5.16 FENPROPATHRIN (185)

TOXICOLOGY

Fenpropathrin is the ISO-approved name for (*RS*)-α-cyano-3-phenoxybenzyl-2,2,3,3-tetramethylcyclopropanecarboxylate (IUPAC), with the CAS number 39515-41-8. Fenpropathrin is a synthetic pyrethroid with insecticidal/acaricidal properties.

Fenpropathrin was evaluated previously by JMPR in 1993, when an ADI of 0–0.03 mg/kg bw was established based on a NOAEL of 3 mg/kg bw per day from a multigeneration reproductive study in rats, a developmental toxicity study in rats and a 1-year toxicity study in dogs and using a 100-fold safety factor. The establishment of an ARfD was not considered by the Meeting in 1993.

Fenpropathrin was reviewed at the present Meeting as part of the periodic review programme of CCPR. Since the last review by JMPR, the following new studies of fenpropathrin have been submitted: acute and subchronic neurotoxicity studies, a developmental neurotoxicity study and an immunotoxicity study. Published studies primarily evaluating the neurotoxicity of fenpropathrin have also been taken into consideration.

Most of the studies do not comply with GLP, as most of the data were generated before the implementation of GLP regulations. Overall, the Meeting considered that the database was adequate for the risk assessment.

Biochemical aspects

Absorption of fenpropathrin following a single oral administration was rapid, and elimination was almost complete (about 57% in urine, about 40% in faeces) within 48 hours. Low concentrations of residues (< 0.6 µg/g tissue) were measured in blood, liver, kidney, fat, muscle and brain within 24 hours after dosing, and concentrations declined rapidly for 8 days, except for those in fat, which were the highest concentrations measured and which also declined, but not as rapidly. Less than 1.5% of the administered dose remained in the body 8 days after treatment. The major biotransformation reactions of fenpropathrin in rats consisted of oxidation at the methyl groups of the acid moiety and at the 2′- and 4′-positions of the alcohol moiety, cleavage of the ester linkage and the conjugation of the resultant carboxylic acids, alcohols and phenols with glucuronic acid, sulfuric acid and glycine.

Most of the urinary metabolites were ester-cleaved products. The predominant urinary metabolites derived from the acid moiety were identified as 2,2,3,3-tetramethylcyclopropane carboxylic acid–glucuronide (TMPA-glucuronide) and TMPA-CH_2OH (*trans*). The major urinary metabolites derived from the alcohol moiety were 3-phenoxybenzoic acid (PB acid) in free form and as glycine conjugate, 4′-OH-PB acid–sulfate and 2′-OH-PB acid–sulfate. The major faecal metabolite was identified as CH_2OH *trans*-fenpropathrin, followed by COOH *trans*-fenpropathrin, 4′-OH-fenpropathrin and 4′-OH-CH_2OH *trans*-fenpropathrin. Depending on the dose administered, 30–50% of the applied radioactivity was excreted in faeces as parent compound. Fenpropathrin and TMPA were the major radiolabelled components in tissues. An aryl-hydroxylated ester (α-cyano-3-(4-hydroxyphenoxy) benzyl ester) was identified in bile.

Toxicological data

Fenpropathrin appears to have both type I and type II properties. It produces repetitive firing of neurons but is associated with type II symptoms. In acute studies with fenpropathrin in mammals, onset of toxic signs is rapid (within a few hours or days), independent of the route of exposure. Recovery of surviving animals is also rapid. Toxic signs are those typical for pyrethroids and include hypersensitivity, fibrillation, tremors, clonic convulsions, salivation, lacrimation, urinary incontinence and hindlimb and/or whole-body ataxia. The acute oral LD_{50} in rats is greater than or equal to 48.5 mg/kg bw, depending on the vehicle. The dermal LD_{50} in a study in rats ranged from 870 mg/kg bw to greater than 5000 mg/kg bw, depending on the vehicle. The acute inhalation LC_{50} in rats was

greater than or equal to 556 mg/m^3. Fenpropathrin is a slight skin irritant and is minimally irritating to the eyes of rabbits. It is not a dermal sensitizer in the Buehler test.

The neurological clinical signs (body tremors, hypersensitivity/hyperreactivity, ataxia and, in dogs only, emesis) and reduced body weight gain are the key and most sensitive toxicological end-points.

In a 28-day toxicity study in mice, the NOAEL was 500 ppm (equal to 63 mg/kg bw per day), based on decreases in body weight gain in males, decreases in feed efficiency in males and clinical signs seen at the LOAEL of 1000 ppm (equal to 123 mg/kg bw per day).

In three 90-day studies of toxicity in rats, the overall NOAEL was 450 ppm (equal to 21.3 mg/kg bw per day).

In a 1-year dietary study of toxicity in dogs, the NOAEL was 100 ppm (equal to 3 mg/kg bw per day), based on reduced body weight gain and clinical signs (emesis, tremors) at 250 ppm (equal to 7.7 mg/kg bw per day). Similar toxic effects were observed at 250 ppm (equal to 7.4 mg/kg bw per day), the lowest dose tested, in a 90-day study of toxicity in dogs.

A 2-year toxicity and carcinogenicity study was performed in mice in which the NOAEL was 600 ppm (equal to 56 mg/kg bw per day), the highest dose tested. No evidence of carcinogenicity was observed. In a second study of carcinogenicity in mice, a dose of 1000 ppm caused the death of 38% of the males and 15% of the females within 13 weeks, indicating a steep toxicity–response curve and permitting the conclusion that the earlier study in which the highest dose tested was 600 ppm (equal to 56 mg/kg bw per day), the maximum achievable dose, was adequate for an assessment of the carcinogenicity of this compound.

Two long-term toxicity and carcinogenicity studies in rats were available. The overall NOAEL was 125 ppm (equal to 5 mg/kg bw per day), based on depression in body weight gain and clinical signs at 600 ppm (equal to 23 mg/kg bw per day). There was no evidence of carcinogenicity.

The Meeting concluded that fenpropathrin was not carcinogenic in mice or rats.

Fenpropathrin was tested for genotoxicity in an adequate range of assays, both in vitro and in vivo. In none of these assays was there any evidence of genotoxic potential.

The Meeting concluded that fenpropathrin was unlikely to be genotoxic.

On the basis of the lack of genotoxicity and the absence of carcinogenicity in mice and rats, the Meeting concluded that fenpropathrin is unlikely to pose a carcinogenic risk to humans.

Two multigeneration reproductive studies are available in rats. The overall NOAEL for parental systemic toxicity was 40 ppm (equal to 2.6 mg/kg bw per day), based on depression of body weight gain, increased mortality in females and the occurrence of body tremors and muscle twitches at 120 ppm (equal to 7.8 mg/kg bw per day). No effects on reproductive parameters were observed at doses up to 360 ppm (equal to 23.3 mg/kg bw per day), the highest dose tested. The overall NOAEL for offspring toxicity was 40 ppm (equal to 2.6 mg/kg bw per day), based on body tremors seen in some pups at 120 ppm (equal to 7.8 mg/kg bw per day).

Two studies of developmental toxicity were available. The overall NOAEL for maternal toxicity was 3 mg/kg bw per day, based on reduced feed consumption and body weight gain at the beginning of treatment seen at 6 mg/kg bw per day. The NOAEL for developmental toxicity was 10 mg/kg bw per day, the highest dose tested.

Developmental toxicity studies were conducted with rabbits. The overall NOAEL for maternal toxicity was 4 mg/kg bw per day, based on clinical signs noted at 12 mg/kg bw per day, whereas the overall developmental NOAEL was 36 mg/kg bw per day, the highest dose tested.

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

In an acute neurotoxicity study, the NOAEL was 10 mg/kg bw, based on tremors at 25 mg/kg bw. In a separate study, no histopathology of sciatic and tibial nerves or increase in β-glucuronidase

activity (indicative of Wallerian degeneration in nerves) was observed in rats at doses up to 500 ppm (equivalent to 25 mg/kg bw per day).

In a published study, effects on motor activity were measured for several pyrethroids, including fenpropathrin, following administration of a single gavage dose in corn oil to rats. Threshold doses (calculated dose at which treated rats did not display any decreases in motor activity) were calculated for these pyrethroids. The threshold dose for fenpropathrin was 3.06 mg/kg bw. In an acute neurotoxicity study in rats, the NOAEL was 15 mg/kg bw, based on slight tremors and clonic convulsions (whole-body tremors) in both sexes at the time of peak effect seen at the LOAEL of 30 mg/kg bw.

In a 90-day neurotoxicity study, treatment at 570 ppm caused the death of 1 of 12 females, decreased body weight gain and feed consumption in both sexes, and led to clinical signs and a number of alterations in functional observational batteries. At 190 ppm, walking on tiptoes and hunched body were observed during the open-field observations in females only. The NOAEL was 60 ppm (equal to 5 mg/kg bw per day for females).

The range-finding study for a guideline developmental neurotoxicity study in rats confirmed the presence of fenpropathrin in milk of lactating females as well as in plasma of mothers and pups, demonstrating that the dietary route of exposure was valid for the main developmental neurotoxicity study. The LOAEL for developmental neurotoxicity was 250 ppm (equal to 19 mg/kg bw per day), based on small pups and decreased body weights and body weight gains during the pre-weaning period, decreased habituation, increased mean overall maximum startle response amplitude and average response amplitude in the females, and decreased absolute brain weights in the males. The NOAEL for developmental neurotoxicity was 100 ppm (equal to 8 mg/kg bw per day).

No signs of neurotoxicity and no histopathological findings were observed in the nervous system of hens treated with fenpropathrin at 1000 mg/kg bw per day.

No immunotoxic potential for fenpropathrin was evidenced in a specific study in which rats were administered up to 450 ppm (42 mg/kg bw per day), a dose level causing systemic toxicity.

No adverse effects were reported by 14 workers engaged in fenpropathrin manufacturing (2002–2011), and no health problems or adverse findings were noted at periodic examinations.

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

Toxicological evaluation

The Meeting reaffirmed the ADI of 0–0.03 mg/kg bw on the basis of an overall NOAEL of 100 ppm (equal to 3.1 mg/kg bw per day) in the 90-day and 1-year toxicity studies in dogs, based on the occurrence of tremors seen at 250 ppm (equal to 7.4 mg/kg bw per day), and using a safety factor of 100. This ADI was supported by the NOAEL of 40 ppm (equal to 2.6 mg/kg bw per day) observed in a multigeneration reproductive study in rats, on the basis of the occurrence of body tremors and muscle twitches and mortality of two females seen at 120 ppm (equal to 7.8 mg/kg bw per day). It is further supported by the NOAEL of 3 mg/kg bw per day observed in the developmental toxicity study in rats, on the basis of decreases in body weight gain and feed consumption seen at 10 mg/kg bw per day.

The Meeting established an ARfD of 0.03 mg/kg bw on the basis of the threshold dose of 3.06 mg/kg bw from a published study measuring motor activity at the time of peak effects following a single oral dose in rats and using a safety factor of 100. This ARfD value was supported by the combined NOAEL of 3 mg/kg bw per day seen in the developmental toxicity studies in rats, based on a decrease in body weight gain and feed consumption in dams during the first 2 days of dosing at 6 mg/kg bw per day.

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	600 ppm, equal to 56 mg/kg bw per day[b]	—
		Carcinogenicity	600 ppm, equal to 56 mg/kg bw per day[b]	—
Rat	Acute neurotoxicity study[c] (published)	Neurotoxicity	Threshold dose: 3.06 mg/kg bw	Estimated ED_{30}: 7.70 mg/kg bw
	Ninety-day studies of toxicity[a,d]	Toxicity	250 ppm, equivalent to 12.5 mg/kg bw per day	600 ppm, equal to 28.8 mg/kg bw per day
	Ninety-day study of neurotoxicity[a]	Toxicity	60 ppm, equal to 5 mg/kg bw per day	190 ppm, equal to 15 mg/kg bw per day
	Two-year studies of toxicity and carcinogenicity[a,d]	Toxicity	125 ppm, equal to 6.25 mg/kg bw per day	450 ppm, equal to 21.9 mg/kg bw per day
		Carcinogenicity	600 ppm, equal to 22.7 mg/kg bw per day[b]	—
	Multigeneration study of reproductive toxicity[a,d]	Reproductive toxicity	360 ppm, equal to 23.3 mg/kg bw per day[b]	—
		Parental toxicity	40 ppm, equal to 2.6 mg/kg bw per day	120 ppm, equal to 7.8 mg/kg bw per day
		Offspring toxicity	40 ppm, equal to 2.6 mg/kg bw per day	120 ppm, equal to 7.8 mg/kg bw per day
	Developmental toxicity studies[c,d]	Maternal toxicity	3 mg/kg bw per day	10 mg/kg bw per day
		Embryo and fetal toxicity	10 mg/kg bw per day[b]	—
Rabbit	Developmental toxicity studies[c,d]	Maternal toxicity	4 mg/kg bw per day	12 mg/kg bw per day
		Embryo and fetal toxicity	36 mg/kg bw per day[b]	—
Dog	Ninety-day and 1-year studies of toxicity[a,d]	Toxicity	100 ppm, equal to 3.1 mg/kg bw per day	250 ppm, equal to 7.4 mg/kg bw per day

ED_{30}, dose (mg/kg bw) required to induce a 30% decrease in total motor activity compared with the corresponding vehicle-treated control group

[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

0.03 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 exposures

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

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid, at least 57%
Dermal absorption	Not available
Distribution	Widely distributed
Potential for accumulation	No
Rate and extent of excretion	Rapid and complete
Metabolism in animals	Extensive
Toxicologically significant compounds in animals, plants and the environment	Parent compound
Acute toxicity	
Rat, LD_{50}, oral	≥ 48.5 mg/kg bw (vehicle dependent)
Rat, LD_{50}, dermal	≥ 870 mg/kg bw (vehicle dependent)
Rat, LC_{50}, inhalation	≥ 556 mg/m^3 (nose-only exposure)
Rabbit, dermal irritation	Slightly irritating
Rabbit, ocular irritation	Mildly irritating
Dermal sensitization	Non-sensitizing, Buehler test
Short-term studies of toxicity	
Target/critical effect	Neurotoxic signs
Lowest relevant oral NOAEL	5 mg/kg bw per day
Lowest relevant dermal NOAEL	3000 mg/kg bw per day (rabbits)
Lowest relevant inhalation NOAEC	Not available
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Neurotoxic signs
Lowest relevant oral NOAEL	3.1 mg/kg bw per day (dog)
Carcinogenicity	Not carcinogenic
Genotoxicity	
	Not genotoxic
Reproductive toxicity	
Target/critical effect	Neurotoxic signs
Lowest relevant parental NOAEL	2.6 mg/kg bw per day
Lowest relevant offspring NOAEL	2.6 mg/kg bw per day
Lowest relevant reproductive NOAEL	23.3 mg/kg bw per day (highest dose tested)
Developmental toxicity	
Target/critical effect	Decreased body weight gain and secondary effects on locomotor activity
Lowest relevant maternal NOAEL	3 mg/kg bw per day
Lowest relevant embryo/fetal NOAEL	10 mg/kg bw per day
Neurotoxicity/delayed neurotoxicity	
Acute and subchronic neurotoxicity	No specific signs of acute or subchronic neurotoxicity
Delayed neurotoxicity NOAEL	1000 mg/kg bw per day
Immunotoxicity	
	42 mg/kg bw per day (highest dose tested)
Medical data	
	No adverse health effects reported in manufacturing plant personnel

Summary

	Value	Study	Safety factor
ADI	0–0.03 mg/kg bw	Ninety-day and 1-year toxicity studies (dog)	100
ARfD	0.03 mg/kg bw	Single-dose neurotoxicity study (rat)	100