorbed material, concentrations elsewhere, including brain, were low. Etofenprox crossed the placenta to the fetus, but placental and fetal concentrations were low relative to maternal plasma concentrations, and elimination from the placenta and the fetus was rapid. Unmetabolized etofenprox was secreted into maternal milk. Depletion from the tissues was rapid except from fat, in which estimated half-lives were approximately 5 and 8.5 days in males and females, respectively. In rats with bile duct cannulae, radiolabelled etofenprox administered at 30 mg/kg bw to males and 180 mg/kg bw to males and females was rapidly eliminated, with almost 90% combined excreted in the bile (10–15%) and faeces (75–78%) and approximately 1–3% in the urine within 48 hours; females receiving 30 mg/kg bw eliminated the radioactivity differently, with 30%, 50% and 3% appearing in bile, faeces and urine, respectively, in 0–48 hours. This difference was not observed in rats without cannulae. The routes and extent of elimination of etofenprox and its metabolites were independent of the dose level and the sex of the rats. No unchanged etofenprox or a key primary metabolite, α-CO, has been recovered from urine.

In dogs given the 1:1 [^{14}C]etofenprox mixture orally, the rate of absorption of radioactivity was quite variable, with maximum plasma concentrations occurring 0.25–6 hours after dosing. The extent of absorption was approximately 40–50%. This was followed by approximately 90% faecal elimination (excretion and non-absorbed etofenprox combined) and 10% urinary excretion, almost all occurring within 24 hours. Very high concentrations were found in bile, none of which was due to parent etofenprox.

In rats, no unchanged etofenprox was found in urine, whereas in faeces, it was one of the major components, most likely due to unabsorbed material. Cleavage of the etofenprox molecule did not appear to be a significant metabolic process, although a significant number of radiolabelled entities were not identified. In faeces, desethyletofenprox occurred at 19.5–25.1% of the dose, and etofenprox hydroxylated in the 4′ position of the phenoxybenzyl moiety occurred at 7.2–13.8% of the dose. Other primary metabolic steps involved oxidation of carbons on either side of the ether linkage, one product of which, α-CO, is a major metabolite or degradation product isolated during plant and soil and photodegradation studies. These carbonyls appear to be rapidly metabolized to scission products, some of which (m-PB-acid, m-PB-alc and 4 -OH-PB) are shared with other pesticides. Glucuronide and sulfate conjugates were also found.

Toxicological data

The acute oral and dermal median lethal dose (LD_{50}) values in rats are both greater than 2000 mg/kg bw. The acute oral LD_{50} value in the dog is greater than 5000 mg/kg bw. The acute 4-hour inhalation median lethal concentration (LC_{50}) value in the rat is greater than 5.88 mg/L. Etofenprox was not irritating to rabbit skin or rabbit eyes. Etofenprox was not a skin sensitizer in the guinea-pig maximization test.

The liver is a common target for the toxicity of etofenprox in mouse, rat and dog. The liver, kidneys and haemolymphoreticular system were identified as target organs in the mouse. The no-observed-adverse-effect level (NOAEL) in a 90-day toxicity study in mice was 3000 ppm (equal to 375 mg/kg bw per day), based on increased mortality and the occurrence of reduced body weight gain and feed consumption, increased water consumption, minor haematological effects, histopathological alterations indicative of kidney damage and minor changes in liver at 15 000 ppm (equal to 1975 mg/kg bw per day).

The liver and thyroid gland were the target organs in the rat. In a 90-day toxicity study in rats, the NOAEL was 300 ppm (equal to 20 mg/kg bw per day), based on liver toxicity (hepatocyte enlargement and clinical evidence of liver dysfunction affecting fat metabolism and the synthesis of blood clotting factors) and thyroid toxicity (an increase in the number of thyroid microfollicles and reduced levels of circulating thyroxine [T_4]) at 1800 ppm (equal to 120 mg/kg bw per day).

The NOAEL in a 1-year dog study was 1000 ppm (equal to 32.2 mg/kg bw per day), based on hepatotoxicity, including increased liver weights in both sexes and histopathological alterations in females at 10 000 ppm (equal to 339 mg/kg bw per day). The hepatic effects were reversible.

The carcinogenic potential of etofenprox was studied in mice and rats. In the 2-year toxicity and carcinogenicity study in mice, the NOAEL for non-neoplastic effects was 30 ppm (equal to 3.1 mg/kg bw per day), based on an increased incidence of dilated/basophilic renal cortical tubules at 100 ppm (equal to 10.4 mg/kg bw per day). At higher doses, the renal lesions were characterized as an increased incidence of cortical scarring and pale coloration, organ enlargement, dilated or cystic Bowman's capsules, dilated medullary tubules, focal loss of tubules, prominent interstitial papillary tissue and papillary mineralization. There were also small increases in reticulum cell sarcomas in female mice at 100 ppm and above. These reticulum cell sarcomas were not considered treatment related because of a lack of a dose–response relationship, and they are common tumours in rats. The combined incidence of renal cortical adenomas and carcinomas was marginally non-statistically significantly increased in males at 700 and 4900 ppm. Nevertheless, these tumours are rare in mice and were slightly above the historical control range. Therefore, they were considered treatment-related tumours. It is plausible that the continuous stimulation by chronic renal toxicity was responsible for renal tumour development. The NOAEL for carcinogenicity in mice was 100 ppm (equal to 10.4 mg/kg bw per day), based on renal cortical tumours at 700 ppm (equal to 75.2 mg/kg bw per day).

In the chronic toxicity and carcinogenicity study in rats, the NOAEL for non-neoplastic effects was 100 ppm (equal to 3.7 mg/kg bw per day), based on an increase in foci or areas of

eosinophilic hepatocytes in males and vacuolated hepatocytes in females and reduced body weight gain in males at 700 ppm (equal to 25.5 mg/kg bw per day). The thyroid follicular cell adenomas and carcinomas combined were statistically significantly increased in females at 4900 ppm. Increased thyroid follicular cell adenomas and carcinomas combined were also observed in males at 4900 ppm, but statistical significance was not achieved. The NOAEL for carcinogenic effects in female rats was 700 ppm (equal to 34.3 mg/kg bw per day), based on an increased incidence of thyroid follicular cell adenomas at 4900 ppm (equal to 249.1 mg/kg bw per day).

A mechanistic study in rats was conducted to clarify the relationship between a primary effect of etofenprox on hepatic microsomal induction and thyroid follicular cell adenoma development. Etofenprox increased uridine diphosphate glucuronosyltransferase (UGT) activity in the liver, which would be expected to increase excretion of T_4 from the blood. Decreased serum T_4 levels were observed with a consequent increase in thyroid stimulating hormone activity, which would be expected to result in follicular cell hyperplasia and, if sustained, tumour development. Rodents are particularly sensitive to the induction of thyroid follicular cell tumours, firstly because of the easy induction of UGT and secondly because of rapid T_4 metabolism in the absence of a specific thyroxine-binding globulin. In other species, this provides a buffering capacity that better controls the dynamic equilibrium of hormones in the pituitary–hypothalamic–thyroid axis.

Based on mode of action analysis for thyroid follicular tumours, the Meeting concluded that these tumours were not relevant for human risk assessment.

The potential genotoxicity of etofenprox was tested in an adequate range of in vitro and in vivo genotoxicity studies. No evidence of genotoxic potential was found.

The Meeting concluded that etofenprox was unlikely to be genotoxic.

On the basis of the absence of genotoxicity, the absence of carcinogenicity in rats by a mode of action relevant to humans and carcinogenicity in mice likely to be secondary to renal toxicity at exposure levels of unlikely human relevance, the Meeting concluded that etofenprox is unlikely to pose a carcinogenic risk to humans.

No reproductive toxicity was observed in two multigeneration reproduction studies in rats at doses up to 4900 ppm (equal to 246 mg/kg bw per day) when administered through the diet and 5000 mg/kg bw per day when administered by gavage. The NOAEL for parental toxicity was 700 ppm (equal to 37 mg/kg bw per day), based on the occurrence of reduced weight gain, increased kidney, liver and thyroid weights and histopathological findings in the liver, kidneys and thyroid at 4900 ppm (equal to 246 mg/kg bw per day). The NOAEL for offspring toxicity was 700 ppm (equal to 37 mg/kg bw per day), based on the occurrence of increased kidney weights in females in the F_{2b} generation at 4900 ppm (equal to 246 mg/kg bw per day).

In a modified developmental toxicity study, rats were administered etofenprox by gavage during gestation days 6–17. The maternal toxicity NOAEL in rats was 250 mg/kg bw per day, based on decreased body weights and clinical signs at the lowest-observed-adverse-effect level (LOAEL) of 5000 mg/kg bw per day, the highest dose tested. The developmental NOAEL was 5000 mg/kg bw per day, the highest dose tested.

In two developmental toxicity studies conducted in rabbits, the overall NOAEL for developmental toxicity and maternal toxicity was 100 mg/kg bw per day, based on the occurrence of reduced maternal body weight gain and feed consumption on gestation day 6 (first day of dosing), mortality and increased post-implantation loss and intrauterine growth retardation at the high dose of 250 mg/kg bw per day.

The Meeting concluded that etofenprox is not teratogenic in rats or rabbits.

No evidence of neurotoxicity was observed in an acute neurotoxicity study in rats at doses up to 2000 mg/kg bw. No evidence of systemic toxicity, including neurotoxicity, was observed in a 13-week neurotoxicity study in rats at doses up to 10 000 ppm (equal to 604 mg/kg bw per day). In a developmental neurotoxicity study in rats, the NOAEL for maternal toxicity was 700 ppm (equal to

57 mg/kg bw per day), based on an increased incidence of rearing behaviour in the functional observational battery at 2100 ppm (equal to 169 mg/kg bw per day). The NOAEL for offspring toxicity was 250 ppm (equal to 28.4 mg/kg bw per day), based on eye abnormalities (increased incidences of dark or opaque and/or enlarged, prominent eyes and a subcutaneous haemorrhagic lesion) in both sexes seen at 700 ppm (equal to 57 mg/kg bw per day). The ocular toxicity seen in these studies is the outcome of the subcutaneous haemorrhage. There was no evidence of neurotoxicity in the offspring.

In immunotoxicity studies in mice and rats, no evidence of immunotoxicity was observed at doses up to 1116 and 1053 mg/kg bw per day in mice and rats, respectively.

Toxicological data on metabolite

Toxicity studies of a plant metabolite of etofenprox, α-CO, were conducted. α-CO has low acute oral and dermal toxicity in the rat. The LD_{50} values are greater than 5000 mg/kg bw and greater than 2000 mg/kg bw for oral and dermal toxicity, respectively.

The lowest NOAEL for α-CO in 4-week and 13-week dietary studies in rats was 54 mg/kg bw per day, based on the effects on the liver, kidney and thyroid in a 13-week dietary study at 10 000 ppm (equal to 805 mg/kg bw per day). The toxicological profile of α-CO is similar to that of etofenprox, but its toxicity is lower than that of the parent (20 mg/kg bw per day). α-CO is not genotoxic.

There were no reports of adverse health effects in manufacturing plant personnel. Also, there were no reports of poisoning with etofenprox.

The Meeting concluded that the existing database on etofenprox was adequate to characterize the potential risk to fetuses, infants and children.

Toxicological evaluation

The Meeting confirmed the ADI of 0–0.03 mg/kg bw on the basis of the NOAEL of 3.1 mg/kg bw per day from the 108-week carcinogenicity study in mice based on renal toxicity (an increased incidence of dilated and basophilic renal tubules) at 10.4 mg/kg bw per day and using a safety factor of 100. The ADI was supported by the NOAEL of 3.7 mg/kg bw per day from the 2-year toxicity and carcinogenicity study in rats, based on an increase in foci or areas of eosinophilic hepatocytes in males and vacuolated hepatocytes in females and reduced body weight gain in males at 25.5 mg/kg bw per day. This ADI is adequately protective of renal cortical tumours occurring at higher doses in mice.

The Meeting established an acute reference dose (ARfD) of 1 mg/kg bw on the basis of the overall NOAEL of 100 mg/kg bw per day from the two developmental toxicity studies in rabbits, based on the occurrence of reduced maternal body weight gain and feed consumption during the early dosing period (gestation day 6) and increased post-implantation loss, which could occur after a single exposure, and using a safety factor of 100.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Two-year study of toxicity and carcinogenicity[a]	Toxicity	30 ppm, equal to 3.1 mg/kg bw per day	100 ppm, equal to 10.4 mg/kg bw per day
		Carcinogenicity	100 ppm, equal to 10.4 mg/kg bw per	700 ppm, equal to 75.2 mg/kg bw per

Species	Study	Effect	NOAEL	LOAEL
			day	day
Rat	Two-year study of toxicity and carcinogenicity[a]	Toxicity	100 ppm, equal to 3.7 mg/kg bw per day	700 ppm, equal to 25.5 mg/kg bw per day
		Carcinogenicity	700 ppm, equal to 34.3 mg/kg bw per day (females)	4900 ppm, equal to 249.1 mg/kg bw per day (females)
	Multigeneration study of reproductive toxicity[a]	Parental toxicity	700 ppm, equal to 37 mg/kg bw per day	4900 ppm, equal to 246 mg/kg bw per day
		Offspring toxicity	700 ppm, equal to 37 mg/kg bw per day	4900 ppm, equal to 246 mg/kg bw per day
		Reproductive toxicity	4900 ppm, equal to 246 mg/kg bw per day[b]	—
	Developmental toxicity study[c]	Maternal toxicity	250 mg/kg bw per day	5000 mg/kg bw per day
		Embryo and fetal toxicity	5000 mg/kg bw per day[b]	—
Rabbit	Developmental toxicity studies[c,d]	Maternal toxicity	100 mg/kg bw per day	250 mg/kg bw day
		Embryo and fetal toxicity	100 mg/kg bw per day	250 mg/kg bw day
Dog	One-year studies of toxicity[a,d]	Toxicity	1000 ppm, equal to 32.2 mg/kg bw per day	10 000 ppm, equal to 339 mg/kg bw per day

[a] Dietary administration.

[b] Highest dose tested.

[c] Gavage administration.

[d] Two or more studies combined.

Estimate of acceptable daily intake for humans

0–0.03 mg/kg bw

Estimate of acute reference dose

1 mg/kg bw

Information that would be useful for the continued evaluation of the compound

Results from epidemiological, occupational health and other such observational studies of human exposure

Critical end-points for setting guidance values for exposure to etofenprox

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid but incomplete, ~50%
Dermal absorption	Not available
Distribution	Distributed throughout the body; highest concentrations in fat, adrenals, liver, ovaries and thyroid
Potential for accumulation	None
Rate and extent of excretion	Rapid and extensive
Metabolism in animals	Desethyletofenprox and hydroxylated etofenprox
Toxicologically significant compounds (animals, plants and the environment)	Parent
Acute toxicity	
Rat, LD_{50}, oral	> 2000 mg/kg bw
Rat, LD_{50}, dermal	> 2000 mg/kg bw
Rat, LC_{50}, inhalation	> 5.88 mg/L
Rabbit, skin irritation	Non-irritating
Rabbit, eye irritation	Non-irritating
Guinea-pig, skin sensitization (maximization test)	Not a sensitizer
Short-term studies of toxicity	
Target/critical effect	Liver, reduced body weight
Lowest relevant oral NOAEL	20 mg/kg bw per day (13-week toxicity study in rats)
Lowest relevant dermal NOAEL	1000 mg/kg bw per day (rabbits, highest dose tested)
Lowest relevant inhalation NOAEC	0.21 mg/L (13-week inhalation study in rats)
Genotoxicity	
	Not genotoxic
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Kidney, liver, haematology, body weights
Lowest relevant NOAEL	3.1 mg/kg bw per day (carcinogenicity study in mice)
Carcinogenicity	Unlikely to pose carcinogenic risk to humans at dietary exposure levels
Reproductive toxicity	
Reproduction target/critical effect	Kidney/increased kidney weight
Lowest relevant reproductive NOAEL	246 mg/kg bw per day, the highest dose tested (multigeneration study in rats)
Developmental target/critical effect	Abortions and post-implantation loss
Lowest relevant developmental NOAEL	100 mg/kg bw per day (rabbits)
Neurotoxicity/delayed neurotoxicity	
Acute neurotoxicity	Not neurotoxic (rats)
Subacute neurotoxicity	Not neurotoxic (13-week study in rats)

Neurodevelopmental toxicity	Not neurodevelopmental toxicant (rats)
Immunotoxicity studies	
	Not immunotoxic (rats and mice)
Medical data	
	No adverse effects have been reported
Mechanistic studies	
	Studies on the thyroid axis that demonstrate a tumour mode of action not relevant to humans

Summary

	Value	Study	Safety factor
ADI	0–0.03 mg/kg bw	Two-year carcinogenicity study in mice, supported by the 2-year toxicity and carcinogenicity study in rats	100
ARfD	1 mg/kg bw	Developmental studies in rabbits	100

RESIDUE AND ANALYTICAL ASPECTS

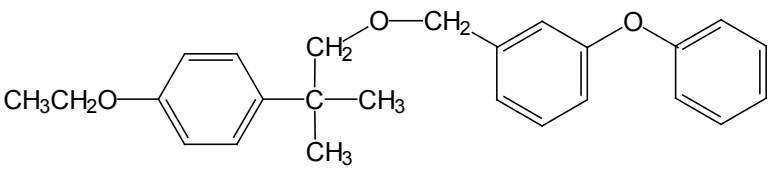
Etofenprox, a pyrethroid-like insecticide, active through contact or ingestion, is effective against a range of agricultural and horticultural insect pests and is also used as an indoor non-food crack and crevice insecticide, a spot treatment for pets, and as an outdoor (fog) treatment to control a variety of flying and crawling insect pests.

Residue and analytical aspects of etofenprox were evaluated by the JMPR in 1993 and the compound was listed in the Periodic Re-Evaluation Program at the Forty-second Session of the CCPR for periodic review by the 2011 JMPR. The most recent toxicological review was in 1993 when an ADI of 0–0.03 mg/kg bw was established for etofenprox. Specifications for etofenprox technical material, emulsifiable concentrate, wettable powder and emulsion (oil-in-water) have been published by FAO in July 2007 (http://www.fao.org/ag/AGP/AGPP/Pesticid/Specs/docs/Pdf/new/Etofenprox07.pdf).

Authorisations exist for the agricultural uses of etofenprox (EC and SC formulations) in Italy, Germany, Brazil and Japan with use in rice in USA being a granular formulation for aerial application.

The manufacturer submitted studies on metabolism, analytical methods, supervised field trials, processing, freezer storage stability, environmental fate in soil and rotational crop residues.

Etofenprox, (2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzyl ether) is virtually insoluble in water (23 µg/L), stable to hydrolysis, of low volatility (8.1×10^{-7} Pa at 25 °C), has a log P_{OW} of 6.9 and is soluble (> 600 g/L) in hexane, dichloromethane, acetone, ethyl acetate, xylene and toluene.



Etofenprox (MTI-500)

The following abbreviations are used for the metabolites discussed below:

α-CO	2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzoate
4'-OH	2-(4-ethoxyphenyl)-2-methylpropyl 3-(4-hydroxyphenoxy) benzyl ether
m-PB-acid	3-phenoxybenzoic acid
4'-OH-PB-acid	3-(4-hydroxyphenoxy) benzoic acid
m-PB-alc	3-phenoxybenzyl alcohol
EPMP	2-(4-ethoxyphenyl)-2-methylpropionic acid
DE	3-phenoxybenzyl 2-(4-hydroxyphenyl)-2-methylpropyl ether (desethyl-etofenprox)
DP	3-hydroxybenzyl 2-(4-ethoxyphenyl)-2-methylpropyl ether
PENA	2-(4-ethoxyphenyl)-2-methylpropyl alcohol
Metabolites identified in italics are common to other pyrethroids	

Animal metabolism

The Meeting received etofenprox metabolism studies on animals (rats, lactating goats and laying hens).

In rats, dosed with a 1:1 mixture of [α-^{14}C-benzyl] and [2-^{14}C-propyl], absorbtion was rapid, but incomplete, with residues in plasma reaching a maximum in 3-5 hours. Distribution and depletion from tissues was rapid except for fat (estimated DT_{50} 5–8.5 days). About 3% AR remained in the carcase after 7 days. No unchanged etofenprox was found in urine but it was a major component in faeces, most likely due to unabsorbed material. Cleavage of the parent molecule did not appear to be a significant metabolic process, although a number of radiolabelled entities were not identified. Desethyl-etofenprox (DE) occurred at 19.5–25.1% of the dose and etofenprox hydroxylated in the 4′ position of the phenoxybenzyl moiety (4'-OH) occurred at 7.2–13.8% of the dose. Other primary metabolic steps involved oxidation of carbons on either side of the ether linkage, one of which (α-CO) is a major metabolite in plants, soil and in photo-degradation studies.

Lactating goats were orally dosed twice daily for 7 days with an encapsulated 1:1 mixture of [α-^{14}C-benzyl] and [2-^{14}C-propyl] labelled etofenprox in acetone at dietary equivalents of 1.5 ppm or 13.5 ppm per day. At the end of the 7-day dosing period, the goats were sacrificed 21 hours after the last administration.

Most of the applied radioactivity (about 78-84%) was excreted via faeces and urine. Transfer to milk was low (less than 0.8% of the applied dose), mostly (47-68%) in the milk fat and with residues reaching a plateau after 3-4 days. About 2-3% of the applied radioactivity was found in fat with 0.5-0.66% in muscle and 0.1-0.2% in liver.

Etofenprox (parent) was the predominant residue in milk and edible tissues, making up 93-97% TRR in milk, muscle and fat, and 33-38% TRR in liver and kidney. The highest residue level was found in fat (0.72 mg/kg for the high dose).

Other metabolites found at low levels were EPMB and m-PB-acid (each at about 0.04 mg/kg in kidney) m-PB-alc/PENA (0.05 mg/kg in liver) and DE (0.02 mg/kg in liver). The α-CO metabolite was not detectable, but is likely to occur as a transitory intermediate leading to the formation of PENA and m-PB-acid.

Laying hens (5 hens per dose group) were dosed each morning for 14 days with a 1:1 mixture of [α-^{14}C-benzyl] and [2-^{14}C-propyl] labelled etofenprox at dietary equivalents of 0.9 ppm or 9.6 ppm.

At the end of the 14-day dosing period, the hens were sacrificed about 24 hours after the last administration. Eggs were collected prior to dosing and during administration twice daily (just before dosing and 5 to 8 hours later).

Excretion of residues was high (83-92% of applied radioactivity). Very little radioactivity was present in eggs (0.6% AR, more than 80% present in the yolk). Edible tissues and organs contained 2.2 to 2.7% AR, mostly in fat.

Etofenprox was the only significant residue, making up about 80% TRR in egg yolk, 69 to 93% TRR in muscle, fat and skin and 15-30% TRR in liver. The remaining extractable radioactivity consisted of unidentified metabolites, except for the DE metabolite which was present at about 0.03 mg/kg (less than 0.08 mg/kg after acid hydrolysis).

In summary, about 80–90% of the applied radioactivity was excreted in lactating goats and laying hens dosed with less than 1% being found in milk and eggs and less than 4% present in edible tissues. The predominant residue in milk, eggs and edible tissues was the parent etofenprox, present at less than 0.1 mg/kg in all tissues except fat (0.7–1.6 mg/kg), up to about 0.7 mg/kg egg yolk and about 0.3 mg/kg in milk, with five identified metabolites present at low levels (up to 0.07 mg/kg).

The proposed metabolic pathways involve desethylation of the ethoxyphenyl group to form the DE metabolite, hydroxylation of the phenoxy ring (to form the 4'-OH metabolite), the formation of the α-CO by oxidation of the benzyl methylene group (in goats) and and the loss of the phenoxy group to form the DP metabolite (in hens). Cleavage of these primary metabolites produces the EPMP, m-PB-acid, PENA, m-PB-alc, OH-P-alc and 4'-OH-PB-acid which subsequently become conjugated.

Plant metabolism

The Meeting received plant metabolism studies on grapes, lettuce, winter rape and rice following foliar applications of a 1:1 mixture of [α-^{14}C-benzyl]-etofenprox and [2-^{14}C-propyl]-etofenprox and on rice following a pre-harvest soil application.

For grapes treated at rates equivalent to 0.3 kg ai/ha (50 g ai/hL) and 3.0 kg ai/ha (500 g ai/hL) as foliar sprays, mature grape bunches were sampled either 28 or 14 days after treatment and washed with water and then ethanol to determine the surface radioactivity. The washed bunches were then separated into stems and grapes with the grapes being homogenised and the juice separated from pulp, skin and pips by centrifugation.

Total residues in grape bunches from the 0.3 kg ai/ha treatments were about 5 mg/kg parent equivalents (14 day PHI) and about 2.5 mg/kg parent equivalents after 28 days. The majority of the radioactive residues were found in the surface washes, 82% TRR after 14 days and decreasing to 60–75% TRR after 28 days. The radioactivity remaining in washed grapes increased from about 12–23% TRR (14 DAT) to 20–23% TRR (28 DAT).

Etofenprox was the major residue in grapes, making up 85–87% TRR, with only low levels of other metabolites being found. The only metabolite found at levels greater than 5% TRR was α-CO, present at levels up to 6.5% TRR.

Eight days after foliar treatment of lettuce plants with etofenprox at 0.18 kg/ha (normal dose) or 1.8 kg ai/ha (high dose), the total radioactive residues were 2.4 mg/kg eq and 19.2 mg/kg eq, respectively. About half the radioactive residue was found in the surface washes of the plants.

The major radioactive residue in lettuce was etofenprox, making up about 90% TRR with α-CO being the only significant metabolite found, at up to 3% TRR.

In foliar-treated paddy rice treated 21 days before harvest with rates equivalent to 0.2 kg ai/ha or 2.0 kg ai/ha, total radioactive residues in brown rice at harvest were about 0.08 mg/kg and 1.1 mg/kg parent equivalents respectively, with levels in chaff and straw being about 4–5 mg/kg (low rate) and 38–51 mg/kg (high rate).

Etofenprox was the predominant residue, making up about 53-76% TRR in whole grain, chaff and brown rice and 49-55% TRR in straw. The metabolite α-CO was found at up to 16% TRR in whole rice, 12% TRR in brown rice, 15% TRR in chaff and 22% TRR in straw.

In paddy rice treated 35 days before harvest with soil treatments of 0.45 kg ai/ha or 2.0 kg ai/ha and re-flooded to simulate paddy field conditions, TRRs at harvest were less than 0.04 mg/kg (low rate) and about 0.1 mg/kg parent equivalents (high rate) in brown rice, with the respective levels in straw being about 0.18 mg/kg and 0.62 mg/kg.

Etofenprox was a significant residue in straw (11-44% TRR), a minor residue in whole grain and was not detected in brown rice. Other metabolites, including α-CO, m-PBAcid and PENA, and conjugates of m-PBAcid, PENA, and 4'-OH-PBAcid, were found at low levels (about 0.002-0.02 in whole grain, brown rice and chaff and < 0.2 mg/kg in straw). Unextracted radioactivity was characterized as carbohydrates, proteins, and lignin, indicating that the majority of the radioactivity in soil-treated rice, resulted from the reincorporation of the radiolabel into natural products.

When winter rape was sprayed with radiolabelled etofenprox at flowering (at the equivalent of 0.12 kg ai/ha or 1.2 kg ai/ha), radioactivity present in mature plants harvested 8 weeks after treatment did not exceed 0.1 and 3.5 mg/kg eq respectively and was found mostly in foliage. In seeds (not directly exposed to the spray), residues did not exceed 0.02 (low rate) or 0.14 mg/kg (high rate).

The predominant residue was etofenprox (up to 62% TRR in seeds) with the α-CO metabolite present at up to 5% TRR in foliage and seeds. Minor metabolites found in seeds, including m-PB-Acid and m-PB-alc, individually did not exceed 0.004 mg/kg.

In summary, plant metabolism studies conducted in four diverse crops (grapes, lettuce, winter rape and rice) showed similar profiles and when applied as a foliar treatment, etofenprox is the major residue, accounting for more than 85% TRR in grapes and lettuce and more than 50% in rice and winter rape. The α-CO metabolite is generally present at less than 10% TRR (12–16% TRR in rice grain and 15–22% TRR in rice chaff and straw).

The proposed metabolic pathway in plants involves an initial oxidation of the benzylic carbon to form the α-CO metabolite, the hydrolysis of ester links to yield the DE and DP metabolites and an aromatic hydroxylation leading to the 4'-OH metabolite. Further metabolism occurs by the cleavage of the first generation metabolites at the oxygen bond, resulting in the formation of m-PB-acid, m-PB-alcohol, EPMP and PENA.

Environmental fate

The Meeting received information the environmental fate and behaviour of etofenprox, including hydrolytic stability, photolysis, behaviour in water/sediment systems and metabolism in rotational crops. A 1:1 mixture of [α-^{14}C-benzyl]-etofenprox and [2-^{14}C-propyl]-etofenprox was used in these studies.

Etofenprox is stable to hydrolysis and is rapidly degraded under simulated sunlight in both buffer solution at pH 7 (DT_{50} 4.7 days) and natural pond water (DT_{50} 7.9 days). The predominant metabolite found at the end of the 15-day study period was α-CO (38-64% applied radioactivity). The α-CO metabolite is stable to hydrolysis at pH 4 and 7 and slowly degraded at pH 9 (calculated DT_{50} of about 43 days).

In water/sediment systems, etofenprox degrades relatively quickly, with DT_{50} values of 1–10 days in the water phases and 6-20 days in the entire systems. One major degradation product, the 4'-OH metabolite, was detected in sediment at levels of up to 12–21% AR. DT_{50} values for this 4'-OH metabolite in water/sediment systems ranged from of 22–57 days.

The Meeting concluded that the residues of etofenprox are not likely to persist in the environment.

Residues in succeeding crops

In rotational crop metabolism studies involving lettuce, carrots and spring barley grown in a silt loam soil treated with ^{14}C-etofenprox and aged for about 4 weeks showed only a very small uptake of radioactivity. The highest concentrations were in barley straw (0.07 mg/kg parent equivalents), in barley grain and lettuce (each at about 0.02 mg/kg parent equivalents). Only very low amounts of the radioactive residues could be extracted, even using aggressive extraction techniques (suggesting that the C^{14} may have entered the carbon pool in the plant) and no further identification of the residue was conducted. Based on these results, significant residues of etofenprox and the α-CO metabolite are not expected in rotational crops.

Analytical methods

Several analytical methods have been reported for the analysis of etofenprox and its α-CO metabolite. The principle of most methods involves extraction steps using organic solvents (predominantly acetone), liquid/liquid partition (commonly hexane), and column chromatographic clean-up (alumina, silica gel, Florisil) and analysis by GC/ECD, GC/MS, HPLC or LC-MS/MS.

The methods have been validated for range of plant and animal substrates with LOQs of 0.01 mg/kg and based on the results of validation studies and the concurrent recovery rates achieved in the supervised field trials, the available analytical methods are considered suitable for determining residues of etofenprox and its α-CO metabolite.

Insufficient information was available to conclude whether etofenprox can be analysed with commonly used multiresidue methods.

Stability of pesticide residues in stored analytical samples

In frozen storage stability studies with a range of representative substrates with a with a high water content (apples, cabbage, peaches), a high starch content (rice grain), a high oil content (rape seed) and a high acid content (grapes), residues of etofenprox and its α-CO metabolite were stable for at least 24 months (rice for 7 months) when samples were stored at -20°C. Sample storage intervals in the supervised field trials were within these storage intervals.

No information was available on the stability of animal matrices under frozen storage. The Meeting noted that in the hen metabolism study, separate radiolabelled liver samples analysed 12 months apart showed no significant change in the relative TLC profiles. Sample storage intervals in the animal metabolism studies were 3-4 months and 1-2 months in the animal feeding studies.

Residue definition

In livestock metabolism studies (goats, hens), the parent compound is the predominant residue in milk, eggs and edible tissues, with the α-CO metabolite not being found. Only low levels (< 0.05%TRR) of other metabolites (EPMP, m-PB-Acid, m-PB-alc/PENA and DE) occurred in liver and kidney.

The Meeting recommended that for animal commodities, the residue definition for both MRL enforcement and dietary intake estimation should be etofenprox.

Based on the ratio of residues in fat and muscle observed in the livestock metabolism and feeding studies (about 50:1) and supported by the log Kow of 6.9, the Meeting concluded that etofenprox residues are fat-soluble.

In plants, the metabolism studies on grapes, lettuce, oilseed rape and rice indicate that the predominant residue following foliar applications of etofenprox is the parent compound.

The only significant residue in plants is the α-CO metabolite, generally present at levels of less than 10% TRR in grapes, lettuce and rape seed and up to about 12% TRR in brown rice. In

supervised trials on pome fruit, stone fruit and grapes, residues of the α-CO metabolite averaged between 14% and 19% of the etofenprox residues in fruit from trials matching GAP.

The Meeting recommended that for plant commodities, the residue definition for MRL enforcement should be etofenprox.

Based on the results of the plant metabolism studies and noting that the NOAEL for α-CO metabolite is about 2.5 times higher than that for etofenprox, the Meeting agreed that although the α-CO metabolite was present in some treated commodities (pome fruit, stone fruit, grapes) at levels averaging 14–19% of the etofenprox residues in samples taken at GAP, this metabolite need not be included in the residue definition for plant commodities for dietary intake estimation.

The Meeting therefore recommended that for plant commodities, the residue definition for dietary intake estimation should be etofenprox.

Analytical methods exist to measure etofenprox residues in animal and plant matrices.

Definition of the residue (for estimation of dietary intake and for compliance with MRL) – plant and animal commodities: *etofenprox*

The residue is fat soluble

Results of supervised trials on crops

The meeting received supervised trial data for foliar applications of etofenprox (EC and SC formulations) on a range of fruit, vegetable, cereal, pulse and oilseed crops and for granular broadcast applications to paddy rice. These trials were conducted mainly in Europe, Brazil, USA (rice) and Japan (rice).

The OECD MRL calculator was used as a tool to assist in the estimation of maximum residue levels from the selected residue data set obtained from the supervised residue trials. As a first step, the Meeting reviewed the trial conditions and other relevant factors related to each data set to arrive at a best estimate of the maximum residue level, using expert judgement. Then the OECD calculator was employed. If the statistical calculation spreadsheet suggested a different value from that recommended by the Meeting, a brief explanation of the deviation was supplied.

Orange

Residue data were provided to the Meeting from trials in Brazil on oranges.

The GAP for use on citrus fruit in Brazil is for 2 applications of up to 0.0025 kg ai/hL, applying about 8 litres of spray mix per tree, and with a PHI of 7 days. No trials matching GAP were available

Apple

Residue data were provided to the Meeting from trials in Brazil (no GAP) and Southern Europe on apples.

The GAP for use on apples and pears in Italy is for foliar sprays of up to 0.014 kg ai/hL, applying about 1500 L/ha, and with a PHI 7 days.

In trials from Italy, Spain and France matching this GAP, residues of etofenprox in apples were: 0.1, 0.12, 0.13, 0.18, 0.2, 0.22, 0.25, 0.26 and 0.34 mg/kg (n = 9).

The Meeting estimated an STMR of 0.2 mg/kg, an HR of 0.34 mg/kg and recommended a maximum residue level of 0.6 mg/kg for etofenprox in apples, agreed to extrapolate these recommendations to pears and to withdraw the previous recommendation of 1.0 mg/kg for pome fruits.

Peach

Residue data were provided to the Meeting from trials in Brazil (no GAP) and Southern Europe on peaches.

The GAP for use on stone fruit (apricot, cherry, peach, plum) in Italy is for foliar sprays of up to 0.014 kg ai/hL, applying about 1500 L/ha, and with a PHI 7 days.

In trials from Italy, Spain and France matching this GAP, residues of etofenprox in peaches were: 0.01, 0.08, 0.08, 0.1, 0.12, 0.14, 0.18, 0.18, 0.2, 0.21, 0.23 and 0.37 mg/kg (n = 12).

The Meeting estimated an STMR of 0.16 mg/kg, an HR of 0.37 mg/kg and recommended a maximum residue level of 0.6 mg/kg for etofenprox in peaches and agreed to extrapolate these recommendations to nectarines.

Grapes

Residue data were provided to the Meeting from trials in Europe on grapes.

The GAP for use on grapes in Italy is for foliar sprays of up to 0.028 kg ai/hL, with a PHI 14 days.

No trials matching this GAP were available, but in trials in southern Europe (Italy, Spain and France), involving spray concentrations of 0.015 kg ai/hL (0.15 kg ai/ha) and a PHI of 14 days, residues of etofenprox in grapes were: 0.25, 0.29, 0.35, 0.38, 0.39, 0.39, 0.53, 0.63, 0.96 and 1.4 mg/kg (n = 10).

The Meeting agreed that the results from these trials could be proportionally adjusted to match the Italian GAP. When scaled to the Italian GAP of 0.028 kg ai/hL (by multiplying by 1.87), etofenprox residues in grapes were: 0.47, 0.54, 0.65, 0.71, 0.73, 0.73, 0.99, 1.2, 1.8 and 2.6 mg/kg (n = 10).

The Meeting recommended an STMR of 0.73 mg/kg, an HR of 2.6 mg/kg and recommended a maximum residue level of 4 mg/kg for etofenprox in grapes.

Cabbage (head)

Residue data were provided to the Meeting from trials in Southern Europe on cabbages (without wrapper leaves).

The GAP for use on cabbages in Italy is for foliar sprays of up to 0.014 kg ai/hL, applying 700–1500 L/ha and with a PHI of 7 days but no trials matching this GAP were available.

Tomatoes

Residue data were provided to the Meeting from trials in Brazil on tomatoes.

The GAP for use in Brazil is for foliar sprays of up to 0.02 kg ai/hL, applying about 300 L/ha and with a PHI of 7 days.

In trials matching this GAP, residues of etofenprox were < 0.01 and < 0.01 mg/kg.

The Meeting agreed the data were not sufficient to estimate an MRL for etofenprox in tomatoes.

Beans (dry)

Residue data were provided to the Meeting from trials in Brazil on dry beans.

The GAP for use in Brazil on beans is for foliar sprays of up to 0.15 kg ai/ha, applying about 300–400 L/ha and with a PHI of 3 days.

In trials matching this GAP, residues of etofenprox in beans (without pods) were: < 0.01, < 0.01, < 0.01, ≤ 0.05, < 0.05, < 0.05 and < 0.05 mg/kg (n = 7).

The Meeting recommended an STMR of 0.05 mg/kg and recommended a maximum residue level of 0.05 mg/kg for etofenprox in beans (dry).

Potato

The results of three residue trials in Brazil were provided to the Meeting, but GAP for the use of etofenprox on potatoes was not available.

The Meeting agreed the data were not sufficient to estimate an MRL for etofenprox in potatoes and withdrew the previous recommendation of 0.01 * mg/kg for potatoes.

Soya bean (dry)

Residue data were provided to the Meeting from trials in Brazil on soya beans.

The GAP for use on soya beans in Brazil is for foliar sprays of up to 0.15 kg ai/ha, applying about 100-250 L/ha and with a PHI of 15 days

In trials matching this GAP, residues of etofenprox on soya bean seeds were: < 0.01, < 0.05 and < 0.05 mg/kg.

The Meeting agreed the data were not sufficient to estimate an MRL for etofenprox in soya bean (dry)

Wheat

Residue data were provided to the Meeting from trials in Brazil on wheat.

The GAP for use on wheat in Brazil is for foliar sprays of up to 0.03 kg ai/ha in about 100 L/ha, and with a PHI of 16 days.

In one trial matching the GAP application rate (0.03 kg ai/ha) and with a PHI of 3 days, etofenprox residues in wheat grain were < 0.01 mg/kg.

The Meeting agreed the data were not sufficient to estimate an MRL for etofenprox in wheat.

Maize

Residue data were provided to the Meeting from trials in Brazil on maize.

The GAP for use on maize in Brazil is for foliar sprays of up to 0.03 kg ai/ha in 300–400 L/ha, and with a PHI of 3 days.

In trials matching this GAP, etofenprox residues in maize kernels were: < 0.01, < 0.05, ≤ 0.05, ≤ 0.05, < 0.05 and < 0.05 mg/kg (n = 6).

Two additional trials involving application rates 1.5 × GAP also reported etofenprox residues of < 0.01 mg/kg (2)

The Meeting estimated an STMR of 0.05 mg/kg, an HR of 0.05 mg/kg and recommended a maximum residue level of 0.05 * mg/kg in maize.

Rice

Residue data were provided to the Meeting from trials in Brazil (no GAP), Japan and USA on rice.

GAP in Japan is for use as a foliar spray, with up to 3 applications of 0.02 kg ai/hL and a 21 day PHI but no trials matching this GAP were available.

GAP in USA is as a granular broadcast application to paddy rice, applying up to 0.3 kg ai/ha, 1–7 days after flooding and with a PHI of 60 days.

In trials in USA matching the GAP of the USA, residues of etofenprox in whole rice grain were: < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01 and < 0.01 mg/kg. In two further trials in USA, involving exaggerated (5×) rates of 1.5 kg ai/ha, residues in whole rice grain were also < 0.01 and < 0.01 mg/kg.

The Meeting estimated an STMR of 0.0 mg/kg and an HR of 0.0 mg/kg and recommended a maximum residue level of 0.01 * mg/kg for etofenprox in rice.

Coffee

Six trials from Brazil on coffee were provided to the meeting, but information on GAP for use on coffee in Brazil was not available.

Cotton seed

Residue data were provided to the Meeting from trials in Brazil on cotton.

GAP in Brazil is for foliar sprays of up to 0.3 kg ai/ha in 300–400 litres water/ha and with a PHI of 15 days.

In trials matching this GAP, etofenprox residues were: < 0.01, < 0.05, < 0.05 and < 0.05 mg/kg.

The Meeting agreed the data were not sufficient to estimate an MRL for etofenprox in cotton seed.

Oil seed rape

Residue data were provided to the Meeting from trials in Northern Europe on oil seed rape.

The GAP for use in Germany is for up to 2 foliar sprays up to the start of flowering, applying up to 0.058 kg ai/ha in about 200 L/ha.

In trials from Germany and UK matching this GAP, etofenprox residues were: < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01 and < 0.01 mg/kg.

The Meeting estimated an STMR of 0.01 mg/kg and an HR of 0.01 mg/kg and recommended a maximum residue level of 0.01 * mg/kg for etofenprox on oil seed rape.

Animal feedstuffs

Rice straw

In trials from USA matching the USA GAP (0.3 kg ai/ha, 1–7 days after flooding, PHI 60 days), etofenprox residues in rice straw were: < 0.01, < 0.01, < 0.01, < 0.01, 0.01 and 0.025 mg/kg.

The Meeting estimated a median residue of 0.01 mg/kg, a highest residue of 0.025 mg/kg and recommended a maximum residue level of 0.05 mg/kg for etofenprox on rice straw.

Fate of residues during processing

The effect of processing on the nature of residues was investigated in buffer solutions under a range of hydrolysis conditions. Etofenprox was shown to be stable under these conditions.

Processing studies reflecting household or commercial practices were provided for rape seeds, grapes, peaches and apples. Estimated processing factors and calculated STMR-Ps for commodities considered at this meeting are summarised below.

Summary of selected processing factors and STMR-Ps for etofenprox

Raw agricultural commodity	STMR (mg/kg)	HR (mg/kg)	Processed commodity	Calculated processing factors [a]	Processing factor	STMR-P (mg/kg)	HR-P (mg/kg)
Grape	0.73	2.6	Juice [b]	< 0.05, < 0.04, < 0.03, < 0.01, 0.007	< 0.03 (median)	0.022	
			Wine [b]	< 0.05, < 0.04, < 0.03	< 0.04 (median	0.029	
			Raisins	2.5, 1.6	2.1 (mean)	1.53	5.46
Apples	0.2	0.34	Puree	0.32, 0.29, < 0.09	0.305 [c]	0.061	
			Juice	< 0.09, < 0.06, 0.045	< 0.06 (median)	0.012	
			Canned apples	< 0.09	< 0.09	0.018	
			Press cake (wet pomace)	3.6, 2.2, 2.2	2.7 (mean)	0.53	
			Dry pomace	13	13	2.6	
Peach	0.16	0.37	Juice	< 0.32, < 0.05, < 0.04	< 0.05 (median)	0.008	
			purée	1.7, 0.67, 0.32	0.67 (median)	0.107	
			Canned peaches	< 0.11	< 0.11	0.018	

[a] Ratio of the total residue in the processed item/total residue in the RAC (if above the LOQ).

[b] Residues < 0.01 in all samples.

[c] Best estimate (mean of the two highest values)

The Meeting noted that the HR for etofenprox in grapes was 2.6 mg/kg and based on the mean processing factor of 2.1, the calculated highest residue in raisins is 5.5 mg/kg and the Meeting recommended a maximum residue level of 8 mg/kg for dried grapes (raisins).

Residues in animal commodities

Farm animal dietary burden

The Meeting estimated the dietary burden of etofenprox in farm animals on the basis of the diets listed in Annex 6 of the 2009 JMPR Report (OECD Feedstuffs Derived from Field Crops) and the STMR or highest residue levels estimated for etofenprox (parent only) at the present Meeting. Dietary burden calculations are provided in Annex X and are summarised below.

Animal dietary burden for etofenprox, ppm of dry matter diet

	Maximum Dietary Burden	Mean Dietary Burden
Beef cattle	0.277 [a]	0.267 [b]
Dairy cattle	0.136 [c]	0.132 [d]
Poultry broiler	0.0	0.0
Poultry layer	0.0	0.0

[a] Used for calculating HRs and estimating maximum residue levels for mammalian tissues, based on highest residue in individual animals in relevant dose groups

[b] Used for calculating STMRs for mammalian tissues, based on mean residues in relevant dose groups

[c] Used for calculating highest residues in milk, based on mean residues in relevant dose groups

[d] Used for calculating the STMR for milk, based on mean residues in relevant dose groups

Farm animal feeding studies

The Meeting received information on the residue levels arising in animal tissues and milk when dairy cows were dosed with etofenprox for 28–30 days at 10, 30 and 1000 mg ai/cow/day (equivalent to about 0.5 ppm, 1.5 ppm and 50 ppm in the diet).

In milk, etofenprox residues were at or below the LOQ (0.05 mg/kg) in the 1× and 3× dose groups and in the 200× dose group, residues of 0.66 mg/l were detected on day 2 of the dosing period, increasing to a maximum of 2.11 mg/l. Over the withdrawal period, residues declined rapidly during the first 5-6 days with a slower decline over the last 7–8 days.

In liver, kidney and skeletal muscle, residues of etofenprox were all below the LOQ (0.05 mg/kg) from cows in the 1× and 3× dose groups. In the 200× dose group, residues were detected in all of the analysed tissues, up to 1.16 mg/kg in kidney, 0.63 mg/kg in liver and 0.35 mg/kg in skeletal muscle and were also measurable in all tissues (except liver) at the end of the 14-day withdrawal period.

Residues in peritoneal fat were up to 0.54 mg/kg (1×) and 1.89 mg/kg (3×) and in subcutaneous fat were up to 0.28 mg/kg (1×) and 0.5 mg/kg (3×). In the 200× dose group, residues were up to 14.3 mg/kg in peritoneal fat and 3.54 mg/kg in subcutaneous fat and were also measurable at the end of the 14-day withdrawal period.

Animal commodity maximum residue levels

Cattle

For MRL estimation, the high residues in the tissues were calculated by extrapolating the maximum dietary burden (0.277 ppm) from the 0.5 ppm feeding level in the dairy cow feeding study and using the highest tissue concentrations from individual animals within those feeding groups.

The STMR values for the tissues were calculated by extrapolating the mean dietary burden (0.267 ppm) from the 0.5 ppm feeding level in the dairy cow feeding study and using the mean tissue concentrations from those feeding groups.

For milk MRL estimation, the high residues in the milk were calculated by extrapolating the maximum dietary burden for dairy cattle (0.136 ppm) from the 0.5 ppm feeding levels in the dairy cow feeding study and using the mean milk concentrations from those feeding groups.

The STMR value for milk was calculated by extrapolating the mean dietary burden for dairy cattle (0.132 ppm) from the 0.5 ppm feeding levels in the dairy cow feeding study and using the mean milk concentrations from those feeding groups.

	Feed level (ppm) for milk residues	Residues (mg/kg) in milk	Feed level (ppm) for tissue residues	Etofenprox residues (mg/kg) in:			
				Muscle	Liver	Kidney	Fat [c]
MRL beef or dairy cattle							
Feeding study [a]	0.5	< 0.05	0.5	< 0.05	< 0.05	< 0.05	0.54
Dietary burden and residue estimate	0.136	< 0.014	0.277	< 0.028	< 0.028	< 0.028	0.3
STMR beef or dairy cattle							
Feeding study [b]	0.5	< 0.05	0.5	< 0.05	< 0.05	< 0.05	0.39
Dietary burden and residue estimate	0.132	< 0.013	0.267	< 0.027	< 0.027	< 0.027	0.208

[a] Highest residues for tissues and mean residues for milk

[b] Mean residues for tissues and for milk

[c] Peritoneal fat

Maximum residues of etofenprox in cattle tissues are: 0.3 mg/kg in fat and < 0.03 mg/kg in muscle, liver and kidney. The mean residue for milk is < 0.014 mg/kg.

The Meeting estimated maximum residue levels of 0.5 mg/kg (fat) for etofenprox in meat (from mammals other than marine mammals), 0.05 mg/kg for edible offal (mammalian) and 0.02 mg/kg for milks.

Estimated HRs for dietary intake estimation for etofenprox are 0.3 mg/kg for mammalian fat and 0.03 mg/kg for mammalian muscle, liver and kidney.

Estimated STMRs for dietary intake estimation for etofenprox are 0.21 mg/kg for mammalian fat, 0.03 mg/kg for muscle, liver and kidney and 0.013 mg/kg for milks.

Poultry

None of the animal feed commodities considered by the Meeting contributed to the dietary burden for poultry layers or broilers.

The Meeting estimated maximum residue levels of 0.01 (*) mg/kg for etofenprox in poultry meat, fat, offal and eggs and the estimated HRs and STMRs for dietary intake estimation are 0.0 mg/kg for poultry meat, fat, offal and eggs.

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Daily Intake (IEDI) for etofenprox was calculated for the food commodities for which STMRs or HRs were estimated and for which consumption data were available. The results are shown in Annex 3.

The International Estimated Daily Intakes of etofenprox for the 13 GEMS/Food regional diets, based on estimated STMRs were 1–3% of the maximum ADI of 0.03 mg/kg bw (Annex 3). The Meeting concluded that the long-term intake of residues of etofenprox from uses that have been considered by the JMPR is unlikely to present a public health concern.

Short-term intake

The International Estimated Short-term Intake (IESTI) for etofenprox was calculated for the food commodities for which STMRs or HRs were estimated and for which consumption data were available (Annex 4).

For etofenprox the IESTI varied from 0–10% of the ARfD (1 mg/kg bw) for the diets submitted in 2011. The Meeting concluded that the short-term intake of residues of etofenprox from uses considered by the Meeting is unlikely to present a public health concern.