FENPROPATHRIN

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Explanation

Fenpropathrin is the International Organization for Standardization (ISO)–approved name for (*RS*)-α-cyano-3-phenoxybenzyl-2,2,3,3-tetramethylcyclopropanecarboxylate (International Union of Pure and Applied Chemistry), with the Chemical Abstracts Service number 39515-41-8. Fenpropathrin is a synthetic pyrethroid with insecticidal/acaricidal properties. Type I pyrethroids act to induce repetitive firing in a cercal sensory nerve. The poisoning symptoms of Type I compounds include restlessness, incoordination, hyperactivity, prostration and paralysis. Type II pyrethroids are generally acyanophenoxybenzyl pyrethroids. They do not induce repetitive firing and are associated with a different set of symptoms, including a pronounced convulsive phase. Fenpropathrin is a unique compound, in that it appears to have both Type I and Type II properties. It produces repetitive firing but is associated with Type II symptoms.

Fenpropathrin 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 no-observed-adverse-effect level (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 acute reference dose (ARfD) was not considered by the Meeting in 1993.

Fenpropathrin 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 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.

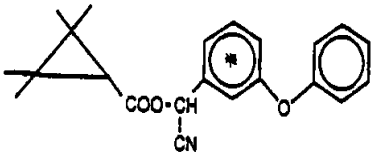
Most of the studies do not comply with good laboratory practice (GLP), as most of the data were generated before the implementation of GLP regulations. Overall, the Meeting considered that the database was adequate for the risk assessment.

Evaluation for acceptable daily intake

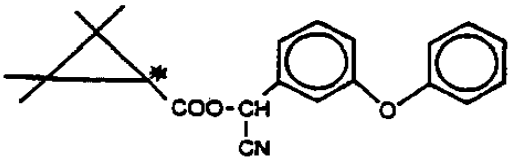
1. Biochemical aspects

Figure 1 shows the radiolabelling position of fenpropathrin used in the absorption, distribution, metabolism and excretion studies in rats.

Figure 1. Structures of the radiolabelled molecules



A. [alcohol-^{14}C]Fenpropathrin, radiolabelled as [phenoxyphenyl-^{14}C]fenpropathrin, also referred to as [^{14}C-benzyl]fenpropathrin



B. [acid-^{14}C]Fenpropathrin, radiolabelled as [cyclopropyl-1-^{14}C]fenpropathrin

1.1 Absorption, distribution and excretion

In an absorption, distribution, metabolism and excretion study, six male and six female Charles River CD rats received a single dose of [^{14}C-benzyl]fenpropathrin (radiochemical purity 99.5%) via gavage in corn oil at a dose of 1.5 mg/kg bw. Treated rats were individually housed in glass metabolism cages to facilitate the collection of urine and faeces. Two rats of each sex were sacrificed at 24 hours, 72 hours and 8 days post-treatment. Blood, kidney, liver, brain, guts, skin, fat, muscle and remaining carcass were analysed for radioactivity. In a separate experiment, two female rats were treated similarly and housed individually in glass metabolism cages equipped with a carbon dioxide trap.

Absorption was rapid and excretion almost complete (97%) within 48 hours. About 56% of the administered dose was found in urine and 40% in faeces at 48 hours (Table 1). The amount of radioactivity excreted via expired air was 0.005%. The low residues found in blood, liver, kidney, fat,

muscle and brain 24 hours after dosing depleted rapidly over the following 7 days to barely detectable levels, and less than 1.5% of the administered dose remained in the body 8 days after treatment (Table 2). The highest residue was found in the fat, probably representing a limited retention of a small amount of the lipophilic substance (Crawford, 1975).

Table 1. Excretion of radioactivity following single oral (gavage) dose of 1.5 mg/kg bw in rats

	Radioactivity (% of administered dose)								
	24 h	48 h	72 h	96 h	120 h	144 h	168 h	192 h	Total
Urine									
Males	48.8	6.7	1.3	0.5	0.3	0.2	0.2	0.1	58.1
Females	48.7	7.3	1.4	1.2	0.5	0.4	0.4	0.07	59.97
Faeces									
Males	18.8	20.6	6.6	1.6	0.2	0.1	0.2	0.03	48.13
Females	12.6	17.8	3.2	0.7	0.3	0.2	0.07	2.46	37.33

From Crawford (1975)

Table 2. Distribution of radioactivity in selected tissues following single oral (gavage) dose of 1.5 mg/kg bw in rats

Tissue	Concentration of radioactivity in tissues (µg/g)					
	Day 1		Day 3		Day 8	
	Males	Females	Males	Females	Males	Females
Liver	0.4	0.6	0.03	0.04	0.01	0.01
Kidney	0.1	0.2	0.03	0.02	0.008	0.007
Fat	0.6	0.5	0.3	0.3	0.2	0.2
Muscle	0.01	0.03	0.005	0.002	0.004	0.002
Brain	0.005	0.009	0.003	0.0008	0.003	0.0002
Blood	0.09	0.2	0.008	0.009	0.001	0.001

From Crawford (1975)

Rapid excretion was also noted following a single oral administration of [^{14}C-cyclopropyl]fenpropathrin, although amounts in urine and faeces were in this case approximately the same (40%) (Crawford, 1975; Crawford & Hutson, 1976, 1977).

In a published study, absorption, distribution and excretion following a single low dose or high dose of fenpropathrin were studied in rats. In this study, fenpropathrin labelled with ^{14}C at the benzyl carbon of the alcohol moiety (^{14}C-alcohol) or at the C1 position of the cyclopropane ring of the acid moiety (^{14}C-acid) and 2,2,3,3-tetramethylcyclopropanecarboxylic acid (TMPA) labelled at the C1 position of the cyclopropane ring were used. Five male and five female Sprague-Dawley rats were given radiolabelled fenpropathrin by oral gavage as a single low dose of 2.4–3.8 mg/kg bw or a single high dose of 18.5–26.8 mg/kg bw. Groups of three male Sprague-Dawley rats were given radiolabelled TMPA as a single oral gavage dose of 1.0–1.1 mg/kg bw (calculated as 2.5 mg/kg bw fenpropathrin equivalent). Corn oil was used as the vehicle (5 ml/kg bw) for administration. Urine and faeces were collected at various time points. Treated rats were sacrificed 7 days after the treatment. Selected tissues were analysed for radioactivity.

Single oral administration of [^{14}C-acid]fenpropathrin and [^{14}C-alcohol]fenpropathrin to male and female rats at 2.4–26.8 mg/kg bw resulted in rapid and almost complete elimination of radiocarbon from the body. Radiolabelled recoveries for the acid and alcohol labellings in the two dose groups were 96.4–101.9% (urine: 26.8–43.8%; and faeces: 58.1–70.4%) and 96.4–98.0% (urine: 26.0–42.7%; and faeces: 54.1–71.0%), respectively, in 7 days. Radioactivity excretion patterns of both labelled preparations into the urine and faeces were very similar in the two dose groups. Faecal excretion of radioactivity was higher in the high-dose groups than in the low-dose groups. There was no significant sex difference in the excretion patterns. When rats were orally dosed with [^{14}C]TMPA, radiocarbon was rapidly excreted mainly into the urine (88% of the dose). No sex-related differences in tissue distribution were observed. Radioactivity in tissue residues was generally very low with both labellings, although the levels were slightly higher in the fat (0.1–1.4 parts per million [ppm]). Tissue residues were generally lower with the alcohol labelling than with the acid labelling (Kaneko et al., 1987).

In a 1994 metabolism study, groups of five male and five female Crl:CD®BR® VAF/Plus (Sprague-Dawley) rats were dosed by oral gavage with radiolabelled fenpropathrin by three protocols. The fenpropathrin was radiolabelled on either the alcohol ([alcohol-^{14}C]fenpropathrin; purity 98.7%; lot no. C-91-089) or acid ([acid-^{14}C]fenpropathrin; purity 98.5%; lot no. C-90-039) portion of the molecule. In Experiment I, rats received 14 daily oral low doses of 2.5 mg/kg bw of unlabelled fenpropathrin followed by a 15th dose of either the alcohol- or acid-radiolabelled fenpropathrin. In Experiments II and III, groups of rats received a single dose of either of the two radiolabelled test articles at 2.5 mg/kg bw (II) or 25 mg/kg bw (III). Corn oil (5 ml/kg bw) was used as the vehicle. Urine and faeces were collected up to 168 hours after gavage dosing. Animals were sacrificed at the end of the exposure period, and various tissues were analysed for radioactivity. Urine, faeces and selected tissues were subjected to various analytical methods to identify and quantify metabolites (see section 1.2).

No clinical signs were seen in any rats. The overall recoveries were 93–108% of the administered dose. The excretion of radioactivity in the urine and faeces was very rapid regardless of the sex, the dose or the radiolabel position (Table 3). The half-life for urinary excretion was 11–16 hours, and the half-life for faecal excretion was 7–9 hours. Slightly higher urinary excretion (52–56%) was observed with repeated dosing compared with the single low dose (30–40%) or single high dose (28–35%). Excretion was slightly higher in the faeces than in the urine in this study (Savides et al., 1994), whereas the excretion of radioactivity in the urine was the same as that in the faeces (around 50%) in the Crawford (1975) study at the low dose, as described above. Less than 1% of the administered radiolabelled dose was present in the tissues at termination (168 hours post-dosing), with the highest concentration of radiolabel in the fat (Savides et al., 1994).

1.2 Biotransformation

The rates of absorption, distribution and excretion of (^{14}C-benzyl)- and (^{14}C-cyclopropyl)-labelled fenpropathrin following a single oral gavage dose of 1.5 mg/kg bw were studied in rats (Crawford, 1975; Crawford & Hutson, 1976, 1977). Elimination of (^{14}C-benzyl)- and (^{14}C-cyclopropyl)-labelled fenpropathrin was studied in bile duct–cannulated rats. The identification of metabolites from urine, faeces and bile samples was conducted using various analytical methods. The abbreviations used for metabolites in this section are explained in footnote a to Table 4.

In the Kaneko et al. (1987) study (see section 1.1), about 29–53% of the parent compound was detected in the faeces (Table 4). No parent compound was detected in the urine.

Table 3. Excretion and tissue distribution of fenpropathrin following a single low, single high or repeated dose in rats at 168 hours[a]

Dose	Label	Sex	% of administered dose								
			Urine				Faeces			Tissues	Total
			12 h	24 h	48 h	Total (168 h)	24 h	48 h	Total (168 h)		
Low 2.5 mg/kg bw	Alcohol	M	16.17	15.55	2.98	35.97	58.72	9.07	69.03	0.47	105.47
		F	17.94	16.14	4.43	39.74	56.22	7.89	64.95	0.25	104.94
	Acid	M	12.79	9.99	5.31	29.87	58.44	8.47	68.39	0.67	98.93
		F	17.57	10.56	4.36	34.24	54.28	8.56	64.68	0.52	99.43
High 25 mg/kg bw	Alcohol	M	14.25	13.80	2.63	31.86	58.69	4.97	65.25	0.31	97.41
		F	10.31	12.59	3.82	27.85	53.38	10.72	65.14	0.27	93.26
	Acid	M	11.61	13.67	4.96	32.04	59.82	7.15	68.60	0.52	101.16
		F	12.74	13.98	6.92	35.37	52.53	10.69	64.99	0.42	100.78
Repeated dose 2.5 mg/kg bw	Alcohol	M	31.42	15.27	3.55	52.30	42.27	10.63	54.66	0.97	107.93
		F	36.51	13.35	3.52	55.39	43.49	6.46	51.14	0.71	107.24
	Acid	M	26.13	18.43	5.13	51.85	38.98	10.72	51.89	1.26	105.01
		F	36.50	14.41	3.91	56.47	38.05	7.25	46.47	0.77	103.70

From Savides et al. (1994), pp. 79–81, 89–91 and 99–101
F, female; M, male
[a] Values represent averages for all animals. Repeated dose = 14 doses of unlabelled fenpropathrin (2.5 mg/kg bw) followed by a single radioactive dose.

Table 4. Proportion of metabolites in the 0- to 2-day faeces and urine after single oral administration of (^{14}C-acid)- or (^{14}C-alcohol)-labelled fenpropathrin in male Sprague-Dawley rats at low and high doses

Metabolites[a]	% of administered dose			
	Acid labelling		Alcohol labelling	
	Low dose	High dose	Low dose	High dose
Faeces				
Fenpropathrin	35.5 ± 13.0[b]	48.2 ± 8.8	29.2 ± 11.6	53.0 ± 4.2
PBald	—	—	0.3 ± 0.1	0.3 ± 0.1
PBacid	—	—	0.7 ± 0.5	0.1 ± 0.1
COOH *trans*-Fenp.	1.5 ± 0.3	1.3 ± 0.4	1.9 ± 0.4	1.0 ± 0.1
4′-OH-Fenp.	2.3 ± 1.8	1.8 ± 0.5	2.0 ± 1.0	1.0 ± 0.4
CH_2OH *trans*-Fenp.	4.5 ± 2.0	6.2 ± 1.9	7.9 ± 1.8	5.3 ± 0.6
4′-OH,CH_2OH *trans*-Fenp.	1.9 ± 0.5	1.4 ± 0.4	2.3 ± 0.6	1.3 ± 0.2
Others	8.9 ± 3.0	7.2 ± 2.3	12.2 ± 6.0	4.9 ± 0.8
Unextractable	3.0 ± 0.5	3.1 ± 1.0	4.4 ± 1.0	2.8 ± 0.4
Total	*57.6 ± 11.5*	*69.2 ± 4.4*	*60.8 ± 8.1*	*69.7 ± 2.7*
Urine				
PBacid	—	—	2.0 ± 0.6	2.3 ± 0.2
PBacid–glycine	—	—	0.9 ± 0.2	0.8 ± 0.2
4′-OH-PBacid–sulfate	—	—	24.8 ± 5.0	18.7 ± 2.3

Table 4 (continued)

Metabolites[a]	% of administered dose			
	Acid labelling		Alcohol labelling	
	Low dose	High dose	Low dose	High dose
2′-OH-PBacid–sulfate	—	—	0.9 ± 0.3	0.5 ± 0.1
TMPA free	0.4 ± 0.2	0.4 ± 0.4	—	—
TMPA–glucuronide	10.3 ± 3.1	8.6 ± 2.2	—	—
TMPA-COOH (*trans*)	2.1 ± 0.6	1.4 ± 0.3	—	—
TMPA-CH_2OH (*trans*) free	5.4 ± 1.8	3.8 ± 0.5	—	—
TMPA-CH_2OH (*trans*)–glucuronide	0.7 ± 0.2	0.6 ± 0.1	—	—
TMPA-CH_2OH-lactone free	1.2 ± 0.4	1.1 ± 0.3	—	—
TMPA-CH_2OH-lactone–glucuronide	1.6 ± 0.5	1.4 ± 0.4	—	—
Others	11.7 ± 3.6	8.5 ± 1.5	4.0 ± 1.1	2.9 ± 0.5
Total	*33.4 ± 9.8*	*25.8 ± 4.1*	*32.6 ± 6.8*	*25.2 ± 3.1*

From Kaneko et al. (1987)

[a] Abbreviations for metabolites:

1. Fenpropathrin = α-cyano-3-phenoxybenzyl 2,2,3,3-tetramethylcyclopropanecarboxylate
2. COOH *trans*-Fenp. = α-cyano-3-phenoxybenzyl 2-carboxy-2,2,3-trimethylcyclopropanecarboxylate
3. 2′-OH-Fenp. = α-cyano-3-(2′-hydroxyphenoxy)benzyl 2,2,3,3-tetramethylcyclopropanecarboxylate
4. 4′-OH-Fenp. = α-cyano-3-(4′-hydroxyphenoxy)benzyl 2,2,3,3-tetramethylcyclopropanecarboxylate
5. CH_2OH *trans*-Fenp. = α-cyano-3-phenoxybenzyl 2-hydroxymethyl-2,3,3-trimethylcyclopropanecarboxylate
6. 2′-OH,CH_2OH *trans*-Fenp. = α-cyano-3-(2′-hydroxyphenoxy)benzyl 2-hydroxymethyl-2,3,3-trimethylcyclopropanecarboxylate
7. 4′-OH,CH_2OH *trans*-Fenp. = α-cyano-3-(4′-hydroxyphenoxy)benzyl 2-hydroxymethyl-2,3,3-trimethylcyclopropanecarboxylate
8. TMPA = 2,2,3,3-tetramethylcyclopropanecarboxylic acid, free or its glucuronide conjugate
9. TMPA-CH_2OH (*trans*) = 2-hydroxymethyl-2,3,3-trimethylcyclopropanecarboxylic acid, free or its glucuronide conjugate
10. TMPA-COOH (*trans*, *cis*) = 2-carboxy-2,3,3-trimethylcyclopropanecarboxylic acid
11. TMPA-lactone = 5,6,6-trimethyl-3-oxabicyclo[3.1.0]hexan-2-one
12. TMPA-$(CH_2OH)_2$ = 2,2-dihydroxymethyl-3,3-dimethylcyclopropanecarboxylic acid
13. TMPA-CH_2OH-lactone = 5-hydroxymethyl-6,6-dimethyl-3-oxabicyclo[3.1.0]hexan-2-one, free or its glucuronide conjugate
14. PBald = 3-phenoxybenzaldehyde
15. 2′-OH-PBacid–sulfate = 3-(2′-hydroxyphenoxy)benzoic acid, sulfate conjugate
16. 4′-OH-PBacid–sulfate = 3-(4′-hydroxyphenoxy)benzoic acid, sulfate conjugate
17. PBacid = 3-phenoxybenzoic acid
18. PBacid–glycine = *N*-3-phenoxybenzoyl-glycine

[b] Mean value of five male rats ± standard deviation.

In the study by Savides et al. (1994) (see section 1.1), urine and faecal samples from 0- to 48-hour collections were pooled together and subjected to metabolic identification. The chromatographic profiles from the faecal extracts were similar, regardless of type of dose, sex or radiolabel position. About 13–34% of the administered dose was excreted as the parent compound (fenpropathrin), about 9–20% as CH_2OH fenpropathrin, about 4–11% as 4′-OH-fenpropathrin and about 2–7% as 4′-OH,CH_2OH fenpropathrin. The chromatographic profiles of the urine from the [acid-^{14}C]fenpropathrin and [alcohol-^{14}C]fenpropathrin groups were different, suggesting that the metabolism of the fenpropathrin molecule involved an ester cleavage between the cyclopropyl and aromatic portions of the molecule. Approximately four metabolites were present in the urine from the [alcohol-^{14}C]fenpropathrin group. All of the major metabolites were identified. The major metabolite in the urine from this group was the sulfate conjugate of 4′-OH-PBacid, representing about 23–44% of

the administered dose. PBacid (1–9% of the administered dose), 4′-OH-PBacid (1–9% of the administered dose) and PBacid–glycine (1–2% of the administered dose) were also excreted in the urine from the [alcohol-^{14}C]fenpropathrin.

The glucuronic acid conjugate of TMPA was positively identified, and TMPA-COOH (*trans*), TMPA-CH_2OH-lactone and TMPA-CH_2OH were tentatively identified in the urine from the [acid-^{14}C]fenpropathrin. Savides et al. (1994) also concluded that the excretion rate, ^{14}C residues and identified metabolites were similar to those obtained in a previous study with fenpropathrin (Crawford & Hutson, 1977). In both the current study and the cited study, predominant biotransformations of fenpropathrin included oxidation at the acid and alcohol moieties, cleavage of the ester linkage and conjugation with sulfuric acid or glucuronic acid (Savides et al., 1994).

On the basis of the identified metabolites, 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 conjugation of the resultant carboxylic acids, alcohols and phenols with glucuronic acid, sulfuric acid and glycine. Most of the urinary metabolites were ester-cleaved ones. The predominant urinary metabolites derived from the acid moiety were identified as TMPA–glucuronide and TMPA-CH_2OH (*trans*). Other metabolites identified were TMPA-COOH (*trans*) and TMPA-CH_2OH-lactone in free form or as the glucuronide. The major urinary metabolites derived from the alcohol moiety were PBacid in free form and as the glycine conjugate, 4′-OH-PBacid–sulfate and 2′-OH-PBacid–sulfate. The urinary metabolites from the alcohol moiety were similar to those from other pyrethroids (e.g. fenvalerate, deltamethrin, cypermethrin). Almost all faecal metabolites retained the ester linkage. 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 components of ^{14}C in tissues. No sex difference was apparent (Kaneko et al., 1987). An aryl-hydroxylated ester (α-cyano-3-(4′-hydroxyphenoxy)benzyl ester) was identified in bile. The ester was eliminated in the bile presumably conjugated (Crawford & Hutson, 1976, 1977).

The proposed metabolic pathway of fenpropathrin in rats is shown in Figure 2.

2. Toxicological studies

2.1 Acute toxicity

(a) Lethal doses

The results of acute toxicity studies with fenpropathrin (including skin and eye irritation and dermal sensitization studies; see below) are summarized in Table 5. All the studies were in compliance with European Union (EU) guidelines of the day and either in compliance with GLP or, where pre-1993, conducted and reported to an adequate standard.

Independent of the route of exposure, onset of toxic signs and lethality are rapid (within a few hours or days, respectively). Recovery in surviving animals is also rapid. Clinical signs of toxicity via oral exposure are indicative of neurotoxicity and include tremors, hindlimb ataxia, decreased spontaneous motor activity, clonic convulsions, salivation, lacrimation, fibrillation and hypersensitivity. In the dog, emesis is also observed; however, the estimated LD_{50} in this species (i.e. > 1000 mg/kg bw; one dog out of the four treated at 1000 mg/kg bw died) appears unreliable, as the subchronic NOAEL and maximum tolerated dose (MTD) are not different from those for other mammalian species.

Non-lethal oral doses range between 10 and 50 mg/kg bw in rats and mice, with the higher value obtained in the same acute oral study for which higher LD_{50} values were determined, and in which 10% gum arabic instead of corn oil was used as the vehicle.

Figure 2. Proposed metabolic pathways of fenpropathrin in mammals

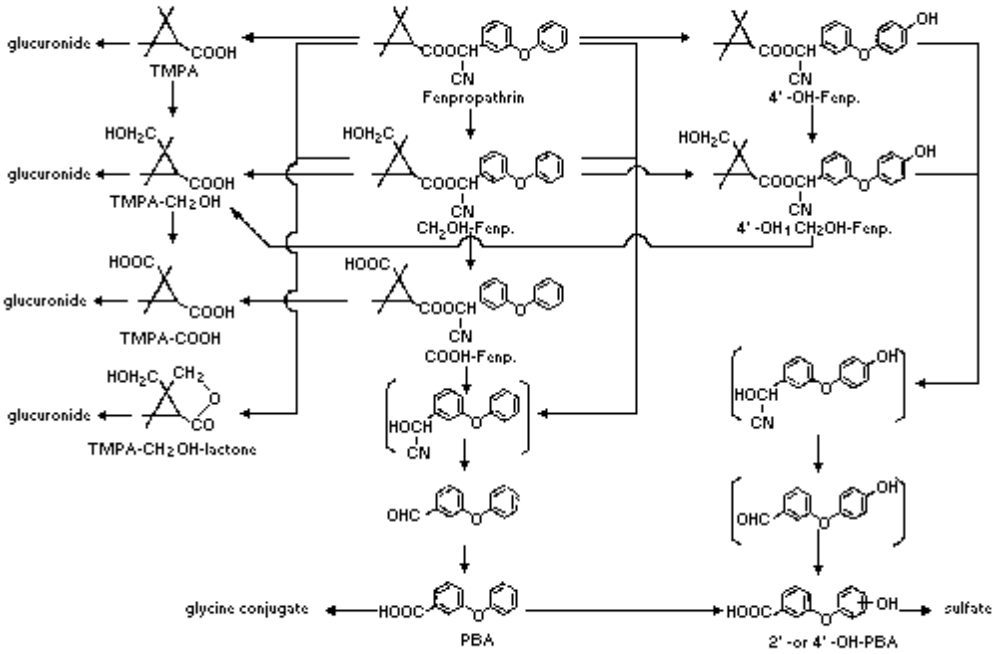


Table 5. Acute toxicity of fenpropathrin

Species	Strain	Sex	Route	Purity; vehicle	Result	Reference
Mouse	dd	M + F	Oral	97.0%; corn oil	LD_{50} M: 67 mg/kg bw F: 58 mg/kg bw	Kohda & Kadota (1975)
Mouse	ICR	M + F	Oral	93.8%; 10% gum arabic	LD_{50} M: 135 mg/kg bw F: 154 mg/kg bw	Suzuki et al. (1986)
Rat	Sprague-Dawley	M + F	Oral	97.0%; corn oil	LD_{50} M: 54.0 mg/kg bw F: 48.5 mg/kg bw	Kohda (1979a)
Rat	Sprague-Dawley	M + F	Oral	97.3%; 10% gum arabic	LD_{50} M: 164 mg/kg bw F: 104 mg/kg bw	Hiromori et al. (1982)
Rat	Sprague-Dawley	M + F	Oral	97.3%; corn oil	LD_{50} M: 77.4 mg/kg bw F: 66.7 mg/kg bw	Hiromori et al. (1983a)
Rat	Sprague-Dawley	M + F	Oral	91.8%; corn oil	LD_{50} M: 70.6 mg/kg bw F: 66.7 mg/kg bw	Hiromori et al. (1983b)
Rat	Sprague-Dawley	M + F	Oral	93.8%; corn oil	LD_{50} M: 60 mg/kg bw F: 70 mg/kg bw	Omodaka et al. (1986a)
Rat	Sprague-Dawley	F	Oral	92.7%; corn oil	LD_{50} > 50 mg/kg bw but < 259 mg/kg bw	Asano (2011a)

Species	Strain	Sex	Route	Purity; vehicle	Result	Reference
Rabbit	Japanese albino	M + F	Oral	96.2%; corn oil	LD_{50} M: 675 mg/kg bw F: 510 mg/kg bw	Hara & Suzuki (1980)
Dog	Beagle	M + F	Oral	96.2% (adjusted to 100% for dose calculation); gelatine capsule	LD_{50} > 1000 mg/kg bw	Pence et al. (1979)
Rat	Sprague-Dawley	M + F	Dermal	97.0%; corn oil	LD_{50} M: 1600 mg/kg bw F: 870 mg/kg bw	Kohda (1979b)
Rat	Sprague-Dawley	M + F	Dermal	93.8%; corn oil	LD_{50} > 5000 mg/kg bw	Omodaka et al. (1986b)
Rat	Sprague-Dawley	M + F	Dermal	92.7%; no vehicle	LD_{50} > 2000 mg/kg bw	Asano (2011b)
Rabbit	New Zealand White	M + F	Dermal	Technical grade; no vehicle	LD_{50} > 2000 mg/kg bw	Marroquin et al. (1981)
Mouse	ICR	M + F	Inhalation (whole body)	97% (formulated at 200 g/l in distilled water)	LC_{50} (3 h) M: 100 mg/m^3 F: 43 mg/m^3 NOEC 4.5 mg/m^3	Kohda et al. (1976)
Mouse	Swiss Webster	M + F	Inhalation (whole body)	94.5%	LC_{50} > 0.009–0.011 mg/l	Bruce et al. (1986)
Rat	Sprague-Dawley	M + F	Inhalation (whole body)	97% (formulated at 200 g/l in distilled water)	LC_{50} (3 h) > 96 mg/m^3 NOEC 12 mg/m^3	Kohda et al. (1976)
Rat	Sprague-Dawley	M + F	Inhalation (whole body)	94.5%	LC_{50} > 0.009–0.011 mg/l	Bruce et al. (1986)
Rat	Sprague-Dawley	M + F	Inhalation (mist, nose only)	92.7%	LC_{50} 556–1340 mg/m^3	Asano (2011c)
Mouse	dd	M + F	Subcutaneous	97.0%; corn oil	LD_{50} M: 1350 mg/kg bw F: 900 mg/kg bw	Kohda & Kadota (1976)
Rat	Sprague-Dawley	M + F	Subcutaneous	97.0%; corn oil	LD_{50} M: 1410 mg/kg bw F: 900 mg/kg bw	Kohda & Kadota (1976)
Mouse	dd	M + F	Intraperitoneal	97.0%; corn oil	LD_{50} M: 230 mg/kg bw F: 210 mg/kg bw	Kohda & Kadota (1976)
Rat	Sprague-Dawley	M + F	Intraperitoneal	97.0%; corn oil	LD_{50} M: 225 mg/kg bw F: 180 mg/kg bw	Kohda & Kadota (1976)

Table 5 (continued)

Species	Strain	Sex	Route	Purity; vehicle	Result	Reference
Mouse	Swiss Webster	M	Intravenous	Not given; glycerol formal	LD_{50} 4.5 mg/kg bw	Summitt & Albert (1980)
Rabbit	Albino	M	Skin irritation	90.2%	Non-irritating	Matsubara et al. (1979)
Rabbit	New Zealand White	M	Skin irritation	93.0%	Slightly irritating	Young-Ha (2011a)
Rabbit	Albino	M	Eye irritation	90.2%	Mildly irritating	Matsubara et al. (1979)
Rabbit	New Zealand White	M	Eye irritation	93.0%	Minimally irritating	Young-Ha (2011b)
Guinea-pig	Hartley	M	Skin sensitization	97%; corn oil	Non-sensitizing	Okuno, Kadota & Miyamoto (1975)
Guinea-pig	Hartley	M	Skin sensitization (Buehler method)	88.1%; acetone	Non-sensitizing	Suzuki & Miyamoto(1981)
Guinea-pig	Hartley	M	Skin sensitization (Buehler method)	93.0%; acetone	Non-sensitizing	Kawabe (2011)
Impurity						
Mouse	dd	M + F	Oral	TMPA-AH > 99%	LD_{50} M: 1450 mg/kg bw F: 1880 mg/kg bw	Misaki et al. (1981)

F, female; LC_{50}, median lethal concentration; LD_{50}, median lethal dose; M, male; NOEC, no-observed-effect concentration; TMPA-AH, 2,2,3,3-tetramethylcyclopropanecarboxylic anhydride

The impurity 2,2,3,3-tetramethylcyclopropanecarboxylic anhydride (purity > 99%) was shown to possess significantly lower toxicity, as the LD_{50} values were 1450 mg/kg bw for male mice and 1880 mg/kg bw for female mice. Deaths occurred at 1000 mg/kg bw and above. The toxic symptoms, such as decreased spontaneous activity, ataxia, limb paralysis, irregular respiration, hyperpnoea followed by dyspnoea, piloerection and urinary incontinence, were observed at 500 mg/kg bw and above in both sexes. These symptoms developed 1–2 hours after treatment and disappeared within 3–5 days (Misaki et al., 1981).

(b) Dermal and ocular irritation

The potential of fenpropathrin to irritate the skin and eyes (see Table 5) was evaluated in rabbits. Fenpropathrin did not cause any irritation to the skin in a first study (Matsubara et al., 1979). In a second study, transient, barely perceptible erythema (degree 1) was observed; no sign of irritation was present in any of the animals 7 days after completion of exposure (Young-Ha, 2011a).

Transient redness and chemosis, disappearing by 72 hours, were observed following instillation into the eye in a first study (Matsubara et al., 1979). In a second study, initial slight redness and chemosis (degree 1) disappeared within 24 hours (Young-Ha, 2011b).

(c) Dermal sensitization

The sensitization potential of fenpropathrin (see Table 5) was evaluated in guinea-pigs in three studies, one of which used intradermal repeated inductions, another used an experimental design similar to the Buehler method and the more recent Buehler study used undiluted technical-grade fenpropathrin for both the three inductions and the challenge applications. Fenpropathrin did not show any sensitizing potential in any of these studies (Okuno, Kadota & Miyamoto, 1975; Suzuki & Miyamoto, 1981; Kawabe, 2011).

2.2 Short-term studies of toxicity

The toxicity of fenpropathrin following short-term exposure was evaluated in mice, rats and dogs. Apart from very old studies and published papers, all the studies were in compliance with modern EU guidelines and either in compliance with GLP or, where pre-1993, conducted and reported to an adequate standard.

(a) Oral administration

Mice

In a first 4-week range-finding study for a carcinogenicity study, groups of eight male and eight female CD-1 mice received fenpropathrin (purity not indicated) in their diet at a concentration of 0, 100, 200 or 300 ppm (equal to 0, 12.1, 26.9 and 40.0 mg/kg bw per day for males and 0, 14.7, 29.2 and 44.7 mg/kg bw per day for females, respectively). Stability and homogeneity of the diets were assessed. Fresh diets were prepared weekly. All animals were observed twice daily for clinical signs and mortality. Body weights were recorded prior to treatment and then weekly thereafter. Feed consumption was measured weekly. All animals were necropsied after 4 weeks of treatment and examined for gross pathology. Absolute and relative organ weights were calculated, and a complete list of tissues/organs was preserved, but not processed further.

In view of the absence of any toxic findings in this study, doses of 500, 1000 and 1500 ppm were chosen for a subsequent range-finding study (Colley et al., 1981a).

In a second 4-week range-finding study, groups of eight male and eight female CD-1 mice received fenpropathrin (purity not indicated) in their diet at a concentration of 0, 500, 1000 or 1500 ppm (equal to 0, 63, 123 and 204 mg/kg bw per day for males and 0, 69, 142 and 216 mg/kg bw per day for females, respectively). Mice were observed twice daily for mortality and clinical signs. Body weights and feed consumption were recorded weekly. Water consumption was visually monitored daily. After 4 weeks of treatment, surviving animals were killed and necropsied. Absolute and relative organ weights were calculated for adrenals, brain, heart, kidney, liver, lung, spleen, testes and ovaries, and a complete list of tissues/organs was preserved, but not processed further.

Three males and two females receiving 1500 ppm were found dead during the 1st day of treatment. An increased incidence of piloerection was noted in the majority of males and females treated at 1500 ppm and in two males at 1000 ppm. On occasion, this sign was associated with hunched posture, lethargy, body tremors and dark discoloration of the eyes for one or two males receiving 1500 ppm and with dark discoloration of the eyes for one male at 1000 ppm. Pallor of the extremities was also noted in two males and two females treated at 1500 ppm and in one female treated at 1000 ppm. Body weight gain was reduced in males receiving 1000 or 1500 ppm. Although feed consumption was not affected by treatment, impaired efficiency of feed utilization was noted for males treated at 1000 ppm and for animals of both sexes at 1500 ppm. Necropsy of decedent mice and of mice sacrificed at termination of the study did not reveal any treatment-related findings. Analysis of organ weight data revealed a dose-related increase in liver weights of male mice, not attaining statistical significance for those treated at 500 ppm. Relative kidney weight was also increased in males at 1500 ppm. These differences were not apparent in females.

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 1000 ppm (equal to 123 mg/kg bw per day). The dose of 1000 ppm was considered suitable for a long-term carcinogenicity study in mice (Colley et al., 1981b).

Although a 2-year carcinogenicity study in CD-1 mice (52 of each sex per dose) with fenpropathrin (purity not indicated) was started with dose levels of 0, 40, 200 and 1000 ppm, as a result of the high mortality in mice receiving 200 and 1000 ppm, the study was terminated after 13 weeks of treatment. Achieved doses until week 13 in that study were 0, 4.9, 24.7 and 130 mg/kg bw per day for male mice and 0, 5.7, 27.8 and 139 mg/kg bw per day for female mice, respectively. At termination, laboratory investigations were not performed. Macroscopic examination was performed on all animals that died prematurely or were killed and on 20 males and 20 females from each group. Histopathological examination was limited to mice that died prematurely or were killed during the first 11 weeks of the treatment.

Occasional body tremors were noted for a few males receiving 1000 ppm from week 1 onwards and for one male receiving 200 ppm in week 2. Nineteen males and eight females receiving 1000 ppm, four males receiving 200 ppm, one male and one female receiving 40 ppm and two control males were found dead. One additional male receiving 1000 ppm was killed due to poor conditions. The cause of death for these animals was not established. The clinical signs (tremors) were mostly observed in moribund animals. Slightly higher feed consumption and body weight gain were noted for males receiving 200 and 1000 ppm. Slightly higher liver weights were recorded for animals treated at 1000 ppm. No treatment-related morphological changes were detected at histopathological examination of decedent animals (Colley et al., 1982c).

Rats

In a 25-day toxicity study, groups of six male and six female Sprague-Dawley rats received fenpropathrin (purity not indicated) in their diet at 0 or 900 ppm (equivalent to 0 and 90 mg/kg bw per day) for 25 days. Daily observations on the general health and behaviour of each animal were made. Following gross pathological examination, sections of sciatic nerve were stained by the cresyl violet–luxol fast blue method for myelin and by the Glees and Marsland method for axons and then examined histologically.

Fine tremors appeared in treated male rats on day 2; by day 12, the tremors were violent, with erratic jumping in three males. One male rat was found dead on each of days 16 and 20. On day 25, the remaining four male rats still exhibiting tremors were sacrificed. In the females treated for 1 day, one rat was found dead, and three out of the five remaining showed tremors. By day 3, all five exhibited tremors, one rat showed erratic jumping and one rat was moribund and sacrificed. By day 5, all treated females were dead or sacrificed. Swelling and disintegration of nerve axons, in some cases apparently involving almost every fibre, were present in all except 1 of the 12 rats treated at 900 ppm, even in those whose survival time was very short. No definitive myelin lesion was seen. The nerves from the control animals were normal (Stevenson et al., 1976).

In a 4-week range-finding study, groups of 10 male and 10 female Sprague-Dawley rats received fenpropathrin (purity not indicated) in their diet at a concentration of 0, 1, 5, 50 or 500 ppm (equal to 0, 0.08, 0.40, 4.04 and 38.4 mg/kg bw per day for males and 0, 0.08, 0.41, 4.40 and 42.8 mg/kg bw per day for females, respectively). Fresh diets were prepared weekly. Stability, homogeneity and dietary concentrations were evaluated periodically. All animals were examined twice daily for mortality and clinical signs. Body weights and feed consumption were recorded weekly. Ophthalmic examinations were performed on all rats of the control and high-dose groups before treatment commenced and during week 4. Blood samples were taken from fasted animals of the control and high-dose groups after 4 weeks for haematology and clinical chemistry. All animals were necropsied at the end of the study and examined for gross pathology. Absolute and relative

organ weights were determined. At terminal sacrifice, a piece of liver was taken and frozen immediately (approximately −70 °C) in a bath of hexane immersed in a bath of acetone containing solid carbon dioxide. A complete list of tissues and organs was preserved in buffered 10% formalin (Davidson's fluid for the eyes). Tissues examined microscopically (liver, kidney, spleen, heart, lungs, tibial and sciatic nerves from all animals of the control and high-dose groups) were stained with haematoxylin and eosin. In addition, frozen sections of liver fixed in buffered formalin were stained with Oil Red O. Fresh frozen sections of liver were also stained with periodic acid–Schiff reagent to demonstrate glycogen. Sections of kidney were stained with Oil Red O or periodic acid–Schiff reagent at the discretion of the pathologist. Nerve tissue was stained with luxol fast blue (Kluver and Borrera method) and silver nitrate (Glees and Marsland method).

There was no mortality or clinical signs. Treatment had no effect on body weight, body weight gain, feed consumption or efficiency of feed utilization. No abnormality was noted at ophthalmic examinations. Haematology did not reveal any difference from controls. At week 4, marginally higher group mean creatinine and alanine aminotransferase (ALT) levels were recorded in males treated at 500 ppm; however, as all individual values were within acceptable limits, these changes were not considered of biological significance. No treatment-related findings were detected at necropsy. Slightly higher relative spleen weight and marginally higher liver weights, not attaining statistical significance, were noted in males treated at 500 ppm. No treatment-related findings were noted at microscopic examination.

The NOAEL was 500 ppm (equal to 38.4 mg/kg bw per day in males), the highest dose tested. A further range-finding study was considered appropriate for setting dose levels for the combined toxicity/carcinogenicity study (Colley et al., 1982a).

In another 4-week range-finding study, groups of 10 male and 10 female Sprague-Dawley rats received fenpropathrin (purity not indicated) in their diet at a concentration of 0, 500, 700, 1000 or 1500 ppm. The mean compound intakes in males were 44 and 65 mg/kg bw per day at 500 and 700 ppm, respectively. The mean compound intakes in females were 51 and 85 mg/kg bw per day at 500 and 700 ppm, respectively. Because of a high incidence of mortality or severe clinical signs, all surviving animals treated at 1000 and 1500 ppm were terminated on days 4 and 3, respectively. Fresh diets were prepared weekly. Stability, homogeneity and concentrations of diets were confirmed analytically. All animals were examined twice daily for mortality and clinical signs. Body weights and feed consumption were recorded weekly. Ophthalmic examinations were performed on all rats of the control and high-dose groups before treatment commenced and during week 4. Samples were taken from all fasted surviving animals after 4 weeks for haematology and clinical chemistry. All animals were necropsied at the end of the study and examined for gross pathology. Absolute and relative organ weights were determined. A complete selection of tissues and organs was preserved, but not processed further.

In the morning of day 2, one male and three females treated at 1500 ppm and one male treated at 700 ppm were found dead. Eight of the remaining nine males and five of the remaining seven females treated at 1500 ppm showed marked body tremors and involuntary movements. Similar but less marked signs were noted in most females treated at 1000 ppm, in one or more males receiving 700 or 1000 ppm and in all females treated at 700 ppm. The severity of the signs was considered to be associated with nocturnal feeding, because they became less severe during the day, although an additional female treated at 1500 ppm died and another one was killed due to marked clinical signs. The following day, further deaths were recorded in male and female rats treated at 1500 ppm; in view of the severity of the clinical signs, the surviving rats of this dose group were terminated. Overnight mortalities were also recorded among rats of all treated groups. Body tremors were noted in most males and a few females treated at 1000 ppm, and less marked signs were noted in a few rats receiving 700 ppm. On day 4, following further overnight mortalities and the presence of severe clinical signs in rats treated at 1000 ppm, all surviving rats of this dose group were terminated. From day 4 onwards, one male and three females at 500 ppm and two males and four females at 700 ppm

were found dead. During this period, body tremors were recorded on isolated occasions in rats treated at 700 ppm and in a few females at 500 ppm. One female at 500 ppm and one male and two females at 700 ppm were killed due to severe clinical signs or moribund conditions. General signs of hypersensitivity were noted in rats of both sexes treated at 500 or 700 ppm. Slightly lower body weight gain was noted in males receiving 700 ppm and in females at 500 ppm. A more marked reduction in body weight gain was noted in the single surviving female at 700 ppm. This was associated with slightly lower feed intake in males, but not in females, whereas efficiency of feed utilization appeared reduced, compared with the controls, in females at 700 ppm only. Haematological examinations at week 4 revealed increases in red blood cell and neutrophil counts and increased haemoglobin concentration with reduced mean corpuscular volumes (not attaining statistical significance) in males at 700 ppm. Slightly lower platelet counts were noted in males at 500 and 700 ppm. Marginally lower total white cell and neutrophil counts were recorded in most females treated at 500 ppm, with a similar effect also noted for the surviving female at 700 ppm. Clinical chemistry revealed lower calcium levels in males at 700 ppm and marginally lower globulin levels in males at 500 and 700 ppm. Marginally lower total protein and albumin levels were recorded in females treated at 500 ppm and in the surviving female at 700 ppm. No changes were noted at ophthalmic examination.

Necropsy of decedent animals, sacrificed animals or animals at termination did not show any treatment-related findings. Relative kidney weight was increased in females at 500 ppm and in males at 700 ppm (not attaining statistical significance).

A NOAEL was not established in this study. The lowest-observed-adverse-effect level (LOAEL) was 500 ppm (equal to 44 mg/kg bw per day) (Colley et al., 1982b).

The difference in results at 500 ppm between the two 4-week oral studies is considered to be related to the achieved test compound intake. This was maximal during the first 2 weeks of dosing and was 45.4 mg/kg bw per day in males and 47.5 mg/kg bw per day in females in the first study, whereas it was 53.13 mg/kg bw per day in males and 59.69 mg/kg bw per day in females in the second study. Results suggest a steep dose–response relationship, with the NOAEL being around 50 mg/kg bw per day in the rat (Heywood, 1982).

In a first 13-week study, groups of 12 male and 12 female Carworth Farm E rats received fenpropathrin (purity 96%) in powdered diets at a concentration of 0, 2, 10, 50 or 250 ppm (equivalent to 0, 0.1, 0.50, 2.5 and 12.5 mg/kg bw per day, respectively); the control group consisted of 24 male and 24 female rats. Daily observations were made on the general health and behaviour of each animal. Body weights and feed intakes were recorded weekly. The animals were necropsied after 13 weeks. Following gross pathological examination, major viscera were weighed, and microscopic examination of a selection of organs from all animals in the control, 50 and 250 ppm groups was carried out. Terminal blood samples were taken by cardiac puncture for haematological and clinical chemistry examinations.

No clinical signs or behavioural changes were noted during the study. In male rats, there were increases in body weight gain at weeks 1, 2 and 3 at all dose levels and at week 4 in those treated at 50 and 250 ppm only. This effect was seen in females only in week 1 at 10, 50 or 250 ppm. Feed intake was comparable among the treated and control groups. A slightly lower relative liver weight was recorded in rats of both sexes treated at 10 ppm, but not in those treated at higher dose levels. Absolute and relative spleen weights were increased in males at 250 ppm; this was the only change concerning organ weights and may present a borderline effect. No treatment-related changes were noted in haematological or clinical chemistry parameters, and no findings related to treatment were noted at histopathology (Hend & Butterworth, 1975).

In a second 13-week study, groups of 12 male and 12 female Sprague-Dawley rats received fenpropathrin (purity 97%) in their diet at a concentration of 0, 3, 30, 100, 300 or 600 ppm (equivalent to 0, 0.15, 1.5, 5, 15 and 30 mg/kg bw per day); the control group consisted of 24 male and 24 female rats. The 600 ppm treatment level was added to the test design late and thus was handled separately from the other treatments and was not included in the block randomization. However, the results for this treatment level were compared with the controls in the main test. Daily observations on the general health and behaviour of each animal were made. Body weights and feed intakes were recorded weekly. The animals were necropsied after 13 weeks. Terminal blood samples were taken by cardiac puncture for haematological and clinical chemistry examinations. Following gross pathological examination, major viscera were weighed, and a selection of organs from all animals in the control, 100, 300 and 600 ppm groups was examined microscopically.

General health and body weight gain were unaffected in all animals except those treated at 600 ppm. Tremors occurred in 1 out of 12 males and 9 out of 12 females. The tremors appeared after 5 weeks of treatment, but disappeared completely later in the study (by week 11). Significant ($P < 0.01$) decreases in body weight (8–14%) were seen in females receiving 600 ppm throughout the study. High-dose males had significant reductions in body weight from week 1 to week 5. Body weights for lower treatment groups were comparable with those of the controls. Examination of haematological parameters revealed decreases in haemoglobin concentration and mean erythrocyte volume and an increase in prothrombin time in males treated at 600 ppm. Clinical chemistry revealed an increase in plasma alkaline phosphatase activity in rats of both sexes receiving 600 ppm (33% males; 42% females) and a slight increase in plasma potassium in males only. Increases in relative kidney weight in males (7.2%) and relative brain weight in females (6.2%) treated at 600 ppm were observed. No microscopic findings were noted at histopathology.

The NOAEL was considered to be 300 ppm (equivalent to 15 mg/kg bw per day), based on clinical signs of tremors, body weight reductions, decreased blood clotting time in females and possibly increased alkaline phosphatase levels (both sexes) at 600 ppm (equivalent to 30 mg/kg bw per day) (Hend & Butterworth, 1976).

In a third 13-week toxicity study, groups of 12 male and 12 female Sprague-Dawley (Crj:CD) rats received fenpropathrin (purity 93.1%) in pulverized diet at a concentration of 0, 15, 50, 150, 450 or 600 ppm (equal to 0, 0.72, 2.49, 7.22, 21.3 and 28.8 mg/kg bw per day for males and 0, 0.82, 2.82, 8.18, 25.2 and 36.1 mg/kg bw per day for females, respectively). Stability, homogeneity and concentrations of the prepared diets were confirmed analytically. All animals were observed daily for clinical signs, and detailed clinical examinations were performed at least weekly. Body weights and feed consumption were recorded weekly. Ophthalmic examinations were carried out on all animals at initiation of treatment and on all surviving animals of the control and 600 ppm groups during week 13. Haematology, clinical chemistry and urine analysis evaluations were performed on all animals during week 13 or at termination. Gross necropsy and histopathology were conducted on all animals; absolute and relative organ weights were determined.

A single female treated at 600 ppm died on day 46, but it was not possible to determine the cause of death. No clinical signs were observed during the study in any of the treated or control animals. Body weights of rats treated at 600 ppm were significantly reduced, compared with controls, during the 1st week of treatment. Thereafter, body weights in males were just slightly, but not significantly, lower than those of controls, whereas body weights of females remained significantly lower than control values for the rest of the study, with terminal body weights 10% lower than control values. Females treated at 450 ppm also showed slightly lower body weights when compared with controls during the first 2 weeks of treatment, with statistical significance attained on week 2 only. At 150 ppm, the mean body weight of males at week 13 was significantly higher than that of controls. Effects on body weight were in general accompanied by reductions in feed consumption, and calculation of efficiency of feed conversion showed lower efficiency for females at 600 ppm for the entire treatment period, with a few exceptions in weeks 3, 4 and 6. No treatment-related observations

were noted at ophthalmic examinations. At urine analysis, increases in urine protein and specific gravity were noted in males treated at 450 and 600 ppm. As there were no changes in total protein or blood urea nitrogen at clinical chemistry and no abnormal findings in kidney at histopathology, the increases in urine protein and specific gravity were not considered to be toxicologically significant. No differences from controls were noted at haematology, whereas clinical chemistry revealed an elevated activity of alkaline phosphatase in females treated at 600 ppm. No treatment-related findings were observed at necropsy; the decedent female at 600 ppm had dark-coloured and oedematous lungs. Analysis of organ weight data showed an increase of relative brain weight in females at 600 ppm, an increase in relative kidney weight in females at 450 ppm and a decrease in absolute testes weight in males at 15, 50 and 150 ppm, with relative testes weight also decreased at 150 ppm. As the changes in relative brain weight were accompanied by a reduction in body weight, these changes were not considered to be indicative of a direct effect of treatment. As the changes in relative kidney weight and testes weights were not observed at the highest dose level of 600 ppm, these changes were not considered treatment related. The incidence of hepatic microgranulomas was significantly increased in males treated at 450 ppm, but not in males at 600 ppm, and decreased in females at 15, 50, 450 and 600 ppm. One female treated at 450 ppm had a nephroblastoma. Pulmonary congestion and oedema were microscopically observed in the decedent female. As the histopathological findings described above were usually observed in young rats or were not observed at the highest dose level of 600 ppm, they were not considered treatment related.

The NOAEL was 450 ppm (equal to 21.3 mg/kg bw per day), based on decreased body weight gain, decreased feed consumption and slightly increased alkaline phosphatase activity seen at 600 ppm (equal to 28.8 mg/kg bw per day) (Yosida et al., 1986).

Dogs

In a first range-finding study, one male and one female purebred Beagle dog received fenpropathrin (purity 96.2%, adjusted to 100% for dosage calculation) in their diet at a concentration of 4000 ppm (equivalent to 100 mg/kg bw per day) for 4 days. They were then returned to control feed because the animals were eating only very small quantities of the treated diet and suffered severe emesis. After 3 days on control feed, the dogs were given a diet containing fenpropathrin at 2000 ppm for the remaining 8 days of the study. All dogs were observed for mortality and clinical signs twice daily. Feed consumption was determined on days 5, 8 and 15. On day 15, all dogs were anaesthetized with thiamylal sodium, sacrificed by exsanguination following an overnight fast and examined macroscopically.

Severe emesis and mucoid or blood mixed with mucoid faeces were noted in the two treated dogs receiving 4000 ppm in the diet. When returned to control diet on day 5, the dogs appeared normal except for one incident of dried food emesis. After day 8, the dogs again received a treated diet at 2000 ppm, and observations included tremors and absence of faeces. On day 15, both dogs were observed to have low posture. The female dog additionally had slight tremors, moderate ataxia and decreased locomotor activity. Both animals were sacrificed the following day. Body weight loss between 1 and 2 kg was observed during the study. This was associated with a marked reduction in feed intake. At necropsy, one dog had no findings, whereas the other one had a kidney with cut surface reddened (Pence et al., 1979).

In a 13-week study, groups of six male and six female Beagle dogs received fenpropathrin (purity 96.2%, adjusted to 100% for dosage calculation) in their diet at a concentration of 0, 250, 500 or 1000/750 ppm (1000 ppm for weeks 1–3, 750 ppm for weeks 4–13). Mean substance intakes were 0, 7.4, 15.5 and 24 mg/kg bw per day for males and 0, 9.6, 15.9 and 28.7 mg/kg bw per day for females, respectively. Fresh diets were prepared weekly. All animals were observed for clinical signs and mortality daily for the first 2 weeks and then weekly for the remainder of the period. Criteria evaluated included survival, appearance and behaviour, body weight (weekly), feed consumption (weekly), clinical laboratory studies (weeks 0, 4, 8 and 13), urine analysis (weeks 0 and 13),

ophthalmic examinations (weeks 0 and 13), terminal body weight and organ weight data, and gross and microscopic pathology.

There were no definite dose-related effects seen in the clinical chemistry, urine analysis, gross necropsy, organ weights, histopathology or ophthalmological analyses. One high-dose male was sacrificed moribund during week 3, showing tremors and decreased locomotor activity. Clinical signs of toxicity at all treatment levels included soft and mucoid stools and/or diarrhoea, emesis, tremors, ataxia and sometimes lethargy, panting and salivation. The tremors and ataxia were generally first observed during the 2nd week of treatment and were of such severity in the high-dose dogs that the dose level for this group was lowered to 750 ppm at the beginning of week 4. The frequency of the observed clinical signs decreased after week 5 in all treated groups. Slight differences in body weight gain were found in the mid-level female group (6% decrease relative to controls) and in both sexes in the high-dose group (6% decrease in males, 7% decrease in females, relative to controls). The mean haematocrit, haemoglobin and erythrocyte count values were decreased in dogs of both sexes treated at the highest concentration at weeks 4, 8 and 13. The LOAEL was 250 ppm (equal to 7.4 mg/kg bw per day), based on effects on the gastrointestinal system, tremors and nervousness. A NOAEL was not established in this study (Pence et al., 1980a,b).

In a 1-year toxicity study, groups of four male and four female Beagle dogs received fenpropathrin (purity 92.5%, adjusted to 100% for dosage calculation) in their diet at a concentration of 0, 100, 250 or 750 ppm (equal to 0, 3.1, 8.2 and 24.4 mg/kg bw per day for males and 0, 3.1, 7.7 and 24.7 mg/kg bw per day for females, respectively). The homogeneity and stability of the diets were assessed by analytical methods. Fresh diets were prepared weekly, and concentrations were confirmed periodically. Haematology, blood biochemistry and urine analysis evaluations were conducted for all animals prior to treatment initiation and at weeks 13, 26 and 52. Ophthalmic examinations were performed on all animals prior to initiation and at termination of treatment. Gross necropsy and histopathological evaluations were performed for all animals at study termination, including myelin- and axon-specific stains (Klüver-Barrera luxol fast blue stain for myelin and Hirano-Zimmerman silver stain for nerves); organ weights were recorded for all animals at termination.

One high-dose male was found dead during week 32. Prior to death, the animal was languid and thin and exhibited ataxia, tremors and polypnoea (excessive respiration). There were numerous gross findings (including soft brain, enlarged and congested liver, enlarged lymph nodes, ulcerations and erosions of the oral cavity, perforations of the tongue and multiple skin sores) and histopathological findings (including adrenal congestion and haemorrhage, pulmonary oedema and congestion, liver, kidney and stomach congestion, decreased spermatogenesis, prostate atrophy, thymus atrophy and multiple lesions of the oral cavity). There were, however, no other deaths and no gross pathological or histopathological lesions in any other treatment group. Clinical signs included tremors (750 ppm during week 1 to termination; 250 ppm starting at week 6 and sporadically thereafter); ataxia (750 ppm starting at week 2 and consistently observed from week 8 to week 32 and sporadically observed from week 33 to week 53); and languid appearance (750 ppm, weeks 7 through 48). Mean body weight of high-dose dogs was reduced (< 11% in males and 20% in females). No effect was seen on body weight in the lower treatment groups. Feed consumption, ophthalmic examinations, haematology, clinical chemistry and urine analysis as well as gross and microscopic pathology and organ weight data did not reveal any treatment-related findings.

The NOAEL was 100 ppm (equal to 3.1 mg/kg bw per day), based on occurrence of tremors in dogs treated at 250 ppm (equal to 7.7 mg/kg bw per day) (Pence et al., 1984).

(b) Dermal application

Rats

In a 21-day dermal toxicity study, fenpropathrin (purity 92.0%) was applied to the shaved intact skin of 10 Sprague-Dawley rats of each sex per dose at a dose level of 0, 50, 200 or 1000 mg/kg

bw per day for 6 hours/day, 7 days/week, for 21 days. At the end of the 6-hour exposure period, the dressings were removed, the residual test article was wiped from the application area with gauze immersed in lukewarm water and the application area was dried with tissue paper. The animals were restrained with neck collars throughout the administration period. The animals were examined for clinical signs and mortality twice a day. Animals were weighed prior to initiation of dosing, on days 1, 4, 8, 11, 15, 18 and 21 and at study termination. The eyes of all animals were examined on the day prior to initiation of treatment, and rats in the control and high-dose groups were examined again during week 3 (day 19). After the end of the administration period, all of the animals were fasted for approximately 18–24 hours, and blood was collected for evaluation of clinical chemistry and haematological parameters. Selected organs were weighed, and a complete macroscopic examination was conducted. Selected tissues and organs from the control and high-dose animals were also examined histopathologically.

All animals survived until scheduled termination, and there were no adverse effects of treatment on clinical observations, body weight, feed consumption, ophthalmoscopic examinations, haematology, organ weights or gross pathology in either sex. A transient change in feed consumption was noted in females on day 1; however, there was no effect on the overall body weight or body weight gain. Triglycerides were increased by 33% over controls in the 200 and 1000 mg/kg bw per day females. However, there were no other differences in clinical chemistry, indicating an effect on lipid metabolism. Similarly, there were no effects of treatment on liver weights and no treatment-related macroscopic or microscopic findings in the liver. Thus, the increased triglycerides were considered of equivocal toxicological significance. Examination of the treated application site indicated squamous cell hyperplasia and mononuclear cell infiltration in the dermis and crust. However, all of these lesions were slight in severity and were not accompanied by other signs of dermal irritation (e.g. oedema, erythema, scabbing or necrosis), and therefore they were not considered adverse.

The NOAEL was 1000 mg/kg bw per day, the highest dose tested (Furukawa, 2006; Ohta, 2006).

Rabbits

In a 21-day dermal toxicity study in rabbits, groups of five male and five female New Zealand White rabbits were dosed 5 days/week for 3 weeks (15 doses) with fenpropathrin (purity 91.4%) on abraded or unabraded skin at a dose of 0, 500, 1200 or 3000 mg/kg bw per day. The test article was premoistened with normal saline and evenly distributed over the rabbits' backs. The high-dose animals were dosed over 15–20% of their total skin surface. The dosing sites were occluded, and the rabbits were fitted with collars to prevent ingestion of the test article. The skin application site was washed with tap water after 6 hours of exposure. The animals were examined for clinical signs and mortality twice a day. Body weight was determined before the start of the administration period in order to randomize the animals and twice weekly thereafter. Skin irritation was scored daily. The blood sample from each treated rabbit was analysed for clinical chemistry and haematological parameters. Selected organs were weighed, and a complete macroscopic examination was conducted. Selected tissues and organs were also examined histopathologically.

A low-dose rabbit died of unknown causes. Many high-dose rabbits had doubtful or barely perceptible erythema and oedema. There were no dose-related effects on mortality, clinical signs, body weight, feed consumption, haematology or clinical chemistry parameters, gross pathology or organ weights. No histopathological findings were noted in the liver or kidneys. Trace or mild "inflammatory cell infiltrate" in the intact and abraded skin, which was noted in males and females receiving all doses, including the controls, was attributed by the study authors to the test material.

The NOAEL was 3000 mg/kg bw per day, the highest dose tested (Riley et al., 1982).

(c) Exposure by inhalation

No studies are available.

2.3 Long-term studies of toxicity and carcinogenicity

All studies were certified as complying with GLP.

Mice

In a carcinogenicity study in mice, groups of 52 CD-1 mice of each sex per dose received fenpropathrin (purity 91.04% and 92.5%) in their diet at a concentration of 0, 40, 150 or 600 ppm for 104 weeks (equal to 0, 3.9, 13.7 and 56.0 mg/kg bw per day for males and 0, 4.2, 16.2 and 65.2 mg/kg bw per day for females, respectively). Each group also contained 40 satellite animals of each sex for interim sacrifice after 26, 52 and 78 weeks of treatment. Stability, homogeneity and dietary concentrations were confirmed analytically. All animals were observed for clinical signs and mortality twice a day during weekdays and once a day during weekends. Body weight and feed consumption were recorded weekly. Water intake was measured daily for 5 days during weeks 24, 50 and 76 and prior to termination. Haematological investigations were performed on 10 animals of each sex per group from the satellite groups at weeks 25, 53 and 79 (all surviving satellite animals) and on all surviving mice at termination. Clinical chemistry investigations were similarly performed at weeks 24, 53 and 79 and at termination. Urine analysis was performed at weeks 26, 51 and 77 and at termination. Interim sacrifices occurred at weeks 26 and 52 (10 animals of each sex per group) and week 78 (all surviving satellite animals). Terminal sacrifice was performed at completion of 104 weeks of treatment. Pathology procedures included necropsy, organ weights and histopathological examination of a complete list of tissues and organs.

Although, in the earlier part of the study, a marginal increase in the number of females receiving 600 ppm showing hyperactivity was noted when compared with controls, there was no evidence of any effect on the incidence of hyperactivity reported after 78 weeks of treatment or beyond. Hyperactivity was primarily observed in animals in moribund condition. There was no evidence of a treatment-related effect on survival. In order of ascending doses, total mortalities at study termination, out of the 52 main mice of each sex per group, were 24, 31, 23 and 24 for males and 23, 23, 33 and 28 for females. No effects on body weight, body weight gain, feed consumption, feed efficiency, urine analysis, macroscopic pathology or organ weights were reported. Changes in haematological parameters at 600 ppm included slight decreases in haemoglobin and mean corpuscular haemoglobin concentration (MCHC) in males and an increase in MCHC in females at week 25. Because these changes were small, occurring only on some occasions and occurring in one sex only, they are not considered to be toxicologically significant. Sporadic changes in clinical chemistry parameters noted at week 53 included a slight decrease in urea nitrogen in males at 600 ppm and in all groups of treated females. Males treated at 600 ppm also had significantly increased ALT and aspartate aminotransferase (AST) levels. Higher ALT and AST levels were also recorded among females receiving 150 or 600 ppm. In view of the absence of these differences at week 79 or at termination, these changes were not considered to be of toxicological significance. Brain weights of mice of both sexes treated at 600 ppm were higher than those of controls at the interim kill on week 27 and at termination. It was also noted that at week 27, brain weights of all treated female groups were higher than those of controls, but without any clear evidence of a treatment-related trend. Increased brain weights were again recorded for females only at week 78, whereas no effect was recorded at the interim sacrifice on week 53. Kidney weights of females treated at 600 ppm were higher than those of controls at the terminal sacrifice. Higher kidney weights were also recorded for females of this group at weeks 27 and 79, although not attaining statistical significance. In males treated at 600 ppm, kidney weights were elevated at week 53. The changes in brain weights and kidney weights were not considered to be of toxicological significance, because the changes were small in magnitude and lacked a clear dose–response relationship and/or statistical significance. No treatment-related effects were noted on the incidence of any of the non-neoplastic findings detected at histopathology.

An increased incidence of lung tumours (adenoma and adenocarcinoma) was observed in males and females of treated groups. The incidences in the satellite groups (spontaneous deaths and interim sacrifice after 26, 52 and 78 weeks) were 10%, 12.5%, 18% and 2.5% for males and 7.5%,

12.5%, 7.5% and 7.5% for females at 0, 40, 150 and 600 ppm, respectively. The incidences in the main study were 12%, 23%, 33% and 31% for males and 10%, 29%, 17% and 13% for females at 0, 40, 150 and 600 ppm, respectively. The incidences did not show a clear dose–response relationship. The absence of any statistical significance between the highest group and controls and any significant trend supports the interpretation that the increased incidences in the treatment groups were not due to a tumorigenic activity of fenpropathrin. Moreover, data on the incidence of lung tumours in historical controls showed that incidences of pulmonary adenoma and adenocarcinoma in untreated animals may vary between 7% and 36%. There was no sex difference concerning lung tumours in these controls. Therefore, the results of this study gave no evidence of fenpropathrin-induced carcinogenic potential.

Fenpropathrin had no carcinogenic effects in mice. The NOAEL was the highest dose tested, 600 ppm (equal to 56.0 mg/kg bw per day in males and 65.2 mg/kg bw per day in females) (Colley et al., 1985; Colley & Gopinath, 1987). A repeat study is not necessary, because the aborted mouse carcinogenicity study (described above in section 2.2) demonstrated that at a slightly higher MTD of 1000 ppm, the test article was lethal to 38% of males and 15% of females after only 13 weeks, indicating a steep toxicity–response curve. Thus, the maximum dose used in the completed study (600 ppm) was very close to the MTD.

Rats

In a combined chronic toxicity and carcinogenicity study, groups of 24 COBS rats of each sex per dose were fed diets containing 0, 1, 5, 25, 125 or 500 ppm (equivalent to 0, 0.05, 0.25, 1.25, 6.25 and 25 mg/kg bw per day) fenpropathrin (purity 97%) for 2 years. The control group consisted of 48 rats of each sex. In addition, groups of six rats of each sex per dose received treated diets at the same concentrations for 6 or 12 months, with concurrent controls consisting of 12 male and 12 female rats. Stability, homogeneity and concentrations of the diet were confirmed analytically. Animals were examined daily for clinical signs and mortality. Rats dying or removed prior to scheduled termination were examined macroscopically. At termination, blood was collected from all animals for haematology and clinical chemistry measurements. At necropsy, all animals were examined macroscopically for any abnormalities. Selected organs were removed, weighed and examined histopathologically.

The treatment did not affect the survival, general health or behaviour of the animals or their clinical chemical or haematological parameters. The depression in body weight gain observed at 500 ppm was statistically significant in females only. Feed consumption of treated animals was comparable with that of control animals at most observation times. Absolute spleen weight was increased at 500 ppm in females of the 6-month satellite group. Relative heart weights were increased at 125 and 500 ppm in females of the 6-month satellite group. Absolute kidney weights were decreased in females at all doses in the 12-month satellite groups without showing a clear dose–response relationship. In the 2-year main study groups, no treatment-related alterations in organ weights were observed, except for relative liver weight, which was statistically significantly increased in females at 125 and 500 ppm. Gross pathological examination showed a higher incidence of white/grey foci or plaques in the lungs at 125 ppm in males at 24 months and 500 ppm in females at 6 and 24 months. In the 2-year main groups, the number of deaths attributable to renal failure in males at 500 ppm was greater than in the other groups, but no increase was observed when animals from the satellite and main study groups were combined. The histopathological neoplastic and non-neoplastic changes found were consistent with the range and severity of changes usually observed in this rat strain and did not give any evidence of carcinogenicity.

The NOAEL was 125 ppm (equivalent to 6.25 mg/kg bw per day), based on depression in body weight gain at 500 ppm (equivalent to 25 mg/kg bw per day) (Hend & Gellatly, 1979; Aitken & Rushton, 1981).

In a second combined chronic toxicity and carcinogenicity study, groups of 50 CD rats of each sex per dose received fenpropathrin (purity 91.4–92.5%) in their diets at a concentration of 0, 50,

150, 450 or 600 ppm (equal to 0, 1.9, 5.7, 17.1 and 22.7 mg/kg bw per day for males and 0, 2.4, 7.1, 21.9 and 38.8 mg/kg bw per day for females, respectively) for 2 years or more, until any one group (each sex separately) had reached a survival rate of 25%. Because of excessive mortality, females treated at 600 ppm were terminated after 52 weeks of treatment. The treated male and female rats were terminated after 104 and 113 weeks of treatment, respectively. Additional satellite groups consisting of 15 CD rats of each sex were treated at the same dose levels and used for blood sampling at intervals up to week 52 before termination after 52 weeks of treatment. Dietary stability, homogeneity and concentrations were confirmed analytically. Treated animals were observed for mortality and moribundity twice during weekdays and once on weekends. Body weights and feed consumption were recorded every week. Ophthalmic examinations were performed before treatment commenced and during weeks 6, 13, 26, 52, 78 and 104 on all control animals and the highest surviving dietary level groups. Haematology, clinical chemistry and urine analyses were conducted on 10 rats of each sex per dose from satellite group rats at weeks 25/26 and 51/52 and from main group animals at weeks 77/78, 103/104 and 107. All surviving animals from the satellite group and the main group were subjected to detailed macroscopic examination and organ weight analysis. A full spectrum of tissue samples was preserved for histopathological examination; however, only nervous tissues and liver and kidneys were processed and examined.

Clinical signs were restricted to body tremors, most prevalent in females receiving 600 ppm, but were also observed in males at the highest dose levels in the first few weeks of the study and in females at 450 ppm. Tremors were observed during the early part of the working day and essentially during weeks 1–52. Mortality increased in males and females receiving 600 ppm and in females receiving 450 ppm during the first 26 weeks of treatment; subsequently, mortality was less than that of control animals, resulting in highest survival rates in males at 600 ppm and in females at 450 ppm. Exposure of main group females receiving 600 ppm was terminated after 52 weeks. Feed consumption was comparable with that of controls except for slightly higher feed consumption reported for the high-dose females during the first 3 months of treatment. Body weight gain was reduced in females at 600 ppm, and feed utilization efficiency was marginally impaired. Ophthalmological examination did not reveal any treatment-related ocular lesions. No abnormal haematological findings were reported. No treatment-related changes in urinary parameters were observed. Changes in clinical chemistry parameters at 450 and 600 ppm included slightly reduced creatinine levels and reduced total protein levels in males. However, these alterations in clinical chemistry were of no toxicological relevance, because they were minimal or marginal changes, with no dose–response relationship and a lack of corroborative histopathological findings. Macroscopic examination revealed no findings that were treatment related, with the exception of an increased incidence of alopecia in females at 600 ppm at 52 weeks. Changes in organ weights (liver, kidney and others) were observed on some occasions, but did not show a treatment-related pattern, and histopathological examination did not reveal changes attributable to treatment. A few lymphoreticular tumours were seen in treated groups of male rats, but none in the control group. The increases observed were not dose related and were within the incidence range of the historical controls for this rat strain. There was no indication of a treatment-related increase in tumour incidence or non-neoplastic organ changes. The electron microscopic examination of tibial nerve did not reveal any treatment-related effects.

The NOAEL for males was 450 ppm (equal to 17.1 mg/kg bw per day), based on increased mortality and body tremors at 600 ppm (equal to 22.7 mg/kg bw per day). The NOAEL for females was 150 ppm (equal to 7.1 mg/kg bw per day), based on increased mortality and body tremors at 450 ppm (equal to 21.9 mg/kg bw per day) (Warren et al., 1986; Dean et al., 1987).

2.4 Genotoxicity

The results of studies of genotoxicity with fenpropathrin are summarized in Table 6. All the studies, either in vitro or in vivo, were negative. Fenpropathrin is not considered to possess any mutagenic or genotoxic potential.

Table 6. Results of studies of genotoxicity with fenpropathrin

Type of study	Organism/cell line	Dose range tested	Purity (%)	Result	Reference
In vitro					
Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and TA1538	10–1000 µg/plate	97	Negative +S9 mix (mouse, 6 strains)	Suzuki (1977)
Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537 and TA1538 and *Escherichia coli* WP2*uvrA*	50–5000 µg/plate	92.5	Negative ±S9 mix	Izumozaki et al. (1984)
Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537 and TA1538 and *E. coli* WP2*uvrA*	100–5000 µg/plate	92.5	Negative ±S9 mix	Kogiso et al. (1987)
Reverse mutation, mitotic crossing-over and mitotic gene conversion	*Saccharomyces cerevisiae* D7	0.001–0.1 mmol/l	92.5	Negative ±S9 mix	Hara et al. (1984)
DNA-damaging capacity	*Bacillus subtilis* M45 rec$^-$ and H17	10–5000 µg/paper disc (−S9 mix)	97	Negative −S9 mix	Kishida et al. (1980)
DNA-damaging capacity	*B. subtilis* M45 rec$^-$ and H17	100–10 000 µg/paper disc	92.5	Negative ±S9 mix	Kogiso (1986)
Gene mutation in mammalian cells	Mouse lymphoma L5178Y cells	50.3–400 µg/ml (−S9 mix) 47.5–300 µg/ml (+S9 mix)	91.4	Negative ±S9 mix	Richold et al. (1982a)
Gene mutation in mammalian cells	Chinese hamster lung cells (V79)	50–500 µg/ml (±S9 mix)	92.4	Negative ±S9 mix	Kogiso (1988)
DNA repair in mammalian cells (autoradiographic method)	HeLa S3 epithelioid cells (human cervical carcinoma)	200–3200 µg/ml (±S9 mix)	91.4	Negative ±S9 mix	Richold et al. (1982b)
Chromosomal aberration	Chinese hamster ovary cells (CHO)	50–500 µg/ml (−S9 mix) 500–5000 µg/ml (+S9 mix)	92.5	Negative ±S9 mix	Mosesso (1984)
Chromosomal aberration	Chinese hamster ovary cells (CHO-K1)	10–30 µg/ml (−S9 mix) 250–1000 µg/ml (+S9 mix)	92.0	Negative ±S9 mix	Kogiso (1989)
Chromosomal aberration	Chinese hamster ovary cells (CHO-K1)	3×10^{-6} to 10^{-4} mol/l (±S9 mix)	92.5	Negative ±S9 mix	Hara (1990)
Sister chromatid exchange	Chinese hamster ovary cells (CHO-K1)	3×10^{-6} to 10^{-4} mol/l (±S9 mix)	92.5	Negative ±S9 mix	Hara & Suzuki (1984a)

Type of study	Organism/cell line	Dose range tested	Purity (%)	Result	Reference
In vivo					
Host-mediated assay	*S. cerevisiae* JD1 – Male Carworth Farm (CF) No. 1 mice	10 and 20 mg/kg bw (orally)	97.0	Negative	Brooks (1976)
Chromosomal aberration in bone marrow	Chinese hamsters (males and females)	10 and 20 mg/kg bw (orally) for 2 consecutive days	97.0	Negative	Dean (1975)
Mouse micronucleus	Male ICR mice	50, 100 and 200 mg/kg bw (intraperitoneally)	92.5	Negative	Hara & Suzuki (1984b); Suzuki (1984)

DNA, deoxyribonucleic acid; S9, 9000 × *g* supernatant fraction of rodent liver homogenate

In addition to the above, two papers investigating possible genotoxicity of fenpropathrin were found in the public domain.

In a paper by Ryu et al. (1996), the genotoxicity of fenpropathrin was examined by means of the in vitro bacterial gene mutation and chromosomal aberration assays in mammalian cell systems and the in vivo micronucleus assay using mouse bone marrow cells. No mutagenic potential was observed, either in vitro or in vivo, but it should be noted that the chemical purity of the tested fenpropathrin was not given.

In vitro micronucleus induction by fenpropathrin (purity 99.6%) using whole blood and isolated human lymphocytes was investigated in a paper by Surrallés et al. (1995), using the cytokinesis block method with cytochalasin B (6 µg/ml). Fenpropathrin slightly increased the number of micronuclei and micronucleated cells in whole blood lymphocyte cultures from two out of three donors. Based on this result, the authors concluded that with certain reservations with respect to the purity and isomer composition of the test compound, the existing information appears to support the idea that fenpropathrin has a weak genotoxic activity in vitro. However, all of the other genotoxicity studies described above, including the in vivo micronucleus assay, were negative. The weight of evidence indicates that the in vitro effects reported in this paper have no corroboration in vivo.

2.5 Reproductive and developmental toxicity

(a) Multigeneration studies

Rats

In a three-generation reproductive toxicity study, fenpropathrin (purity 97%) was fed to rats (COBS; 30 of each sex per group) at a dietary concentration of 0, 5, 25 or 250 ppm (equivalent to 0, 0.3, 1.7 and 16.7 mg/kg bw per day, respectively). Observations were made on health, behaviour, body weight, feed consumption and reproductive performance of each animal. Each parent animal, sacrificed at weaning of the relevant second litter, was subjected to a complete necropsy; a proportion of F_{3B} pups were also subjected to postmortem examination. Ten male and 10 female F_2 parent animals and 10 male and 10 female F_{3B} pups from the control and high-dose (250 ppm) groups were examined microscopically.

No treatment-related effects on general health, mortality, body weight gain, feed consumption or pregnancy rates were observed. Statistically significant increases in pup weights were seen in the F_{1A} generation at 250 ppm on days 7, 14 and 21. Analysis of individual male and female pup weights at weaning revealed statistically significant increases in all treated groups compared with controls. No statistically significant changes in litter weight or mean pup weight calculated from total litter weight were seen in the F_{1B} generation, although statistically significant increases in female pup weight at day 21 were observed in all treated groups. With the exception of a small decrease in male pup weight

at weaning seen in all treated groups, no litter or pup weight effects were seen in the F_2 generation that could be related to treatment. Mean pup weights in the F_{3A} generation were reduced at 250 ppm on days 14 and 21 (Table 7). This reduction was also seen in male pup weights at 25 and 250 ppm and in female pup weights at all treatment levels. No statistically significant changes in litter weight or pup weight at day 21 were seen in the F_{3B} generation; therefore, this reduction in pup weights at 250 ppm was not considered adverse (Table 8). No macroscopic or microscopic lesions were attributable to treatment. A very small number of cases of locomotor incoordination occurred in pups fed 5 and 250 ppm. Most pups in the 5 ppm group showing these signs were from one litter in the F_{1B} generation. No similar lesions were observed in the second litter of that pair or in the following generation, and no macroscopic lesions were identified in these animals. Histopathological examination (F_2 parents, F_{3B} pups) did not reveal treatment-related tissue lesions.

The NOAELs for parental toxicity and reproductive toxicity were 250 ppm (equivalent to 16.7 mg/kg bw per day), the highest dose tested. The NOAEL for offspring toxicity was 25 ppm (equivalent to 1.7 mg/kg bw per day), based on decreased pup weights in the F_{3A} generation at 250 ppm (equivalent to 16.7 mg/kg bw per day) (Fleming, 1979; Hend, Gellatly & Fleming, 1979; Else & Rushton, 1981).

In a second three-generation reproduction study, fenpropathrin (purity 92.5%) was administered to groups of 28 male and 28 female Sprague-Dawley rats (CrL: COBS CD(SD)BR) in the diet at 0, 40, 120 or 360 ppm. Mean achieved concentrations for the F_0 generation were 0, 2.6, 7.8 and 23.3 mg/kg bw per day for males and 0, 3.1, 9.1 and 27.7 mg/kg bw per day for females, respectively. Animals of the last generation (F_2) were reared to maturity. At all matings, litter values were recorded and organ weight analyses were performed on representative weanlings; organ weights were also recorded for F_0, F_{1B} and F_{2B} adults. Tissues from F_0, F_{1B} and F_{2B} adults and F_{2B} weanlings in the control and high-dose groups were submitted to histopathological examination.

There were no clear adverse effects on feed consumption, mating performance, duration of gestation or live births in the parental animals. There were no clinical signs reported for males, and no males receiving 360 ppm died. At the high dose, a total of 18 females died (2 F_0, 1 F_{1A}, 13 F_{1B} and 2 F_{2B}). Deaths of females (10) generally occurred during lactation in the F_{1B} dams. At 360 ppm, most females that littered showed body tremors associated with muscle twitches and increased sensitivity. These signs were generally observed during the lactation period. At 120 ppm, 2 of 24 F_{1B} females died during lactation, and 1 F_{1B} female showed the clinical signs observed for the high-dose group during lactation week 2; these deaths were considered related to treatment. A total of three females treated at 40 ppm died; one F_{1B} dam was killed on day 25 of gestation after showing signs of dystocia, one F_0 dam died during gestation subsequent to the second pairing (two large misshaped fetuses were found in the uterus) and one F_{1A} female died when 9 weeks old. In the absence of any clinical signs, these deaths were considered unrelated to treatment. Mean body weight gains of males in the F_{1A}, F_{1B} and F_{2B} generations were reduced at 360 ppm. F_{1B} females at 360 and 120 ppm also showed some indication of retarded weight gain. There were no clear effects on absolute body weight or body weight gain during gestation or lactation for any generation. No treatment-related macroscopic or microscopic abnormalities were observed at terminal sacrifice. Organ weight data revealed statistically significantly increased absolute and relative liver weights in F_0 females at 360 ppm.

Three F_{2B} pups at 120 ppm showed body tremors prior to weaning, and two of these pups died subsequently. A slight reduction in litter size was observed at 360 ppm in F_0 animals (second mating) and in both matings of F_{1B} animals from days 4 to 21. At 360 ppm, pup weights were lower in all generations.

The NOAEL for parental systemic toxicity was 40 ppm (equal to 2.6 mg/kg bw per day), based on mortality of two females, reduced body weights in F_{1B} females and occurrence of body tremors and muscle twitches in one F_{1B} female seen at 120 ppm (equal to 7.8 mg/kg bw per day). The NOAEL for reproductive toxicity was 360 ppm (equal to 23.3 mg/kg bw per day), the highest dose tested. The NOAEL for offspring toxicity was 40 ppm (equal to 2.6 mg/kg bw per day), based on body tremors seen in three F_{2B} pups at 120 ppm (equal to 7.8 mg/kg bw per day) (Cozens et al., 1986).

Table 7. Litter and pup weights in a three-generation study with fenpropathrin

Generation	Litter	Dietary concentration (ppm)	Day 1		Day 4		Day 7		Day 14		Day 21	
			Mean litter weight (g)	Mean pup weight (g)	Mean litter weight (g)	Mean pup weight (g)	Mean litter weight (g)	Mean pup weight (g)	Mean litter weight (g)	Mean pup weight (g)	Mean litter weight (g)	Mean pup weight (g)
F_1	A	0	92.9	7.2	140.2	10.9	205.3	16.1	370.6	29.8	625.2	50.3
		5	101.2	7.5*	150.9	11.5*	215.2	16.6	390.6	30.9	659.5	52.3
		25	92.4	7.3	135.8	11.1	192.7	16.6	353.0	31.6	596.0	53.3
		250	91.3	7.7*	138.5	11.8**	198.9	17.0*	359.0	31.9*	620.8	55.0**
	B	0	88.5	7.5	133.2	11.6	197.5	17.4	367.1	32.6	609.9	54.3
		5	96.2	7.6	147.0	11.8	218.6	17.9	402.0	33.2	667.3	55.6
		25	93.9	7.7	143.9	12.0	212.8	18.2	385.1	33.2	636.0	54.8
		250	83.2	7.6	127.4	12.0	189.8	18.1	354.2	34.3	599.2	57.4
F_2	A	0	73.3	7.0	113.0	11.0	169.1	16.9	325.9	32.8	521.0	52.1
		5	68.3	6.7	100.6	10.6	150.9	16.3	293.8	32.5	464.4	51.5
		25	65.3	6.8	98.9	10.6	144.5	15.9	272.1	30.9	436.9	50.0
		250	71.5	7.0	106.8	10.8	161.3	16.2	296.4	31.6	483.4	51.7
	B	0	72.6	7.4	114.1	11.8	168.3	17.7	320.3	33.8	519.9	55.4
		5	55.4	7.9	86.1	12.3	129.6	18.8	241.3	35.5	364.3	53.5
		25	68.1	7.8	124.6	12.3	156.2	18.5	291.7	35.2	464.3	55.2
		250	73.3	7.7	129.6	12.2	165.1	18.2	305.6	34.4	489.9	55.2
F_3	A	0	67.4	7.3	101.7	11.3	148.7	16.8	283.4	34.1	491.5	58.4
		5	72.3	6.9	106.6	11.1	157.2	17.1	289.9	33.4	501.2	57.1
		25	72.3	6.7	107.4	10.5	152.1	15.6	274.7	31.4	482.2	55.1
		250	73.1	7.1	104.5	10.4	145.1	14.8	266.6	29.8*	456.6	51.1**
	B	0	72.2	7.5	114.0	12.2	169.5	18.4	232.9	35.6	539.3	58.7
		5	52.8	7.5	85.6	12.0	128.9	18.9	242.6	36.3	394.6	59.6
		25	69.6	7.8	10.38	12.3	149.1	18.1	270.3	33.7	454.0	55.9
		250	70.2	7.6	106.0	12.0	152.8	17.9	280.7	33.3	469.2	55.4

From Hend, Gellatly & Fleming (1979)
* $P < 0.05$; ** $P < 0.01$ (Wilcoxon's test)

Table 8. Mean litter weight data for rats aged 21 days fed fenpropathrin during a three-generation reproductive toxicity study (from individual body weights measured at weaning)

Generation	Litter	Dietary concentration (ppm)	Males			Females		
			No. of observations	Mean pup weight (g)	% of control	No. of observations	Mean pup weight (g)	% of control
F_1	A	0	204	49.9		181	47.8	
		5	198	52.9**		186	50.4**	
		25	165	51.8**		186	50.5**	
		250	188	55.2**		156	53.3**	
	B	0	171	55.3		172	51.6	
		5	190	55.9		174	54.3	
		25	174	55.4		181	52.5	
		250	167	56.0		149	53.9**	
F_2	A	0	159	52.9		139	48.7	
		5	140	50.7*		138	50.0	
		25	126	49.9*		126	47.5	
		250	137	51.1*		135	48.3	
	B	0	135	54.9		137	52.1	
		5	107	53.3		106	50.7	
		25	114	55.1		129	52.2	
		250	125	55.0		139	51.0	
F_3	A	0	87	57.1		112	56.6	
		5	84	55.8		99	53.7*	
		25	90	54.3*		90	52.8**	
		250	109	51.1**		89	50.8**	
	B	0	104	56.3		116	56.1	
		5	60	59.8		64	54.8	
		25	85	56.5		77	55.3	
		250	81	57.3		107	53.8	

From Hend, Gellatly & Fleming (1979)
* $P < 0.05$; ** $P < 0.01$

(b) Developmental toxicity

Mice

A teratogenicity study in mice was reported, using "technical grade fenpropathrin" (purity not indicated), sourced from Rallis Agricultural Research Centre, India. Groups of 10 female Swiss albino mice were mated and then treated with fenpropathrin in corn oil at 0, 0.29 or 0.59 mg/kg bw per day during days 5–14 or 14–17 of gestation. A laparotomy was performed on day 18 of pregnancy. The number of live, dead and resorbed fetuses was recorded. Live fetuses and placental discs were removed and weighed. Fetal sex and any external abnormalities were recorded. Fetuses were then fixed and processed separately for skeletal (alizarin red; Dawson, 1926) and visceral (Wilson, 1965) examination.

Maternal toxicity was evidenced by reduced weight gain during gestation at both doses. In addition, one dam treated at the highest dose on days 14–17 of gestation died. Mean fetal weight was decreased compared with controls. Fenpropathrin caused a dosed-related increase in the percentage of

resorbed fetuses. Examination of the fetuses for external anomalies revealed the occurrence of open or slit eye in a significant number of fetuses. Other signs of teratogenicity (e.g. enlarged ventricles, microphthalmia, enlarged renal pelvis, reduced ossification of skull bones, sternebrae and extremities, presence of 13th rudimentary or absent rib) were also reported, but a number of observations from the tabular data presented failed to reveal any dose–response relationship (Dhar et al., 2004). The study does not meet Organisation for Economic Co-operation and Development guidelines for numbers of animals tested, and there is no claim of compliance with GLP. The source of the fenpropathrin is unclear.

Rats

In a developmental toxicity study, approximately 30 mated female Fischer 344 rats were given fenpropathrin (purity 96.2%; doses were corrected for purity) suspended in corn oil by oral gavage at a dose of 0, 0.4, 2 or 10 mg/kg bw per day from day 6 to day 15 of gestation. All dams were sacrificed on day 19 of gestation, and the uterine contents were examined.

One mid-dose and nine high-dose females were found dead during the study. Clinical signs noted at a somewhat greater incidence in the treated animals included soft faeces, red or lacrimating eyes, alopecia or hunched appearance. Post-dose tremors occurred on a few occasions in some high-dose females. Body weight gain was reduced in high-dose females during the treatment period and increased slightly afterwards, resulting in an overall change comparable with the control group. Feed consumption was also reduced at the highest dose level. Various gross lesions were found in animals that died during the study. The findings included discolorations of organs, but no specific target organ was identified. The pregnancy rate was lower in the high-dose group compared with the other dose groups, but other reproduction parameters (e.g. number of corpora lutea, resorptions, fetal viability) were not impaired by treatment. No visceral or skeletal anomalies were noted in the pups. Visceral or skeletal variants did not show dose-related increases. No teratogenic effects were observed.

The NOAEL for maternal toxicity was 2 mg/kg bw per day, based on decreased body weight gain and feed consumption during the dosing period and clinical signs at 10 mg/kg bw per day. The NOAEL for embryotoxicity and teratogenicity was 10 mg/kg bw per day, the highest dose tested (Pence et al., 1980c; Cox, 1986, 1987).

In a second prenatal developmental toxicity study, groups of 30 mated female Fischer 344 rats were given fenpropathrin (purity 91.9%; doses were corrected for purity) suspended in corn oil by oral gavage at a dose of 0, 0.4, 1.5, 2, 3, 6 or 10 mg/kg bw per day from day 6 to day 15 of gestation. All dams were sacrificed on day 20 of gestation, and the uterine contents were examined.

In the high-dose group, six dams died between gestation days (GDs) 7 and 13, and one was sacrificed moribund on day 8 because of convulsions and prostration. Neither death nor moribundity was found in the other groups. Clinical signs seen in the majority of high-dose dams included ataxia, sensitivity to external stimuli, spastic jumping and tremors. These signs were most severe 2 hours after dosing and during the first days of dosing, although sensitivity to external stimuli persisted throughout the dosing period. At 6 and 10 mg/kg bw per day, mean maternal body weight gains and feed consumption were lower during the dosing period (Table 9). Body weight gain was significantly decreased in the 10 and 6 mg/kg bw per day groups between GDs 6 and 8, 6 and 11, 6 and 15 and 6 and 16. Decreases ranged from 29% to more than 97% for the high-dose group and from 14% to 80% at 6 mg/kg bw per day. Over the course of the study (GDs 0–20 or 6–20), however, body weights, gravid uterine weights, corrected body weights and feed consumption were similar in all groups. The corrected body weight (terminal weight minus gravid uterine weight) for the high-dose dams was significantly less (4%) than the control value, and the net weight change (corrected weight minus day 0 body weight) was also significantly less (40%) than the control value. For the 6 mg/kg bw per day group, there was a non-significant 16% reduction in the net weight change. Feed consumption was also significantly decreased (18% or 11%) in the 10 or 6 mg/kg bw per day groups, respectively, between GDs 6 and 8. Between GDs 8 and 11, there was a significant reduction (7%) in feed

consumption for the 10 mg/kg bw per day group. Throughout the remainder of the study, feed consumption was unaffected by treatment.

Table 9. Mean maternal body weights during gestation

Interval		Dose (mg/kg bw per day) (no. of dams)						
		0 (*n* = 30)	0.4 (*n* = 28)	1.5 (*n* = 28)	2 (*n* = 29)	3 (*n* = 28)	6 (*n* = 28)	10 (*n* = 27–21)
Pretreatment	Day 0	170	171	173	173	172	174	172
Treatment	Day 6	180	181	184	182	180	183	181
	Day 8	184	184	187	186	184	184	180
	Day 11	192	193	195	195	191	192	187
	Day 15	203	204	207	206	202	203	197
Post-treatment	Day 16	208	210	212	211	207	207	201
	Day 20	236	240	242	241	237	239	233
Corrected body weights[a]		195	195	200	198	195	195	188* (−4%)
Net weight change[b]		25	24	26	26	23	21 (−16%)	15** (−40%)

From Morseth (1990)
* $P < 0.05$; ** $P < 0.01$
[a] Corrected weight = terminal body weight – gravid uterine weight.
[b] Net weight change from day 0 = corrected weight – day 0 body weight.

The pregnancy rate of high-dose females was slightly lower (90%) than that of the other treatment groups (93–97%). Treatment had no influence on reproduction parameters, such as resorptions, fetal viability or fetal body weight. No visceral or skeletal anomalies were observed that were considered treatment related. Skeletal variations and differences in ossifications were noted in all groups without a clear dose–response relationship, and statistical significances were not achieved.

The NOAEL for maternal toxicity was 3 mg/kg bw per day, based on slightly decreased body weight gain and feed consumption, mortality and clinical signs at 6 mg/kg bw per day. The NOAEL for developmental toxicity was 10 mg/kg bw per day, the highest dose tested (Morseth, 1990).

Rabbits

In a prenatal developmental toxicity study, groups of 20–31 mated female banded Dutch rabbits were given fenpropathrin in corn oil (purity 97%) by means of two gelatine capsules at a dose of 0, 0 (100 µl/kg bw corn oil control), 1.5, 3 or 6 mg/kg bw per day from day 6 to day 18 (inclusive) of gestation. All does were sacrificed on day 28 of gestation, and the uterine contents were examined for viability and teratological changes.

No clinical signs of intoxication were observed. There were several mortalities among animals treated at 3 and 6 mg/kg bw per day, but the causes of death were unrelated to treatment (dosing injuries, pneumonia and pleuritis associated with *Pasteurella multocida* infection, haemorrhage in the pleural cavity). One rabbit in the corn oil group (day 28), one rabbit in the 1.5 mg/kg bw per day group (day 27) and two rabbits in the 3 mg/kg bw per day group (days 27 and 28) aborted, with one of those at 3 mg/kg bw per day dying shortly afterwards. Treatment had no effect on body weight of the dams. No adverse effects were observed with respect to preimplantation loss, number of resorptions, fetal deaths, litter size or pup weight. Increased incidences of minor skeletal

and visceral abnormalities (e.g. enlarged fontanelles, interparietal bones, fused sternebrae, extra centres of ossification) were noted at 3 mg/kg bw per day, but not at the highest dose. Therefore, these changes were not considered treatment related.

The NOAELs for maternal toxicity, embryotoxicity and teratogenicity were 6 mg/kg bw per day, the highest dose tested (Van der Pouw et al., 1975; Dix, 1985).

In a second prenatal developmental toxicity study, groups of 17–19 mated female New Zealand White rabbits received fenpropathrin (purity 92.5%) in corn oil by oral gavage at a dose of 0, 4, 12 or 36 mg/kg bw per day daily from day 7 to day 19 of gestation. All does were sacrificed on day 29 of gestation, litter parameters determined and fetuses subsequently examined for visceral and skeletal anomalies.

A dose-related increase in the incidence of grooming was observed in all dose groups, which was nonspecific and therefore not considered as adverse. At 12 and 36 mg/kg bw per day, flicking of forepaws was also observed, with a few animals at 36 mg/kg bw per day showing shaky movements and tremor. Among the several animals dying during the study, one and two dams at 12 and 36 mg/kg bw per day, respectively, aborted, and one from each group was sacrificed because of poor conditions. None of the mortalities occurring in the study was considered to be treatment related. Slight reductions in body weight gain and reduced feed consumption were noted at 36 mg/kg bw per day. There was no effect of treatment on litter parameters or increased incidence of skeletal anomalies.

The maternal NOAEL was 4 mg/kg bw per day, based on clinical signs noted at 12 mg/kg bw per day. The developmental NOAEL was 36 mg/kg bw per day, the highest dose tested (Cozens, 1985).

2.6 Special studies

(a) Acute neurotoxicity

Mice

The aim of a study published by Nieradko-Iwanicka & Borzęcki (2010) was to investigate a potential hazard to memory for elderly patients undergoing a transient ischaemic event. The model used bilateral clamping of carotid arteries, a model for ischaemia, together with fenpropathrin (stated purity 99%) given intraperitoneally, testing memory, movement activity and coordination in mice. In this study, female Swiss mice with bilateral clamping of carotid arteries were injected (intraperitoneally) 24 hours after their surgery with 0.1 LD_{50} fenpropathrin (23.8 mg/kg bw). The authors concluded that "BCCA [bilateral clamping of carotid arteries] together with fenpropathrin significantly reduced latency in a passive avoidance task compared to controls. There were no significant differences among the groups with respect to the Y-maze, movement activity, or movement coordination".

Rats

In a special study, the neurotoxic effect of fenpropathrin in rats was assessed by the mean slip angle test. Groups of 10 male Sprague-Dawley rats received fenpropathrin (purity 93.8%) in corn oil once by oral gavage at a dose of 0, 10, 25, 50, 75 or 100 mg/kg bw at a volume of 5 ml/kg bw. The determination of the mean slip angle was carried out by using an originally designed apparatus. The determination of mean slip angle was performed on day 0 (just before dosing), 1, 3, 5, 7 and 9 hours after dosing and daily thereafter for 3 days.

The mean slip angle in the control animals was progressively but slightly lowered from the initial value. The mean slip angle in rats dosed at 10 and 25 mg/kg bw was comparable with that of the controls at each determination. The mean slip angle at 50 mg/kg bw and above was progressively lowered 3–5 hours after dosing. The mean slip angle of all treated groups was comparable with that of the controls 24 hours after dosing and thereafter. A total of two, five and seven rats died, respectively,

following administration of 50, 75 and 100 mg/kg bw. All deaths occurred between 5 hours and 1 day after dosing.

Slight tremors (noted as trembling of the root of the tail) were noted in rats treated at 25 mg/kg bw from 3 to 9 hours after dosing. In rats treated at 50 mg/kg bw, slight to moderate tremor (trembling limbs) appeared at 3 hours. Ataxia, limb paralysis and acoustic startle response to sound were also observed at 5–7 hours. Slight to moderate tremors appeared at 1 hour in animals treated at 75 and 100 mg/kg bw. The severe tremor, ataxia, limb paralysis and acoustic startle response were observed at 5–9 hours post-dosing at 75 mg/kg bw and at 3–7 hours at 100 mg/kg bw. These clinical signs completely disappeared in most of surviving animals within 24 hours of administration.

The NOAEL of this study was 10 mg/kg bw, based on tremors observed at 25 mg/kg bw (Hiromori et al., 1986a).

Functional testing was performed on two animals of each sex at 0, 125 or 500 ppm (equivalent to 0, 6.25 and 25 mg/kg bw per day), satellite groups of the long-term study in rats (Hend & Gellatly, 1979), using the "inclined plane test". Preliminary results revealed an impaired performance in animals fed 500 ppm. Measurements of β-glucuronidase activity (parameter indicative of Wallerian degeneration in nerves) did not reveal a clear increase, as would be expected as a result of toxic neuropathy. Macroscopy and histopathology of sciatic and tibial nerves did not show treatment-related changes (Hend et al., 1980).

Wolansky et al. (2006) reported on a study in which motor activity effects were used as an end-point to determine a dose–response curve and relative potency after acute exposure to 11 commonly used pyrethroids (Type I: bifenthrin, *S*-bioallethrin, permethrin, resmethrin, tefluthrin; Type II: beta-cyfluthrin, lamda-cyhalothrin, cypermethrin, deltamethrin, esfenvalerate; and one mixed Type I/II: fenpropathrin). In this study, adult male Long-Evans rats were administered each test chemical as a single gavage dose in corn oil (1 ml/kg bw); each group consisted of 8–18 animals, and each experiment was divided into at least two blocks, with vehicle control animals included in each block. Motor activity was measured for 1 hour using 16 figure-eight mazes at the time of peak effects. The time of peak effects was obtained from pilot time course studies using motor activity testing or behavioural observations. The motor activity data were analysed using a non-linear exponential threshold activity model (Casey et al., 2004). Relative potencies were calculated from ED_{30}s (defined as the dose associated with a 30% decrease in motor activity) using deltamethrin as the index chemical. Fenpropathrin (purity 91.8%) was given at eight doses ranging between 0.01 and 24 mg/kg bw and tested for motor activity 2 hours after dosing. Excessive signs (i.e. prolonged [lasting more than 4 hours] clinical signs) were observed at 24 mg/kg bw, and this dose was not used in any data analysis.

All pyrethroids, including fenpropathrin, induced dose-dependent decreases in motor activity. The threshold dose is defined as an estimate of the highest no-effect level at which treated rats did not display any decreases in motor activity. The threshold dose for fenpropathrin was 3.06 mg/kg bw, with a 95% confidence interval of 1.76–4.37 mg/kg bw. The ED_{30} for fenpropathrin was 7.70 ± 0.65 mg/kg bw (Wolansky et al., 2006).

In a range-finding study for acute neurotoxicity assessments, fenpropathrin (purity 92%) in corn oil was administered orally by gavage as a single dose to three Crl:CD(SD) rats of each sex per group at a dose level of 6, 24, 36 or 54 mg/kg bw. A concurrent control group (three of each sex) received the vehicle on a comparable regimen. The dosage volume was 5 ml/kg bw for all groups. Dietary stability, homogeneity and concentrations were confirmed analytically. All animals were observed twice daily for mortality and moribundity. Individual body weights were recorded on the day of test substance administration (day 0). Clinical examinations were conducted simultaneously with modified functional observational battery evaluations. Modified functional observational battery

data were recorded for all animals at approximately 1, 2, 3, 4, 5, 6, 7 and 8 hours following dose administration. All animals found dead or euthanized in extremis received a complete necropsy. All surviving animals were euthanized and discarded following the completion of the functional observational battery evaluation for each animal.

One male in the 54 mg/kg bw group died following the 4-hour post-dosing modified functional observational battery, and one female in each of the 36 and 54 mg/kg bw groups was euthanized in extremis immediately following the 6- and 4-hour modified functional observational battery evaluations; these deaths were attributed to treatment with fenpropathrin and indicate that these dose levels were above the MTD. The predominant findings noted at the modified functional observational batteries were convulsions, tremors, Straub tail and altered gait. Time of peak effect was 3 hours post-dosing for males and females. Signs of neurotoxicity were most severe and were observed at the highest incidence at 36 and 54 mg/kg bw. Treatment-related effects on modified functional observational battery parameters at the time of peak effect in the 24 mg/kg bw group included tremors and gait alterations (walking on tiptoes or hunched appearance). In addition, one female in this group was noted with Straub tail. Slight tremors and altered gait were noted at 6 mg/kg bw. However, in a following range-finding study (Knapp, 2006b), seven animals of each sex per group were evaluated at 3 and 6 mg/kg bw, and there were no clinical signs observed. In addition, there were no test substance–related effects on locomotor activity evaluations. Therefore, it was uncertain whether these findings (slight tremors and altered gait) in the 6 mg/kg bw group in this study were treatment related. No treatment-related effects were observed macroscopically for the animals that were found dead or euthanized in extremis (Knapp, 2006a).

In a second range-finding study for acute neurotoxicity assessments, fenpropathrin (purity 92.0%) in the corn oil vehicle was administered orally by gavage as a single dose to two groups of seven Crl:CD(SD) rats of each sex per group at a dose level of 3 or 6 mg/kg bw. A concurrent control group (group 1) received the vehicle on a comparable regimen. The dosage volume was 5 ml/kg bw for all groups. The other experimental details mentioned in the above-described range-finding study (Knapp, 2006a) were followed.

No treatment-related effects on survival and modified functional observational battery or locomotor activity evaluations performed at the time of peak effect (approximately 3 hours after treatment) were noted following a 3 or 6 mg/kg bw oral gavage dose (Knapp, 2006b).

In an acute neurotoxicity study (main study), fenpropathrin (purity 92.0%) in corn oil was administered once via gavage (5 ml/kg bw) to 12 Crl:CD(SD) rats of each sex per group at a dose level of 0, 3, 6, 15 or 30 mg/kg bw. Dietary stability, homogeneity and concentrations were confirmed analytically. All animals were observed twice daily for mortality and moribundity. Clinical examinations were performed daily. Individual body weights were recorded weekly. Functional observational battery and locomotor activity data were recorded for all animals prior to the initiation of dose administration, at the time of peak effect (approximately 3 hours post-dosing) on study day 0 and on study days 7 and 14. All animals were euthanized on study day 15 and perfused in situ with a buffered 4.0% paraformaldehyde/1.4% glutaraldehyde solution. Brain weights (excluding olfactory bulbs) and brain dimensions were recorded for each of these animals. In addition, a neuropathological evaluation was performed on six animals of each sex in the control and 30 mg/kg bw groups. Acceptable positive control data were provided.

No compound-related effects on mortality, clinical signs of toxicity, body weight, body weight gain, motor activity, brain weight and morphology, gross pathology or neuropathology (30 mg/kg bw group) were observed in either sex.

At 30 mg/kg bw, the following functional observational battery effects (no. affected/12 versus 0/12 controls) were noted at 3 hours post-dosing (time of peak effect): 1) slight tremors in 10 animals of each sex during the open-field observations; 2) clonic convulsions (whole-body tremors) in one rat

of each sex during the open-field observations; and 3) slight tremors in two males and one female during the home cage observations. These behavioural changes were apparently reversible, as all animals appeared normal by day 7. Findings at 15 mg/kg bw were limited to slight tremors in two females at 3 hours post-dosing during the open-field observations. In the absence of other neurotoxic effects in this group and the absence of any findings in the 15 mg/kg bw males, this finding is considered equivocal for neurotoxicity. Handling, sensorimotor, neuromuscular and physiological observations were not affected on study day 0. No treatment-related effects were apparent when functional observational battery evaluations were performed on study days 7 and 14. A significant decrease in overall total motor activity counts was obtained in males treated at 30 mg/kg bw (147.67; 9.7% reduction in total activity) during the time of peak effect compared with the mean control group value (163.60). However, owing to the magnitude of the difference, this decrease was not considered related to treatment. No effects were apparent in mean ambulatory and total motor activity counts on study days 7 and 14. No remarkable shifts in the pattern of habituation occurred in any of the treated groups when the animals were evaluated on study days 0, 7 and 14.

The NOAEL for neurotoxicity was 15 mg/kg bw, based on slight tremors and clonic convulsions (whole-body tremors) in both sexes at the time of peak effect at 30 mg/kg bw (Knapp, 2007a). However, the registrant established a no-observed-effect level (NOEL) for neurotoxicity of 15 mg/kg bw for males and 6 mg/kg bw for females, probably because the registrant considered tremors (two rats) seen at the 15 mg/kg bw as an adverse effect.

In a study published by Weiner et al. (2009), 12 commercial pyrethroid insecticides (technical-grade active ingredients) were evaluated for acute neurobehavioural manifestations of toxicity under conditions suited to assist with determining whether they act by a common mechanism of toxicity. Young adult male Sprague-Dawley rats (10 per dose group) were administered a single dose of pyrethroid by oral gavage, in corn oil, at a volume of 5 ml/kg bw. Each was tested at a range of two or three dose levels, including a minimally toxic dose, to establish the more sensitive manifestations of toxicity, and a more toxic dose, to establish a more complete spectrum of neurobehavioural manifestations. Animals were evaluated using a functional observational battery that was designed to characterize and distinguish effects classically associated with tremor or choreoathetosis with salivation syndromes of intoxication. The functional observational battery was performed at the time of peak effect (2, 4 or 8 hours post-dosing) by observers who were blinded to dose group assignment. The dose levels for fenpropathrin were 15 and 30 mg/kg bw.

The results indicate that some pyrethroids clearly exhibit the historic classification symptoms of the tremor or choreoathetosis with salivation syndromes, whereas others do so less obviously. Use of the statistical technique of principal component analysis further helped interpret the study findings. Based on a review of the functional observational battery data, analysed by principal component analysis, and other published data, two common mechanism groups were proposed. Group 1 would include pyrethrins, bifenthrin, resmethrin, permethrin, *S*-bioallethrin and tefluthrin. Group 2 would include cypermethrin, deltamethrin, esfenvalerate, beta-cyfluthrin and lamda-cyhalothrin. Fenpropathrin exhibited features of both groups (Weiner et al., 2009). Assessments performed in this study did not include motor activity, so the relative effectiveness of motor activity compared with other functional observational battery assessments was not determined.

(b) Subchronic neurotoxicity

Hens

The neurotoxic potential of fenpropathrin was investigated in adult laying hens in a study that predated GLP. Six adult domesticated laying hens were given five successive daily doses of fenpropathrin (purity 96%) dissolved in dimethyl sulfoxide at 1000 mg/kg bw. The dosing regimen was repeated after a 3-week treatment-free period, and the birds were sacrificed a further 3 weeks later. A positive control group was pretreated with an intramuscular dose of pralidoxime chloride and atropine sulfate and dosed with 0.5 ml/kg bw of tri-*ortho*-tolyl phosphate (TOTP). A third group,

which was not dosed, acted as the negative control. All birds were observed daily and tested at intervals for their ability to land properly when forced to fly.

All birds receiving the positive control dose of TOTP developed signs of neurological damage and lesions in the nervous system. None of the birds dosed with fenpropathrin showed any signs of intoxication. Histological examination of their nervous system showed no lesions (Milner & Butterworth, 1977).

Rats

In a dietary 28-day range-finding study for a subsequent subchronic neurotoxicity study, groups of six Crl:CD(SD) rats of each sex per dose received fenpropathrin (purity 92%) continuously in their diet for 28 consecutive days at a concentration of 0, 60, 300 or 600 ppm (equal to 0, 5, 26 and 53 mg/kg bw per day for males and 0, 6, 31 and 64 mg/kg bw per day for females, respectively). Stability, homogeneity and concentrations in the diets were confirmed analytically. All animals were observed twice daily for mortality and moribundity. Detailed physical examinations, body weights and feed consumption were recorded weekly. Functional observational battery and locomotor activity data were recorded for all animals during study week 3. Gross necropsies were conducted on all animals, and selected organs were weighed.

No treatment-related effects on mortality, brain weight or gross pathology were noted in either sex. In the 300 ppm males, decreases were noted in cumulative body weight gain from week 0 to week 3 (16%) and overall (20%, weeks 0–4) and in feed efficiency (32%) during weeks 3–4. At 600 ppm, clinical signs of toxicity observed included tremors, head and/or body twitches and/or hypersensitivity to sound in both sexes; and popcorn seizures (two females on day 5) and red and/or yellow material on the ventral abdominal and/or urogenital areas in the females. Body weights were decreased throughout the study by 9–12% in the males and by 8–12% in the females. Body weight gains were decreased by 38% in the males and by 48% in the females during the 1st week of treatment. Cumulative body weight gains were decreased throughout the study by 26–38% in the males and by 29–48% in the females, which resulted in overall (weeks 0–4) gains being decreased by 26–29% in both sexes. During the 1st week of treatment, decreases in feed consumption (12–19%) and feed efficiency (29–36%) were also noted in both sexes. The following functional observational battery effects (no. affected/6 versus 0/6 controls) were noted: 1) during the home cage observations, clonic convulsions, whole-body convulsions and markedly coarse tremors were observed in one female; 2) during handling, soiled fur was noted in two females; 3) during open-field observations, five females displayed abnormal gait (walking on tiptoes or dragging hindlimbs), and one female was ataxic; four females displayed slight to moderately coarse tremors, and two females displayed slight to considerable mobility impairment; and 4) during sensory observations, two females displayed an increased startle response, and one female displayed slightly uncoordinated air-righting reflex, whereas two other females landed on their backs. Overall session total and ambulatory motor activities were decreased in the females. Habituation to the test environment was generally noted in these animals.

The NOAEL was 60 ppm (equal to 5 mg/kg bw per day), based on decreased body weight gain and feed efficiency in males at 300 ppm (equal to 26 mg/kg bw per day) (Knapp, 2007b).

In another subchronic neurotoxicity study, fenpropathrin (purity 92%) was administered orally via the diet for 90 consecutive days to groups of 12 Crl:CD(SD) rats of each sex per dose at a dose level of 0, 60, 190 or 570 ppm (equal to 0, 4, 13 and 38 mg/kg bw per day for males and 0, 5, 15 and 50 mg/kg bw per day for females, respectively). Stability, homogeneity and concentrations in the diet were confirmed analytically. All animals were euthanized following 13 weeks of treatment. All animals were observed twice daily for mortality and moribundity. Detailed physical examinations were performed weekly. Individual body weights and feed consumption were recorded weekly. Functional observational battery and locomotor activity data were recorded for all animals prior to the initiation of treatment and during study weeks 3, 7 and 12. Ophthalmic examinations were performed

during study weeks −2 and 11. All animals were euthanized and perfused in situ with a buffered 4.0% paraformaldehyde/1.4% glutaraldehyde solution. Brain weights (excluding olfactory bulbs) and brain dimensions were recorded for each of these animals. In addition, a neuropathological evaluation was performed on six animals of each sex in the control and 570 ppm groups. A gross necropsy was performed on the animal found dead.

No compound-related effects were observed in ophthalmoscopic examinations, motor activity, brain weight and morphology, or gross pathology and neuropathology in either sex. At 570 ppm, one female that displayed tremors and hypersensitivity to sound during the first 6 days of test article administration was found dead on day 7. The following clinical signs of toxicity were observed (no. affected/12 versus 0/12 controls): 1) tremors (10 males and 12 females); 2) hypersensitivity to sound (12 rats of each sex); and 3) popcorn seizures (4 females). The frequency of tremors and hypersensitivity to sound were greater in the females than in the males. At 570 ppm, body weights were decreased throughout the study by 11–13% in the males and by 8–13% in the females. Feed consumption was decreased (10–19%) in males throughout the study. Mean feed efficiency (body weight gained as a percentage of feed consumed) was decreased by 27% in the males during week 0–1 and by 29–59% in the females during weeks 0–1, 1–2 and 4–5 compared with controls.

Differences in functional observational battery parameters were noted in animals of both sexes treated at 570 ppm during the study week 3, 7 and/or 12 evaluations, with the greatest incidence of findings occurring in the females treated at 570 ppm. Treatment-related functional observational battery effects were predominantly observed in the 570 ppm females and included the following (no. affected/11 females versus 0/12 controls): During the home cage observations, slight to markedly coarse tremors were noted in 3–5 females throughout the treatment period. During the handling observations, soft and flabby muscle tone was noted in three females during week 3. In the open field, slight to markedly coarse tremors were noted in 3–7 females throughout the treatment period and in 1 male at week 3; slightly to moderately impaired mobility was noted in 2–3 females during weeks 3 and 12; clonic convulsions (whole-body tremors) were observed in 3 females during weeks 3 and 7; slight to moderately impaired gait score was noted in 2–3 females throughout the treatment period, and 1 male displayed body dragging during week 3; abnormal gait (walking on tiptoes) was noted in 2 females at week 12, and hunched body was noted in 3 females at week 12; and the mean number of rears was increased by 91% in the males during week 3 and by 100% in the females during week 12. During the sensory observations, a more energetic startle response was noted in 3 females during weeks 3 and 12, and slightly uncoordinated air-righting reflex was noted in 1–3 females during weeks 3 and 12. Also during the air-righting reflex testing, 1 additional female landed on its side or back during weeks 3 and 7, respectively. During the neuromuscular observations, mean hindlimb grip strength was decreased by 27% in the females during week 3; rotarod performance was decreased by 51–68% in the females throughout treatment; and hindlimb foot splay was decreased by 34% in the females during week 3. Additional findings observed at this dose in the home cage or open field included ataxia in 2 females during week 3 and in 1 female at week 7, whole-body tremors in 1 female at weeks 3 and 12, biting the cage or self in 2 females at week 12, and popcorn seizure in 1 female each at weeks 3 and 7. Effects noted at 190 ppm were limited to abnormal gait (2 females each displayed walking on tiptoes and hunched body) at week 12. There were no treatment-related clinical findings noted in animals of either sex treated at 60 ppm or in males treated at 190 ppm; body weights and feed consumption at these dose levels were unaffected by treatment. There were no treatment-related effects on handling observations during the functional observational battery evaluations. Locomotor activity was unaffected by test article administration at all dose levels.

In summary, neurotoxicity of fenpropathrin administered via diet was observed at dose levels of 190 ppm in females (equal to 15 mg/kg bw per day) and 570 ppm in males and females (equal to 38 and 50 mg/kg bw per day, respectively). Neurotoxic effects were evidenced by walking on tiptoes and hunched body (females at 190 ppm); abnormal gait and tremors (570 ppm, both sexes); convulsions, excessive biting, impaired mobility, vertical jumping, increased rearing, uncoordinated righting reflex, excessive startle response and lower hindlimb grip strength, foot splay and rotarod performance (570 ppm, females).

The NOAEL in females was 60 ppm (equal to 5 mg/kg bw per day), based on abnormal gait (two females each displayed walking on tiptoes and hunched body) at 190 ppm (equal to 15 mg/kg bw per day) at week 12 (Knapp, 2007c).

(c) Developmental neurotoxicity

Rats

A preliminary range-finding study was conducted to determine the dietary concentrations of the test substance appropriate for use in the definitive developmental neurotoxicity study and to provide data regarding the level of exposure of the offspring at critical periods of development (GD 20 and lactation days [LDs] 4, 10 and 16) following maternal dietary exposure during gestation and lactation. In a dose range–finding developmental neurotoxicity study, fenpropathrin (purity 92.0%) was administered in the diet to two groups of presumed pregnant Sprague-Dawley (Crl:CD[SD]) rats per dose at a dose of 0, 50, 180 or 360 ppm (equal to 0, 4, 13 and 27 mg/kg bw per day during gestation and 0, 7, 25 and 44 mg/kg bw per day during lactation, respectively). In Subset I, 5 females per dose group were dosed continuously from GD 6 to GD 20; in Subset II, 10 females per dose group were dosed continuously from GD 6 through LD 21. Subset I females were killed on GD 20, and their pregnancy status was determined by caesarean section. Subset II females were allowed to litter normally and rear their offspring to LD 21. The pups were not directly dosed. On postnatal day (PND) 4, litters were randomly standardized to eight pups per litter (four of each sex where possible). In addition to the normal systemic measurements, concentrations of the test substance in the plasma were measured in the Subset I females and their fetuses on GD 20, and concentrations of the test substance in the milk and plasma were measured in the Subset II females (five females per dose group for milk and plasma, respectively) and their pups on LD 4 (culled pups pooled by litter), LD 10 (two pups of each sex per litter, pooled by sex within litter) and LD 16 (one pup of each sex per litter). Motor activity assessments were performed on one Subset II pup of each sex per litter on PND 21. All Subset II dams and surviving pups were killed and necropsied on PND 21.

There were no effects of treatment observed on mortality, pregnancy status, mean gestation duration, the process of parturition or macroscopic pathology.

At 360 ppm, two dams had total litter losses: one on LD 16 and the other on LD 20. Slight tremors were observed in 14 of 15 dams during gestation; 5 of these animals also had piloerection on 1–3 occasions during GDs 17–20. In the Subset II females, slight tremors were noted in all animals generally beginning on LD 0; tremors were noted on most days during lactation until termination. The severity generally progressed from slight to moderate to severe, with dams used for milk collection affected to a greater extent than those used for plasma collection. This was attributed to the greater compound consumption later in lactation due to the increased maternal demand on the milk collection females; the litter sizes of these females were approximately twice the sizes of the litters of the plasma collection females, whose offspring were being killed for plasma collection on LDs 10 and 16.

Additionally at this dose, body weights were decreased ($P \leq 0.05$) by 5–8% during GDs 9–20, resulting in decreased body weight gains during GDs 6–20 (22%; $P \leq 0.01$). Body weights were generally decreased ($P \leq 0.05$) throughout lactation in both plasma and milk collection females (9–18%; not significant on LD 21). Overall (LDs 1–21) lactational body weight gains were decreased (not significantly) by 59%, and overall absolute lactational feed consumption (g/rat per day) and relative lactational feed consumption (g/kg bw per day) were decreased ($P \leq 0.01$) by 32% and 23%, respectively, in the milk collection females.

There were no effects of treatment on the number of pups born, sex ratio at birth, live litter size on PND 0, live birth index or macroscopic pathology.

At 360 ppm, the weaning index was decreased (82.5% versus 100%; not significant) for the milk collection pups. Seven blood collection and nine milk collection pups were found dead; eight blood collection pups (litter no. 27772) had cool bodies on PND 7; and 15 milk collection pups (eight

pups in litter no. 27834 and seven pups in litter no. 27788) were noted with cool bodies during PNDs 6–21.

Additionally at this dose, pup body weights were decreased from PND 4 (pre-cull) to PND 21 in both the blood and milk collection pups (20–58%; $P \leq 0.05$, except not significant for the blood collection males on PNDs 17 and 21), resulting in decreased body weight gains for all intervals (47–92%; $P \leq 0.05$, except not significant for the blood collection males and 0.1 g body weight loss for the blood collection females on PNDs 17–21). During motor activity testing, neither the males nor females showed habituation on PND 21. This was considered to be indicative of a developmental delay, which was corroborated by the decreases in body weights and body weight gains, and not an indication of developmental neurotoxicity.

Concentrations of the test compound were lower in fetal plasma than in maternal plasma at all dietary concentrations on GD 20. The concentration of fenpropathrin in maternal plasma samples collected on GD 20 increased with increasing dietary concentration. Fenpropathrin was also measurable in the plasma of fetuses in the 180 and 360 ppm groups, but was not measurable in the fetuses in the 50 ppm group. Maternal and fetal plasma fenpropathrin concentration data are summarized in Table 10.

Table 10. Plasma fenpropathrin concentrations on PND 20

PND sample	Mean levels (ppm) of fenpropathrin ± SD in plasma; (range)/*N*			
	0 ppm	50 ppm	180 ppm	360 ppm
Day 20 dams	< LOQ[a]/5	0.021 ± 0.006 (0.011–0.027)/5	0.073 ± 0.035 (0.043–0.126)/5	0.154 ± 0.068 (0.092–0.268)/5
Day 20 fetuses (litter means)	< LOQ/5	< LOQ/5	0.038 ± 0.015 (0.018–0.056)/5	0.056 ± 0.020 (0.032–0.077)/5

From Stump (2007)
LOQ, limit of quantification; SD, standard deviation
[a] Calculated concentration was less than 0.01 ppm.

Concentrations of fenpropathrin in maternal plasma samples increased with increasing dietary concentration on LDs 4, 10 and 16. Mean concentrations were relatively similar for each dose on all days of testing, although there was some variability in individual concentrations. Fenpropathrin was also measurable in the plasma of male and female pups on all days of testing. Concentrations in these pups increased in an exposure-related manner on PNDs 4 and 10, but not on PND 16. Across groups, mean plasma concentrations in the pups were 44% and 64% of maternal plasma concentrations on PNDs 4 and 10, whereas on PND 16, plasma concentrations in the pups were 70–85% of the maternal values at 50 and 180 ppm and approximately 30% of the maternal values at 360 ppm. The lower pup to maternal plasma fenpropathrin concentration ratios in the 360 ppm groups correspond to the severe developmental delays in this group, which resulted in the pups initiating self-feeding later in the postnatal period. Maternal and fetal plasma fenpropathrin concentration data during lactation are summarized in Table 11.

Concentrations of fenpropathrin in milk increased with dietary concentration and also generally increased as lactation progressed, although the values on LDs 10 and 16 were not remarkably different, which was consistent with the calculated test article consumption values for all groups for these time frames. Maternal milk fenpropathrin concentration data are summarized in Table 12.

The levels of fenpropathrin in plasma and milk were approximately 2- to 3.4-fold higher in dams compared with pups. The NOAEL for maternal toxicity was 180 ppm (equivalent to 13/25 mg/kg bw per day during gestation/lactation, respectively), based on total litter losses, tremors, decreased gestational and lactational body weights and body weight gains, and decreased absolute and

relative lactational feed consumption at 360 ppm (equivalent to 27/44 mg/kg bw per day during gestation/lactation, respectively).

Table 11. Plasma fenpropathrin concentrations during lactation

PND sample	Mean levels (ppm) of fenpropathrin ± SD in plasma; (range)/*N*			
	0 ppm	50 ppm	180 ppm	360 ppm
Day 4 dams	< LOQ[a]/5	0.0594 ± 0.017 (0.038–0.075)/5	0.265 ± 0.050 (0.215–0.325)/5	0.555 ± 0.17 (0.387–0.781)/5
Day 4 pups (pooled litter means)	< LOQ/5	0.036 ± 0.014 (0.022–0.054)/5	0.133 ± 0.053 (0.091–0.225)/5	0.269 ± 0.086 (0.161–0.394)/5
Day 10 dams	< LOQ/5	0.070 ± 0.021 (0.041–0.087)/4	0.253 ± 0.060 (0.187–0.350)/5	0.559 ± 0.130 (0.399–0.743)/5
Day 10 male pups (2/litter)	< LOQ/5	0.038 ± 0.011 (0.025–0.051)/5	0.155 ± 0.033 (0.118–0.192)/5	0.245 ± 0.160 (0.097–0.498)/5
Day 10 female pups (2/litter)	< LOQ/5	0.039 ± 0.009 (0.028–0.049)/5	0.162 ± 0.022 (0.134–0.191)/5	0.266 ± 0.0120 (0.142–0.455)/5
Day 16 dams	< LOQ/5	0.061 ± 0.014 (0.050–0.080)/4	0.242 ± 0.035 (0.181–0.267)/5	0.454 ± 0.100 (0.337–0.550)/5
Day 16 male pups (2/litter)	< LOQ/5	0.043 ± 0.015 (0.028–0.064)/5	0.198 ± 0.054 (0.127–0.256)/5	0.135 ± 0.054 (0.073–0.165)/2
Day 16 female pups (2/litter)	< LOQ/5	0.050 ± 0.016 (0.033–0.072)/5	0.206 ± 0.075 (0.118–0.313)/5	0.150 ± 0.025 (0.132–0.167)/2

From Stump (2007)
LOQ, limit of quantification; SD, standard deviation
[a] Calculated concentration was less than 0.01 ppm.

Table 12. Milk fenpropathrin concentrations during lactation

PND sample	Mean levels (ppm) of fenpropathrin ± SD in milk; (range)/*N*			
	0 ppm	50 ppm	180 ppm	360 ppm
Day 4	< LOQ[a]/5	2.55 ± 0.30 (2.17–2.85)/5	10.2 ± 7.0 (5.42–20.4)/4	22.2 ± 11.0 (5.94–34.6)/5
Day 10	< LOQ/5	3.61 ± 1.2 (2.69–5.69)/5	18.8 ± 5.6 (11.2–24.6)/4	31.9 ± 5.9 (23.5–38.6)/5
Day 16	< LOQ/5	3.74 ± 1.3 (2.65–6.00)/5	17.0 ± 5.0 (11.4–22.4)/4	30.8 ± 9.0 (20.1–44.5)/5

From Stump (2007)
LOQ, limit of quantification; SD, standard deviation
[a] Calculated concentration was less than 0.01 ppm.

The NOAEL for offspring toxicity was 180 ppm (equivalent to 13/25 mg/kg bw per day during gestation/lactation, respectively), based on decreased weaning index, pups with cool bodies, and decreased body weights and body weight gains at 360 ppm (equivalent to 27/44 mg/kg bw per day during gestation/lactation, respectively).

A NOAEL for developmental neurotoxicity could not be assigned, as insufficient parameters were examined to determine this end-point.

Based on the maternal milk and pup plasma concentrations of fenpropathrin, the dietary route of administration was confirmed to be appropriate for a developmental neurotoxicity study in rats (Stump, 2007).

In a developmental neurotoxicity study (main study), fenpropathrin (purity 92.0%) was administered in the diet to 25 presumed pregnant Sprague-Dawley (Crl:CD[SD]) rats per dose from GD 6 through LD 21 at a dose of 0, 40, 100 or 250 ppm (equal to 0, 3, 8 and 19 mg/kg bw per day during gestation and 0, 7, 16 and 40 mg/kg bw per day during lactation, respectively). The pups were not directly dosed. Dams were allowed to deliver naturally and were killed on LD 21. On PND 4, litters were randomly standardized to eight pups per litter (four of each sex where possible), and the remaining offspring were sacrificed without further examination. Subsequently, pups were allocated to Subset A, B or C. In Subset A (20 pups of each sex per dose group), the following parameters were examined: functional observational battery on PNDs 4, 11, 21, 35, 45 and 60; motor activity on PNDs 13, 17, 21 and 61; auditory startle response on PNDs 20 and 60; and learning and memory beginning on PND 62. Fifteen animals of each sex per dose group were selected from Subset A for brain weight evaluations on PND 72; of these, 10 animals of each sex from the control and 250 ppm groups were selected for neuropathological and morphometric evaluations on PND 72. All Subset A animals were also examined for balanopreputial separation or vaginal patency, as appropriate. For Subset B (20 pups of each sex per dose group), learning and memory testing was initiated on PND 25. For Subset C, 15 animals of each sex per dose group were selected for brain weight evaluations on PND 21; of these, 10 animals of each sex from the control and 250 ppm groups were selected for neuropathological and morphometric evaluations on PND 21.

A single female treated at 40 ppm died on LD 5, but the death was not considered treatment related. In the dams, there were no effects of treatment observed on mortality, body weight, body weight gain, feed consumption, reproductive parameters, gestation duration or macroscopic pathology. Treatment-related tremors were noted for 24 of 25 females treated at 250 ppm during lactation, with onset occurring between LDs 3 and 16. One female in this group also exhibited tremors on GD 13. The severity of the tremors generally increased as lactation progressed, consistent with the increased achieved intake of fenpropathrin on a milligram per kilogram body weight basis during lactation (40 mg/kg bw per day) compared with gestation (19 mg/kg bw per day). Modified functional observational battery assessments of the maternal animals on GD 10 revealed higher mean grooming counts for females treated at 250 ppm. At functional observational battery evaluation on LD 10, higher mean grooming counts and a higher number of females with slight tremors were noted in the 250 ppm group. In addition, one female in this group had moderately coarse tremors and slightly impaired mobility (LD 10) and splayed hindlimbs (LD 21). At the LD 21 evaluation, only one female in this group continued to exhibit slight tremors.

There were no effects of treatment on the number of pups born, sex ratio at birth, live litter size on PND 0, postnatal survival indices, the number of pups found dead, killed in extremis and/or missing or the general physical condition of the pups. Sexual developmental parameters (balanopreputial separation and vaginal patency) were also unaffected by maternal exposure.

During lactation, increased numbers of pups that were small in size were observed in the 250 ppm litters. This finding was often observed on multiple occasions in the affected pups and correlated with decreased pup body weights. Offspring preweaning body weights were decreased by 10–16% in both sexes from PNDs 7 through 21. Interval body weight gains for the corresponding intervals were also decreased by 11–21%. There were no effects of treatment on the functional observational battery, learning and memory, gross or microscopic pathology, or brain morphometric measurements.

Secondary neurobehavioural effects of the periweaning growth retardation observed in the 250 ppm group offspring included a tendency towards lessened habituation to the locomotor activity testing environment on PNDs 17 and 21. Test substance–related changes in acoustic startle response were observed in the 250 ppm group females on PND 60 relative to the control group.

Lower mean absolute brain weight and length were noted for F_1 male offspring on PND 21. Delayed brain development and thus smaller brains are seen in juvenile animals when caloric or nutrient restriction occurs during early postnatal development (Garman et al., 2001), and these effects may diminish or disappear completely in adults. The smaller brain weight and length in PND 21 males may indicate a test article–related effect on brain development, but an effect secondary to nutrition cannot be ruled out, especially as final body and brain weights recovered by PND 72. Lower mean brain length in males was noted on PND 72. However, brain weights were similar to those in controls, no changes in mean brain width were noted and there were no test article–related behavioural effects noted during functional observational battery evaluations. From this weight of evidence, it was considered that the lower mean brain length in males was spurious and unrelated to test substance administration. The lower mean brain weight and length changes in males at PND 21 were considered probable test substance–related changes; however, the possibility that these changes were wholly or partially nutritionally induced cannot be discounted. Mean final body and brain weights recovered by PND 72.

The NOAEL for maternal toxicity was 100 ppm (equal to 8 mg/kg bw per day), based on tremors during lactation and effects on body weight and feed consumption at 250 ppm (equal to 19 mg/kg bw per day). The NOAEL for developmental neurotoxicity was 100 ppm (equal to 8 mg/kg bw per day), based on small size of pups and decreased body weights and body weight gains during the preweaning 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 at 250 ppm (equal to 19 mg/kg bw per day) (Stump, 2008).

(d) Immunotoxicity

In an immunotoxicity study, fenpropathrin (purity 93%) was administered in the diet to female Crl:CD (SD) rats (10 per group) at a concentration of 0 (control), 150, 300 or 450 ppm for 28 consecutive days (days 0–28). Mean test substance consumptions were 0, 14, 26 and 42 mg/kg bw per day, respectively. On day 24, animals in all groups were immunized with a suspension of sheep red blood cells by intravenous injection (2×10^8 sheep red blood cells per animal, 0.5 ml/animal dose volume). A positive control group (10 females) received intraperitoneal injection of cyclophosphamide at a dose of 50 mg/kg bw (10 ml/kg bw) on study days 24–27. Animals were sacrificed on day 29. All animals were evaluated for mortality, clinical signs, body weight changes, feed consumption, water consumption, organ weights and gross pathology. Immunotoxicity was assessed for all animals by the antibody-forming cell (AFC) assay; spleen, thymus and adrenal gland weights were determined at necropsy. The dose levels were selected based on a range-finding study in which decreased body weights and body weight gains were seen at 450 ppm, but no treatment-related effects were observed at 150 and 300 ppm.

There were no effects of test substance treatment on mortality, water consumption, gross pathology or organ weights. Body weight gains were lower at 450 ppm during study days 0–3 and 7–10 compared with controls, and cumulative body weights were statistically significantly lower throughout the study except from study days 0 to 28. As a result, body weight in the 450 ppm group at study day 28 was 6.2% lower than that in the control group, although this was not statistically significant. Treatment-related clinical signs seen at 450 ppm were hyperactivity, hyperreactivity to touch, increased activity and twitching. There were no treatment-related effects on spleen cell number and no effect on the AFC response to the T cell–dependent antigen sheep red blood cells (i.e. specific activity and total spleen activity). A high interindividual variability was noted in all the treatment groups as well as in the control group. Evaluation of individual animal data did not show any trend or distribution that would demonstrate significant suppression of the anti–sheep red blood cell antibody response. Animals in the positive control group showed marked decreases in the anti–sheep red blood cell AFC response. The positive control group confirmed the validity of the immunotoxicity assay. A natural killer (NK) cell activity assay was not performed in this study.

The NOAEL for systemic toxicity was 300 ppm (equal to 26 mg/kg bw per day), based on lower body weight, reduced body weight gain and clinical signs at 450 ppm (equal to 42 mg/kg bw

per day). The NOAEL for immunotoxicity was 450 ppm (equal to 42 mg/kg bw per day), the highest dose tested, based on an AFC assay for a T cell–dependent antibody response to immunization with sheep red blood cells. A LOAEL for immunotoxicity of fenpropathrin in female rats was not determined (Crittenden, 2011).

A series of studies by Stelzer & Gordon (1984a,b, 1985) showed that pyrethroids can affect the membrane lipid packing order of splenic lymphocytes and reported that fenpropathrin was able to inhibit mitogenic responsiveness of murine splenic lymphocytes to concanavalin A, thus suggesting possible concern for an immune suppression activity. However, the fully compliant immunotoxicity study, which includes evaluation of mitogenic responsiveness of splenic lymphocytes, submitted by the notifier demonstrated that the effects observed in vitro have no corroboration in vivo.

(e) Induction of hepatic microsomal enzymes

A preliminary investigation was performed to study the possible effect of fenpropathrin on the induction of hepatic microsomal enzymes. Four male Sprague-Dawley rats (one per dose) received fenpropathrin (purity 97%) in their diets at 1, 10, 100 or 1000 ppm over 2 weeks. Two positive controls received diets containing 100 ppm dieldrin. Liver homogenates were used to measure in vitro *O*-dealkylation of [^{14}C]chlorfenvinphos. The rate of *O*-deethylation of [^{14}C]chlorfenvinphos of fenpropathrin-treated rats was comparable to that of the controls. No dose-related increased in liver weights was observed. Rats treated with 100 ppm dieldrin showed a 16-fold increase in liver weights.

Therefore, the results of this study do not provide any evidence for an inducing effect of fenpropathrin on liver microsomal enzymes (Creedy & Potter, 1976).

(f) Study on antidotes

The therapeutic potency of intraperitoneally administered methocarbamol, or 3-(*o*-methoxy phenoxy)-1,2-propanediol 1-carbamate, was examined against acute oral intoxication of rats after treatment with lethal doses of fenpropathrin (100 mg/kg bw) and some other pyrethroids. Methocarbamol was initially administered intraperitoneally at a dose of 400 mg/kg bw, followed by repeated doses of 200 mg/kg bw. Treatment with methocarbamol reduced the mortality from 60% to 0% and depressed tremors (Hiromori et al., 1986b).

(g) Study on paraesthesia

To quantitatively evaluate the intensity of facial paraesthesia following exposure to fenpropathrin and other pyrethroids, the rabbit was used as the experimental model in a study performed in 1983. Groups of six rabbits were shaved 1 day before the study. A circle (2.54 cm in diameter) was marked at the centre. The animals were housed in well-illuminated cages, with a fan producing wind conditions (0.5 m/s) and allowing up and down observations through a mirror. The duration of licking and/or biting behaviour following application of 50 µl of the substance at different concentrations in acetone was recorded every 10 minutes for 2 hours. To evaluate the effectiveness of the treatment, additional animals were treated with 0.1 mg of the substance, and 400 mg of petroleum jelly–based 5% benzocaine ointment or undiluted vitamin E was applied within a 7.6 cm diameter circle, inclusive of the application site, 1 minute after application of pyrethroids.

The frequency of licking and/or biting after application showed a clear dose–response relationship with all pyrethroids tested. Post-treatment with petroleum jelly–based 5% benzocaine ointment (local anaesthetic) was effective in reducing the intensity of animal response. Post-treatment application of undiluted vitamin E was also effective for treatment of facial paraesthesia (Hiromori & Takemura, 1983).

(h) Endocrine effects

Andersen et al. (2002) tested 24 pesticides largely used in Denmark for interaction with the estrogen receptor and the androgen receptor in transactivation assays. Estrogen-like effects on MCF-7

cell proliferation and effects on cytochrome P450 19 aromatase activity in human placental microsomes were also investigated. Fenpropathrin was negative in all the assays.

3. Observations in humans

In a field study in Japan, six workers participated in two tests (four workers participating in both studies) using a 5% emulsifiable concentrate. The spray concentrations were 25–50 ppm (active ingredient), and the spraying time was 2 hours. A motor-mounted sprayer was used. The workers wore protective clothing. No effects were reported for all six subjective symptoms evaluated (i.e. headache, nasal discharge, itching, burning, pain in face or limbs) (Fujita, 1980).

In a paper by Matsumoto & Suzuki (no date), a case report describing facial sensation produced by fenpropathrin in 23 workers exposed to pyrethroids in the laboratory, during formulation processes or in field trials was discussed. As exposure to the different pyrethroids varied, it was not possible to determine which compounds were more likely to produce symptoms. It was concluded that fenpropathrin produces facial sensation in humans, and vitamin E and benzocaine proved to be effective therapeutics (Matsumoto & Suzuki, no date).

In a survey of 18 operators using a 10% emulsifiable concentrate fenpropathrin formulation, no adverse effects were reported, with the exception of slight nasal irritation (single report). All operators wore protective clothing (Shell Chemical Ltd, 1987).

Fourteen workers were engaged in fenpropathrin manufacturing at Sumitomo Chemical's Oita Works for the previous decade (2002–2011). Production volume ranged between 50 and 220 tonnes in each fiscal year. Periodic medical examinations were carried out at least once per year on each worker, according to the Japanese requirements. The medical examination included investigation of medical history and work habits, smoking, body measurements, eyesight and hearing, chest X-ray examination, blood pressure measurement, haematology measurements, liver function tests, blood lipid examination, blood sugar, renal function tests, urine analysis and electrocardiogram examination. No adverse effects were reported by the engaged workers, and no health problems or adverse findings were noted at the periodic examinations (Nishioka, 2011).

Comments

Biochemical aspects

Absorption of fenpropathrin following a single oral administration was rapid, and elimination was almost complete (about 57% in urine and 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 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 TMPA–glucuronide and TMPA-CH_2OH (*trans*). The major urinary metabolites derived from the alcohol moiety were PBacid in free form and as glycine conjugate, 4′-OH-PBacid–sulfate and 2′-OH-PBacid–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 compounds 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 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), based on decreased body weight gain, decreased feed consumption and slightly increased alkaline phosphatase activity seen at 600 ppm (equal to 28.8 mg/kg bw per day).

In a 1-year dietary study of toxicity in dogs, the NOAEL was 100 ppm (equal to 3.1 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 first 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 150 ppm (equal to 7.1 mg/kg bw per day), based on depression in body weight gain and clinical signs at 450 ppm (equal to 21.9 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 in rats 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. The ED_{30} for fenpropathrin was 7.70 ± 0.65 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 (equal to 15 mg/kg bw per day for females), 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 preweaning 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 combined NOAEL of 3 mg/kg bw per day observed in the developmental toxicity studies in rats, on the basis of decreases in body weight gain and feed consumption seen at 6 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.

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	Ninety-day studies of toxicity[a,c]	Toxicity	450 ppm, equal to 21.3 mg/kg bw per day	600 ppm, equal to 28.8 mg/kg bw per day
	Two-year studies of toxicity and carcinogenicity[a,c]	Toxicity	150 ppm, equal to 7.1 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 studies of reproductive toxicity[a,c]	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	6 mg/kg bw per day
		Embryo and fetal toxicity	10 mg/kg bw per day[b]	—
	Acute neurotoxicity study[d] (published)	Neurotoxicity	Threshold dose: 3.06 mg/kg bw	Estimated ED_{30}: 7.70 mg/kg bw
	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
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,c]	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] Two or more studies combined.

[d] Gavage administration.

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	3.1 mg/kg bw per day (dog)
Lowest relevant dermal NOAEL	1000 mg/kg bw per day (rat)
Lowest relevant inhalation NOAEC	Not available
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Neurotoxic signs
Lowest relevant oral NOAEL	Combined 7.1 mg/kg bw per day (rat)
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	
Developmental target/critical effect	Decreased body weight gain and secondary effects on locomotor activity
Lowest maternal NOAEL	3 mg/kg bw per day
Lowest embryo/fetal NOAEL	10 mg/kg bw per day
Neurotoxicity/delayed neurotoxicity	
Acute neurotoxicity NOAEL	3 mg/kg bw
Subchronic neurotoxicity NOAEL	5 mg/kg bw per day
Developmental neurotoxicity NOAEL	8 mg/kg bw per day
Delayed neurotoxicity	No signs of delayed neurotoxicity
Immunotoxicity	
Immunotoxicity NOAEL	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

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