BIFENTHRIN

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Explanation

Bifenthrin is the International Organization for Standardization (ISO)–approved name for (2-methyl-3-phenylphenyl) methyl (1*RS*, 3*RS*)-3-[(*Z*)-2-chloro-3,3,3-trifluoroprop-1-enyl]-2,2-dimethylcyclopropane-1-carboxylate (International Union of Pure and Applied Chemistry [IUPAC]), for which the Chemical Abstracts Service (CAS) No. is 82657-04-3. Bifenthrin is a synthetic pyrethroid insecticide and acaricide.

The toxicity of bifenthrin was first evaluated by the 1992 Joint FAO/WHO Meeting on Pesticide Residues (JMPR). The Meeting established an acceptable daily intake (ADI) of 0–0.02 mg/kg body weight (bw) on the basis of a no-observed-adverse-effect level (NOAEL) of 1.5 mg/kg bw per day for decreased body weight gain in males and dose-related tremors in a 1-year study of oral toxicity in dogs and with a safety factor of 100.

New studies of acute and dermal toxicity, sensitization, neurotoxicity, developmental toxicity and genotoxicity and a pathology re-evaluation of the tumours observed in the study of carcinogenicity in mice became available since the last review by JMPR. Bifenthrin was reviewed by the present Meeting within the periodic review programme of the Codex Committee on Pesticide Residues. All pivotal studies with bifenthrin were certified as complying with good laboratory practice (GLP).

Evaluation for acceptable daily intake

Unless otherwise stated, studies evaluated in this monograph were performed by GLP-certified laboratories and complied with the relevant Organisation for Economic Co-operation and Development (OECD) and/or United States Environmental Protection Agency (USEPA) test guideline(s).

1. Biochemical aspects

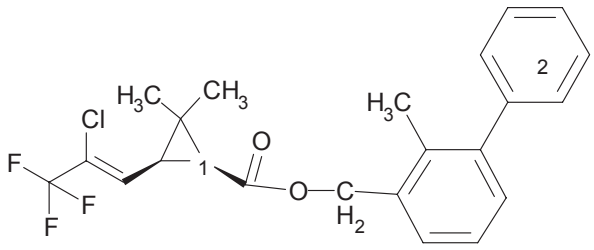
1.1 Absorption, distribution, metabolism and excretion

(a) Oral administration

Rats

The absorption, distribution and elimination of bifenthrin were studied after oral dosing of rats with bifenthrin radiolabelled with ^{14}C, as shown in Figure 1.

Figure 1. Position of the radiolabel on bifenthrin used in pharmacokinetic studies in rats



1: Acid (cyclopropyl) ^{14}C bifenthrin

2: Alcohol (phenyl) ^{14}C bifenthrin

The absorption, distribution and metabolism of bifenthrin labelled with ^{14}C in either the alcohol (phenyl) or acid (cyclopropyl) ring were studied in Sprague-Dawley rats (three rats of each sex per dose) following a single gavage dose of 5 mg/kg bw in corn oil. Treated animals were kept individually in metal metabolism cages for collection of urine and faeces. Samples of urine and faeces were collected at the following time intervals: 0–8, 8–12, 12–24, 24–48, 48–72, 72–96, 96–120, 120–144 and 144–168 h post-dosing. Treated rats were sacrificed after 7 days, and radioactivity in various tissues and organs was analysed. Samples of urine and faeces were extracted and analysed for metabolites using thin-layer chromatography (TLC) and high-performance liquid chromatography (HPLC). Approximately 90.7% and 91.9% of the administered dose of alcohol-labelled bifenthrin were recovered in the excreta of male and female rats, respectively, in 7 days. Approximately 86.0% and 86.5% of the administered dose of acid-labelled bifenthrin were recovered in the excreta of male and female rats, respectively, in 7 days. Most of the orally administered dose (for both labels) was recovered in the excreta, predominantly in faeces, in the first 48 h following dosing. In the first 48 h, 76.2–79.5% and 72.9–74.0% of the administered dose were recovered in faeces and 5.6–6.9% and 8.4–9.2% in urine for the alcohol and acid labels, respectively. The highest level of radioactivity was detected in fat (1.7 and 0.8 parts per million [ppm] for alcohol- and acid-labelled bifenthrin, respectively) in 7 days. TLC analysis and comparison of the 0–48 h extractable faecal metabolites obtained from alcohol- and acid-labelled bifenthrin, for both male and female rats, showed identical numbers of metabolites, with intact unmetabolized parent compound predominating. The results suggested that the intact pyrethroid ester group was stable and that very minimal hydrolysis of both labels occurred. This preliminary study demonstrated that most of the orally administered dose of bifenthrin in rats was excreted in the first 48 h, predominantly in faeces, and there was no influence of sex or radiolabelling position of bifenthrin on the absorption, distribution, metabolism or elimination in rats. The analytical profile of extractable ^{14}C residues from both labels showed a similar chromatographic pattern, indicating no extensive esterase splitting activity on the parent compound (ElNaggar, 1987).

In toxicokinetic studies, groups of male and female Sprague-Dawley rats (five of each sex per dose) were given radiolabelled bifenthrin as a single oral dose at 4 or 35 mg/kg bw by gavage or as 14 repeated oral doses of 4 mg/kg bw per day followed by a single oral dose of radioactive bifenthrin at 4 mg/kg bw. All female rats received bifenthrin (purity 98%) labelled with ^{14}C in the alcohol (phenyl) ring, and all male rats were dosed with bifenthrin (purity 97.3%) labelled with ^{14}C in the acid (cyclopropyl) ring. Treated rats were housed in stainless steel metabolism cages for 7 days. Urine and faeces were collected at the following time intervals: 0–4, 4–8, 8–12, 12–24, 24–36, 36–48, 48–72, 72–96, 96–120, 120–144 and 144–168 h. At each collection, cages were rinsed with water and cage washings collected together with the urine. At the end of 7 days, animals were sacrificed, and blood, tissues and organs were analysed for radioactivity. In a separate experiment, two male and two female rats were dosed with a single gavage dose of radiolabelled bifenthrin at 4 mg/kg bw and housed in Roth metabolism cages for collection of expired air and organic volatiles using a solution of 2:1 ethanolamine:Cellosolve at intervals of 4, 8, 12, 24 and 48 h.

Clinical signs of toxicity and mortality were observed in the 35 mg/kg bw dosed group but not at the 4 mg/kg bw single dose or repeated dose. The amounts of radioactivity recovered in the expired air and volatile trap were 0.028% and 0.053% of the administered dose in females and males, respectively, in 48 h. Organic volatiles were not collected because a preliminary study indicated a small quantity of radioactivity in this fraction. A majority of bifenthrin-derived radioactivity from the single oral low dose, single oral high dose and multiple oral low doses (acid or alcohol labelled) was excreted in faeces, amounting to 73–83%, 69–71% and 66–73% of the administered dose, respectively. Urine contained only 13–20%, 22% and 18–25% following the single oral low dose, single oral high dose and multiple oral low doses, respectively. Elimination of most ^{14}C-labelled bifenthrin

Table 1. Distribution of radioactivity recovered in rats following gavage dosing of bifenthrin at 168 h post-dosing

Dose (mg/kg bw)	Sex	Distribution of radioactivity (% of administered dose)			
		Urine	Faeces	Tissues	Total
4	Male[a]	13.39 (± 5.77)[c]	82.80 (± 8.85)	3.76 (± 2.65)	100.95 (± 6.86)
	Female[b]	19.65 (± 4.93)	72.87 (± 4.98)	3.94 (± 0.95)	96.46 (± 1.43)
35	Male	21.60 (± 7.93)	68.89 (± 6.64)	3.40 (± 1.83)	93.90 (± 5.19)
	Female	21.76 (± 1.85)	70.93 (± 5.69)	4.22 (± 1.93)	96.92 (± 5.64)
4 (repeated dose)	Male	18.36 (± 3.58)	73.22 (± 4.82)	3.13 (± 1.09)	94.71 (± 3.98)
	Female	25.01 (± 7.26)	65.80 (± 9.60)	4.05 (± 1.27)	94.85 (± 4.69)

Data extracted from Selim (1987), Table 28-33

[a] Males were dosed with bifenthrin labelled with ^{14}C in the acid (cyclopropyl) ring.

[b] Females were dosed with bifenthrin labelled with ^{14}C in the alcohol (phenyl) ring.

[c] Values in parentheses are reported as standard deviations.

was complete within 48 h of dosing. A summary of the per cent distribution of bifenthrin following various dosing regimes is given in Table 1.

For the single and multiple low doses, the radiolabel residue in most tissues was <0.1 ppm bifenthrin equivalents, except for fat, pancreas, skin, liver and lungs, which contained higher residues. Mean radioactivity recovered in various tissues was less than 5% of the administered dose after 7 days. The results of this study suggest that orally administered bifenthrin was quickly eliminated from the body (within 48 h after dosing), and no significant differences in elimination or tissue retention were observed following single low and high doses or repeated dosing at the low dose for 14 days (Selim, 1987).

Samples of urine and faeces from the Selim (1987) study were further subjected to metabolic identification. Faecal samples (0–48 h) were pooled from the single low dose or single high dose studies, and 0–72 h faecal samples were pooled from the repeated-dose study. Analysis of rat faeces was done by solvent extraction (equal volumes of acetone and methanol) followed by solvent partitioning (equal volumes of acetonitrile and hexane). Rat urine was partitioned with methylene chloride. The aqueous layer was subjected to acid hydrolysis and repartitioned with methylene chloride and ethyl acetate. After suitable preparation/separation steps, the individual metabolites were identified using HPLC, TLC, gas chromatography–mass spectrometry (GC-MS) or nuclear magnetic resonance (NMR). Faecal extraction of the alcohol- and acid-labelled bifenthrin showed that 51.5–57.8% and 55.3–64.4% of the administered dose were recovered in the acetonitrile fraction (free metabolites), 2.2–3.4% and 2.9–7.0% in the hexane fraction and 11.7–13.7% and 10.7–12.7% as bound residues (post-extraction solids) for both labels, respectively. Analysis of these residues showed that parent chemical was the major product (17.2–44.2% of the administered dose). Twelve other metabolites derived from hydrolysis and oxidation of the parent chemical were also detected. The intact hydroxylated metabolites were identified as 4′-hydroxy-hydroxymethyl-bifenthrin, 3′-hydroxy-hydroxymethyl-bifenthrin, hydroxymethyl-bifenthrin, 4′-hydroxy-bifenthrin, 3′-monomethyl-catechol-bifenthrin and 4′-monomethyl-catechol-bifenthrin, along with the hydrolytic and oxidative-hydrolytic products of bifenthrin, including biphenyl alcohol, 4′-hydroxy-biphenyl alcohol, biphenyl aldehyde, biphenyl acid, trifluoropropenyl (TFP) acid and hydroxymethyl-TFP acid. Unknown metabolites (three) ranged between 0.2% and 3.6% of the total administered dose.

Total organosoluble residues of the urine ranged from 10.6% to 17.6% of the administered dose. Analysis of these fractions indicated that parent chemical was a negligible product (0.1%, possibly due to faecal contamination). The urinary metabolites from hydrolysis and hydrolysis–oxidation products of bifenthrin included TFP acid, hydroxymethyl-TFP acid, biphenyl alcohol, 4′-hydroxy-biphenyl

Table 2. Metabolic distribution of orally administered bifenthrin in the urine and faeces of rats

Metabolic product	Metabolic distribution (% of administered dose)					
	4 mg/kg bw (single low dose)		4 mg/kg bw per day (repeated low dose)		35 mg/kg bw (single high dose)	
	Male[a]	Female[b]	Male	Female	Male	Female
4′-Hydroxy-biphenyl alcohol[c]	NA	2.5	NA	3.3	NA	3.3
Monomethyl-catechol-biphenyl alcohol[d]	NA	0.7	NA	1.3	NA	1.6
4′-Hydroxy-biphenyl acid	NA	0.2	NA	0.4	NA	0.2
Biphenyl acid	NA	1.4	NA	2.1	NA	1.7
TFP acid	3.3	NA	4.8	NA	5.9	NA
4′-Hydroxy-biphenyl acid methyl ester	NA	1.1	NA	1.5	NA	1.0
Cis-, *trans*-hydroxymethyl-TFP acid	4.7	NA	8.6	NA	7.9	NA
Biphenyl alcohol	NA	1.7	NA	2.6	NA	2.1
Biphenyl aldehyde	NA	ND	NA	0.6	NA	1.0
4′-Hydroxy-hydroxymethyl-bifenthrin	2.2	3.7	3.1	4.2	1.8	4.4
3′-Hydroxy-hydroxymethyl-bifenthrin	2.1	3.5	3.0	3.9	1.8	4.1
Hydroxymethyl-bifenthrin	0.7	4.1	2.5	3.5	0.7	2.4
4′-Hydroxy-bifenthrin	1.2	7.4	3.2	7.1	1.8	4.9
3′-Monomethyl-catechol-bifenthrin	3.4	4.9	2.2	4.9	2.0	4.9
4′-Monomethyl-catechol-bifenthrin	3.0	4.3	2.0	4.2	1.7	4.3
Bifenthrin from FMC Corporation	44.2	26.4	25.3	17.2	33.2	22.5
Total	64.6	61.9	54.0	56.8	56.1	58.4

Data extracted from ElNaggar & Wu (1986), Table 18
NA, not applicable; ND, not detected
[a] Males were dosed with bifenthrin labelled with ^{14}C in the acid (cyclopropyl) ring.
[b] Females were dosed with bifenthrin labelled with ^{14}C in the alcohol (phenyl) ring.
[c] Includes 3′-hydroxy-biphenyl alcohol.
[d] Includes 3′- and 4′-monomethyl-catechol-biphenyl alcohol.

alcohol, 3′-hydroxy-biphenyl alcohol, 3′-monomethyl-catechol-biphenyl alcohol, 4′-monomethyl-catechol-biphenyl alcohol, biphenyl acid, 4′-hydroxy-biphenyl acid and 4′-hydroxy-biphenyl acid methyl ester. Four unknown metabolites together did not exceed 1% of the dose. Maximum levels of polar, water-soluble degradate amounted to 5.5% of the dose. A summary of the metabolic distribution of orally administered bifenthrin in the faeces and urine is shown in Table 2.

In summary, the extraction of bifenthrin-derived radioactivity from urine and faecal samples was nearly complete. In faeces, the major identified component was the parent compound (17.2–44.2% of the administered dose). A small quantity of the parent compound (<0.1% of the administered dose) was detected in the urine, possibly due to faecal contamination. Identifiable products in faeces and urine included a parent compound and 16 metabolites. The study results suggest that orally administered bifenthrin had undergone extensive hydrolysis and oxidation (ElNaggar & Wu, 1986).

In another study, the absorption, distribution and metabolism of bifenthrin labelled with ^{14}C in the alcohol (phenyl) ring or in the acid (cyclopropyl) ring were studied in Crl:CD (SD) BR rats following single oral gavage dosing. The dosing regime was as follows: the control group received the vehicle (corn oil) only, the second group received a single dose of 5.43 mg/kg bw, the third group received multiple low doses at 4.0 mg/kg bw for 14 days followed by a single radiolabelled gavage dose and a fourth group received a single dose at 35.71 mg/kg bw. Five male and five female rats were used per group.

Table 3. Distribution of radioactivity recovered in male and female rats in 7 days following oral administration of bifenthrin[a]

Dose group (mg/kg bw)	Sex	Distribution of radioactivity (% of administered dose)				
		Urine[b]	Faeces	Tissues	Carcass	Total
5.43	Male	9.37	83.41	0.14	2.65	95.57
	Female	12.13	74.44	0.15	3.71	90.42
35.71	Male	12.43	75.68	0.13	2.38	90.62
	Female[c]	14.46	71.15	0.22	5.01	90.83
4.0 (repeated dose)	Male	11.96	83.50	0.22	3.15	98.82
	Female	14.29	74.01	0.21	5.33	93.84

Data extracted from Cheng (1988), Table 6-8

[a] Males were dosed with bifenthrin labelled with ^{14}C in the acid (cyclopropyl) ring; females were dosed with bifenthrin labelled with ^{14}C in the alcohol (phenyl) ring.

[b] Includes cage rinse, cage wash and cage wipe.

[c] Tissue and carcass data were reported from the initial group, whereas data for faeces and urine were derived from the repeat group.

Males received acid-labelled bifenthrin, and females received alcohol-labelled bifenthrin. Treated animals were kept individually in metal metabolism cages for collection of urine and faeces. Exhaled air and volatiles were not collected based on a preliminary study indicating that <1.0% of the administered dose was recovered in these fractions. Samples of urine and faeces were collected at the following time intervals: 0–8, 8–12, 12–24, 24–48, 48–72, 72–96, 96–120, 120–144 and 144–168 h post-dosing. Treated rats were sacrificed after 7 days, and radioactivity in various tissues and organs was analysed.

The total radioactivity recovery ranged from 90.4% to 98.82% of the administered dose (Table 3). The majority of the radioactivity was found in the faeces (71.2–83.5% of the administered dose) and urine (9.4–14.5% of the administered dose). Less than 0.22% and 5.33% of the administered dose were recovered in tissues and carcasses, respectively, in 7 days after dosing.

The distribution of radioactivity in various tissues and organs after 7 days is shown in Table 4 following oral dosing of rats with bifenthrin. The highest concentrations of radioactivity were observed in fat (1.1–15.6 ppm). The concentration of radioactivity in fat was highest following a single gavage dose of 35.71 mg/kg bw compared with the two other dose groups.

The study author concluded that the rate of elimination was moderate and that the majority of the radioactivity was excreted into urine and faeces within the first 36 h and 72 h for the low dose groups (5.43 mg/kg bw and repeated-dose group) and high dose group, respectively. No sex differences in ^{14}C elimination or distribution were observed for any of the dosing regimes (Cheng, 1988).

Urine and faecal samples from the Cheng (1988) study were further subjected to metabolic identification. Individual homogenized faecal samples were thawed, and 0–48 h samples were combined into one main group for each label independently by sex for both single low dose and multiple low dose. Samples from single high dose for 0–72 h were also combined by sex and label. The urine samples were also pooled in a similar fashion. The pooled samples of urine and faeces were subjected to suitable extraction and separation steps and analysed for the parent compound and metabolite content by TLC, HPLC and liquid scintillation counting.

Faecal metabolites were excreted primarily as non-conjugates, whereas urinary metabolites were eliminated in both conjugated and non-conjugated forms. The metabolite profile appeared to be similar among the three dosing regimes, whereas the excretion rate appeared to be slower in high-dose rats. A summary of the distribution of bifenthrin and its metabolites is shown in Table 5 for faeces and Table 6 for urine.

Table 4. Tissue distribution after 7 days following oral gavage administration of bifenthrin to rats[a]

Tissue/matrix	Tissue distribution (ppm)					
	5.43 mg/kg bw (single oral gavage low dose)		4.0 mg/kg bw (multiple oral gavage doses)		35.71 mg/kg bw (single oral gavage high dose)	
	Male	Female	Male	Female	Male	Female
Blood	0.021	0.006	0.027	0.008	0.106	0.039
Bone	0.019	0.082	0.026	0.086	0.095	0.381
Brain	0.001	0.006	0.002	0.008	ND	0.044
Carcass	0.141	0.208	0.169	0.258	0.897	2.204
Fat	1.118	1.183	1.443	1.267	7.655	15.601
Hair	0.063	0.031	0.052	0.032	1.120	1.038
Heart	0.010	0.022	0.012	0.035	0.094	0.200
Kidney	0.028	0.041	0.035	0.043	0.163	0.400
Liver	0.082	0.091	0.114	0.113	0.510	0.623
Lungs	0.064	0.105	0.044	0.115	0.189	1.411
Muscle	0.007	0.015	0.014	0.025	0.035	0.182
Ovary	NA	0.118	NA	0.056	NA	0.736
Pancreas	0.056	0.124	0.068	0.118	0.267	0.876
Prostate	0.061	NA	0.010	NA	0.184	NA
Seminal vesicles	0.044	NA	0.015	NA	0.330	NA
Skin	0.143	0.184	0.185	0.214	0.726	2.162
Spleen	0.009	0.018	0.020	0.026	0.031	0.143
Testes	0.007	NA	0.011	NA	0.046	NA
Uterus	NA	0.012	NA	0.006	NA	0.207

Data extracted from Cheng (1988), Table 9-11

NA, not applicable

[a] Males were dosed with bifenthrin labelled with ^{14}C in the acid (cyclopropyl) ring; females were dosed with bifenthrin labelled with ^{14}C in the alcohol (phenyl) ring.

Analysis of metabolite fractions indicated that the major faecal metabolites were primarily derived from hydroxylated parent compound, namely: hydroxymethyl-bifenthrin, 4′-hydroxy-bifenthrin, 3′-hydroxy-hydroxymethyl-bifenthrin, 4′-hydroxy-hydroxymethyl-bifenthrin, 3′-monomethyl-catechol-bifenthrin, 4′-monomethyl-catechol-bifenthrin, dimethoxy-bifenthrin and 4′-methoxy-bifenthrin. Hydrolytic products related to monohydroxylated and dihydroxylated intact parent chemical were also detected, which included 4′-hydroxy-biphenyl alcohol, 4′-hydroxy-biphenyl alcohol, dimethoxy-biphenyl acid, dimethoxy-biphenyl alcohol, 4′-methoxy-biphenyl alcohol, biphenyl alcohol, TFP acid, and *cis*- and *trans*-hydroxymethyl-TFP acid.

Analyses of metabolites from urine fractions indicated that no significant intact metabolites were detected. The majority of ^{14}C residues were from hydrolytic or oxidative degradation, as follows: 4′-hydroxy-biphenyl acid, biphenyl acid, 4′-hydroxy-biphenyl alcohol, dimethoxy-biphenyl acid, 4′-methoxy-biphenyl acid, dimethoxy-biphenyl alcohol, biphenyl alcohol, TFP acid, and *cis*- and *trans*-hydroxymethyl-TFP acid.

In summary, when bifenthrin is dosed orally to rats, it is eliminated primarily in faeces as intact parent compound and its hydroxylated metabolites. A small percentage of the administered dose is eliminated through excretion in urine as either hydrolytic or hydrolytic/oxidative metabolites of the parent chemical and/or its intact metabolites. A mild inductive effect was observed, as the products

Table 5. Profile of metabolites in rat faeces[a]

Metabolic product	% of dose					
	5.43 mg/kg bw (single dose)		4.0 mg/kg bw per day (repeated dose)		35.71 or 42.94 mg/kg bw (single dose)	
	Male	Female	Male	Female	Male	Female
Polar[b]	3.25	3.39	5.06	4.46	2.00	2.36
Hydroxymethyl-TFP acid	NA	1.13	NA	1.31	NA	1.12
TFP acid	NA	1.48	NA	1.68	NA	1.26
4′-Hydroxy-biphenyl acid	0.69	NA	1.32	NA	0.66	NA
Dimethoxy-biphenyl acid	0.41	NA	1.35	NA	0.36	NA
4′-Methoxy-biphenyl acid (biphenyl acid)	0.87	NA	1.32	NA	0.84	NA
4′-Hydroxy-biphenyl alcohol	1.45	NA	4.29	NA	1.78	NA
Dimethoxy-biphenyl alcohol	1.22	NA	1.85	NA	1.19	NA
4′-Methoxy-biphenyl alcohol (biphenyl alcohol)	1.79	NA	2.72	NA	1.35	NA
3′- or 4′-Hydroxy-hydroxymethyl bifenthrin (biphenyl aldehyde)	0.77	3.84	3.37	6.50	1.75	4.22
Hydroxymethyl-bifenthrin	0.93	4.13	2.09	6.74	0.97	3.52
4′-Hydroxy-bifenthrin	1.80	3.98	2.85	5.63	1.48	3.26
3′- or 4′-Monomethyl-catechol	2.25	3.81	3.57	6.17	2.20	4.66
Dimethoxy-bifenthrin	1.80	0.93	1.45	0.96	2.09	0.72
4′-Methoxy-bifenthrin	1.24	0.69	0.97	0.45	1.36	0.83
Bifenthrin	39.22	31.17	25.45	21.80	38.25	35.31
Non-polar[c]	9.08	8.90	5.99	5.41	8.53	3.87
Other unknowns[d]	8.32	4.10	12.32	4.93	5.21	3.81
Water soluble	1.20	0.57	0.81	0.56	0.73	0.07
Post-extraction solids	3.94	3.35	3.87	3.43	2.19	3.85
Total	80.24	71.47	80.65	70.03	72.94	68.85

Data extracted from the study report (Wu, 1988), Table 13
NA, not applicable
[a] Males were dosed with bifenthrin labelled with ^{14}C in the acid (cyclopropyl) ring; females were dosed with bifenthrin labelled with ^{14}C in the alcohol (phenyl) ring.
[b] Products eluted prior to hydroxymethyl-TFP acid.
[c] Products eluted after bifenthrin.
[d] Fractions in entire HPLC run not designated to any specified standard.

in faeces were present to a greater degree as hydroxylated intact chemical and less parent compound in the multiple low dose group compared with those of single-dose rats. The rate of excretion was slower in the high dose group (toxic level) compared with the low dose groups.

The study author suggested that bifenthrin metabolism in the rat is similar to that of other pyrethroids, which also metabolize through typical hydrolytic, oxidative and conjugation processes, as summarized in the proposed metabolic pathway in Figure 2 (Wu, 1988).

In a repeated-dose distribution study, female Sprague-Dawley rats were administered a single daily oral gavage dose of bifenthrin (radiochemical purity >99.0%) labelled with ^{14}C in the alcohol (phenyl) ring at 0.5 mg/kg bw per day in corn oil for 70 days. Three treated rats and one control were

Table 6. Profile of metabolites in rat urine[a]

Metabolic product	% of dose					
	5.43 mg/kg bw (single dose)		4.0 mg/kg bw per day (repeated dose)		35.71 or 42.94 mg/kg bw (single dose)	
	Male	Female	Male	Female	Male	Female
4′-Hydroxy-biphenyl acid	1.74	NA	2.15	NA	1.65	NA
Dimethoxy-biphenyl acid	0.30	NA	0.23	NA	0.16	NA
Biphenyl acid	0.95	NA	1.07	NA	0.90	NA
4′-Methoxy-biphenyl acid	0.09	NA	0.12	NA	0.09	NA
4′-Hydroxy-biphenyl alcohol	0.31	NA	0.42	NA	0.35	NA
Dimethoxy-biphenyl alcohol	0.26	NA	0.34	NA	0.28	NA
Biphenyl alcohol	0.06	NA	0.08	NA	0.08	NA
Bifenthrin	0.00	0.00	0.00	0.00	0.01	0.00
TFP acid	NA	1.85	NA	1.63	NA	2.09
cis-Hydroxymethyl TFP acid	NA	0.78	NA	1.48	NA	1.00
trans-Hydroxymethyl TFP acid	NA	0.58	NA	0.78	NA	0.69
Polar origin	1.92	3.23	3.04	5.49	1.77	3.02
Polar unknowns	1.19	0.78	1.75	1.06	1.25	1.14
Non-polar unknowns	0.05	0.36	0.05	0.42	0.00	0.64
Aqueous	0.67	0.36	1.32	0.41	0.72	0.28
Total	7.54	7.94	10.56	11.27	7.26	8.86

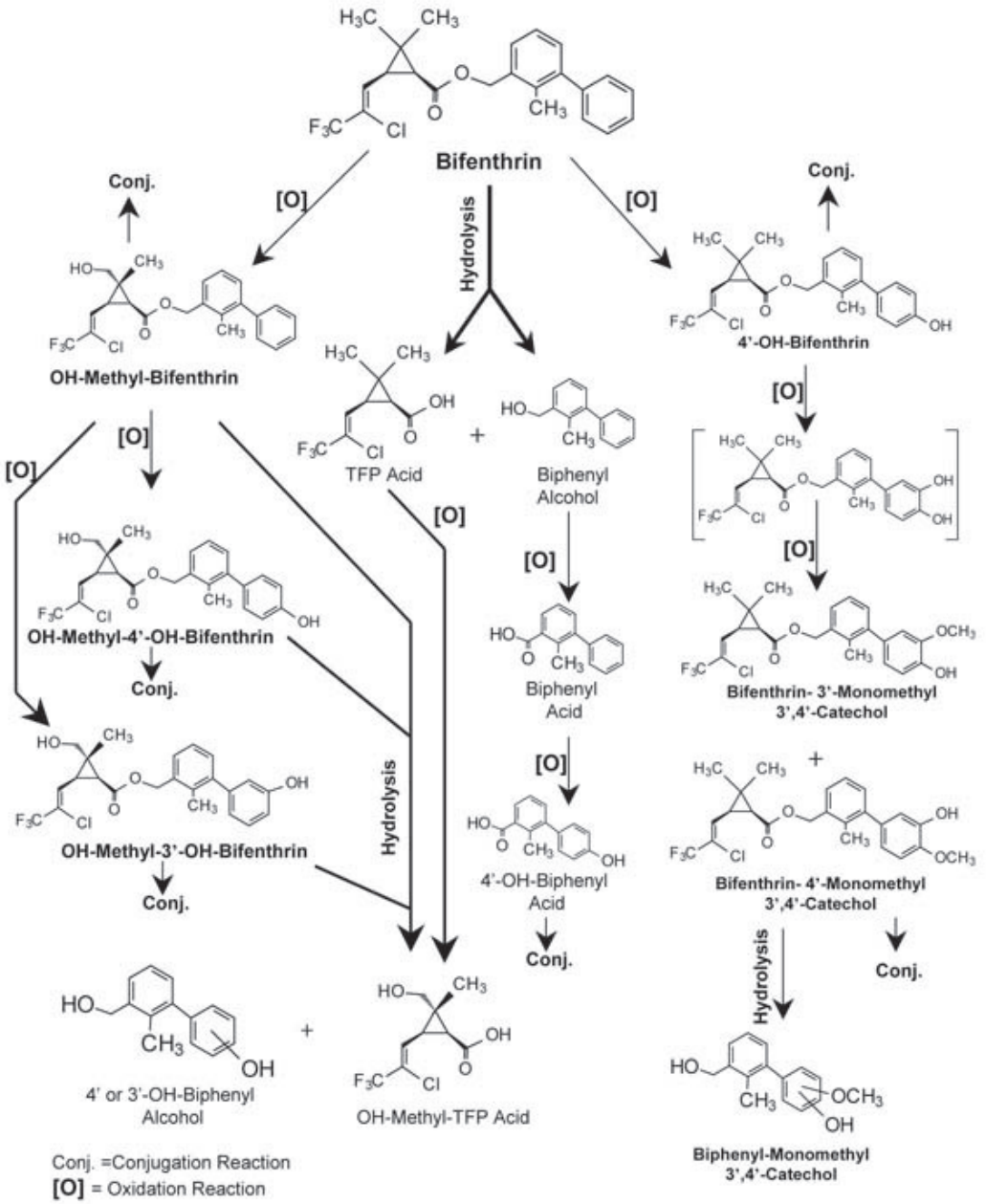
Data extracted from the study report (Wu, 1988), Table 23
NA, not applicable
[a] Males were dosed with bifenthrin labelled with ^{14}C in the acid (cyclopropyl) ring; females were dosed with bifenthrin labelled with ^{14}C in the alcohol (phenyl) ring.

sacrificed periodically during the dosing period, and blood, liver, kidneys, ovaries, fat (sample) and skin were analysed for radioactivity. The sciatic nerve was also removed from animals sacrificed at 56, 63, 70, 73, 99, 113, 127 and 155 days. The nature of radioactivity in the fat was also evaluated using the TLC method. Analysis was extended for an additional 85 days (depuration phase) following cessation of dosing.

At all sacrifice times and in all animals, the highest concentrations of radioactivity were found in fat. Concentrations in the liver, kidney, skin and ovaries were also significantly higher than the corresponding plasma concentrations. Plasma concentrations of radioactivity were similar from day 21 to day 70 (0.04–0.06 µg/ml) and then decreased rapidly to 0.01 µg/ml at 78 days and <0.1 µg/ml at the remaining sacrifice times. The concentrations in the whole blood were very similar to plasma concentrations, indicating some uptake of radioactivity in blood cells but no specific accumulation. Mean concentrations of radioactivity in fat were 0.33 µg/g at 1 day, 0.87 µg/g at 3 days and 2.44 µg/g at 14 days. Concentrations in fat then increased slowly, with mean concentrations of radioactivity between 4.47 and 9.62 µg/g during the remaining dosing period. After the final dose, mean concentrations of radioactivity in fat declined with an approximate half-life of 51 days to 8.79 µg/g, 5.44 µg/g, 4.53 µg/g and 2.74 µg/g at 78, 92, 113 and 155 days, respectively.

Average peak concentrations of bifenthrin radioactivity in fat, skin, liver, kidney, ovaries, sciatic nerve, whole blood and plasma amounted to 9.62 µg/g, 1.74 µg/g, 0.40 µg/g, 0.32 µg/g, 1.69 µg/g, 3.25 µg/g, 0.06 µg/g and 0.06 µg/g, respectively. Estimated half-lives of 51 days (fat), 50 days (skin), 19 days (liver), 28 days (kidney) and 40 days (ovaries and sciatic nerve) were derived from ^{14}C depuration.

Figure 2. Proposed metabolic pathway for bifenthrin in the rat



Analysis of fat samples by hexane extraction, acetonitrile extracts and TLC determined that the presence of unchanged bifenthrin accounted for 65% of the radioactivity in the 1- and 14-day samples and 72–85% in the 7- to 155-day samples. Another component in fat accounted for 5.3% of the total radioactivity on day 1 and 19.5% of the total radioactivity on day 155. The remaining radioactivity in the fat was associated with two polar components (Hawkins, Elsom & Jackson, 1986).

In a plasma kinetics determination study, male Sprague-Dawley rats (Crl:CD (SD) BR) were administered bifenthrin (radiochemical purity 98.0%) labelled with ^{14}C in the alcohol (phenyl) ring as a single oral gavage dose at 4 or 35 mg/kg bw in corn oil. Blood was collected from five treated rats from

each dose group at 1, 2, 3, 4, 6, 8, 10, 12, 48 and 72 h post-dosing. A group of five animals was sacrificed by heart puncture at 2, 4, 10 and 24 h after dosing for the low dose group and at 3, 6, 10 and 24 h after dosing for the high dose group. These time intervals for sacrifice were based on the results of the preliminary study indicating that the peak blood levels were reached between 4 and 8 h after dosing for both the low and the high dose groups. The results of the main study indicated that the blood level of radioactivity for both the low and high dose groups followed a similar pattern. The radioactivity was slowly absorbed, with a time to peak plasma level of 4 h for the low dose and 6 h for the high dose. The decline of radioactivity was slow, with detectable radioactivity at 24 and 48 h after dosing (Selim, 1986).

The plasma samples from the Selim (1986) study were further analysed to identify the nature of the radioactivity. Pooled plasma from five rats from each of five sampling intervals was deproteinized and extracted with acetone, and the whole plasma was analysed by HPLC and liquid scintillation counting. HPLC analysis of the acetone organosoluble residues at the two peak intervals indicated the presence of parent compound (25–38% of the total radiolabel). Biphenyl alcohol (29–33%) and biphenyl acid (21–34%) comprised a majority of the remaining plasma radiocarbon residues. Parent chemical and its metabolites declined in plasma over time, with a corresponding increase in protein-bound residues of the total radiolabel (unextractable residues).

In summary, the results of this study suggest that the disposition of radiocarbon-labelled bifenthrin in rat plasma appears to be primarily hydrolysis of the ester group and oxidation of the resulting alcohol and acids (Tullman, 1986).

Bile duct–cannulated Sprague-Dawley rats were dosed with bifenthrin (radiochemical purity 98.0%) labelled with ^{14}C in the alcohol (phenyl) ring administered as a single gavage dose of 2.7 mg/kg bw to four females and 5.2 mg/kg bw to four males. Corn oil was used as a vehicle. Samples of urine, faeces and bile were collected at 0–12, 12–24, 24–36, 36–48 and 48–72 h. Treated animals were sacrificed at 72 h after dosing, and various organs and tissues were analysed for radioactivity. Faeces, gastrointestinal tract contents and bile samples were further subjected to metabolite identification.

In female rats dosed at 2.7 mg/kg bw, mean excretion of radioactivity was 30.0%, 15.0% and 48.7% of the administered dose in the bile, urine and faeces, respectively, 72 h post-dosing. Approximately 4.8% of the dose in female rats was recovered in the gastrointestinal tract, skin and liver. In male rats dosed at 5.2 mg/kg bw, mean excretion of radioactivity was 18.6%, 10.7% and 24.9% of the administered dose in the bile, urine and faeces, respectively, 72 h post-dosing. Approximately 6.3% of the dose in male rats was recovered in the gastrointestinal tract, skin and liver. The chromatographic profile of the faeces indicated that the majority of the radioactivity was the parent compound, averaging 89.5% and 92.3% of the extractable radiocarbon in female and male rats, respectively. Hydrolytic products resulting from gut microflora in faeces were minor, averaging 10.5% and 7.7% for female and male rats, respectively. The major product in the gastrointestinal tract contents of all samples was unchanged bifenthrin, averaging 84.3% and 91.9% of the extractable radiocarbon for female and male rats, respectively. Hydrolytic degradates and metabolites detected in the gastrointestinal tract contents were minor but slightly higher than in faeces, averaging 15.7% and 8.1% for female and male rats, respectively. Analysis of bile indicated that less than 1% of the radiocarbon was attributable to parent compound, with the remainder composed of polar and conjugated metabolites. The metabolic products in the bile were derived from hydroxylated parent compound, namely: hydroxymethyl-bifenthrin, 4′-hydroxy-bifenthrin, dihydroxy-bifenthrin, bifenthrin-guaiacol (3′- or 4′-monomethyl catechol-bifenthrin) and other hydrolytic products, which included biphenyl alcohol and biphenyl acid. The overall profile of bile metabolites (i.e. aglycones) corresponded closely to the metabolite profile in faeces from the previously described rat metabolism studies.

Total absorption of bifenthrin using the sum of average biliary and urinary excretion and tissue concentrations yielded a value of 49.8% of the administered dose for females and 35.6% of the

dose for males. The results of this bioavailability study suggest that the faecal metabolites and other non-bifenthrin-related radioactivity in the faeces identified in the previously described rat metabolism studies were due to enterohepatic absorption of bifenthrin, biotransformation in the liver and subsequent biliary excretion. In previous studies, virtually no differences in absorption were noted between male and female rats. In this study, differences arose due to differing dosing regime. Male rats were given doses of bifenthrin approximating the low dose in the previous study, but this proved too stressful for the surgically modified rats. The females, studied after the conclusion of the male rat study, were dosed at a lower rate to increase the survivability and health of the animals; consequently, they absorbed a higher percentage of bifenthrin dose. In this regard, it may also be noted that despite the obvious stress on the male rats (evidenced by low biliary excretion and decreased defecation), the ratio of radioactivity distributed between bile and urine as a percentage of the dose (1.7:1) was still very similar to that observed for the females (2:1). This indicates that although absorption may have been impaired, the partitioning of absorbed material between biliary and urinary excretory routes was nevertheless similar to that observed in non-cannulated rats (ElNaggar & Tullman, 1991).

(b) Dermal application

In a percutaneous absorption study, three groups (24 per group) of male rats (Crl:Crn(SD)BR) received single doses of aqueous suspensions of bifenthrin labelled with ^{14}C on the alcohol ring on a previously clipped area of the skin on the back. The rats each received an average of 49.2, 514 or 5252 µg of the test material. Four rats were sacrificed for each dose at 0.5, 1, 2, 4, 10 or 24 h after dermal application. The disposition of the administered ^{14}C was followed. The radioactivity at the application site was extracted and analysed.

The amounts of bifenthrin equivalents eliminated in the urine and faeces of individual rats, even after 24 h of exposure to the test material, were less than 1% of the amount applied to the skin. At the lowest dose level, measurable levels of the test compound did not appear in the excreta until after 10 h of exposure. At the highest dose level, levels of test compound equivalents appeared after 24 h, but the total amount in excreta after 24 h was only 0.2% of the dose. Small quantities of bifenthrin-derived radioactivity were detected in the blood and carcasses. The amount absorbed was defined as the sum of the ^{14}C present in the excreta, the carcass and the skin at and adjacent to the application site (following removal of residual test material with several water washes). There appears to be fairly rapid absorption through the skin during the first half hour after application, and the amounts of absorbed compound did not increase with time. There was also a direct correlation between the concentration applied and the amount absorbed. At 24 h, approximately 70.8%, 44.8% and 53.4% of the dermally applied doses of 49.2, 514 and 5252 µg, respectively, were absorbed (Craine, 1986).

In a second percutaneous absorption study, male Sprague-Dawley rats were dermally dosed with the aqueous emulsion CAPTURE 2EC containing 36.2 µg of bifenthrin (107 kBq, 200 µl). Four rats were killed at 0, 4, 10 and 24 h post-dose. The total amount of ^{14}C radioactivity removed by a skin wash procedure and the total amount of ^{14}C radioactivity remaining on washed, dosed skin were determined. Samples of blood, urine, faeces and residual carcass were collected and analysed for ^{14}C content. The radioactivity recovered in the skin wash was 96.83%, 84.75%, 76.86% and 72.88% of the total administered dose at 0, 4, 10 and 24 h after dermal application, respectively. The radioactivity recovered in the skin application site after wash was 4.04%, 12.00%, 16.55% and 19.44% at 0, 4, 10 and 24 h after dermal application. The sums of the applied dose recovered in blood, plasma and carcass were 0.09%, 0.87%, 0.85% and 1.67% at 0, 4, 10 and 24 h post-application. The sums of the applied dose recovered in urine and faeces were 0.14%, 0.43% and 3.23% at 4, 10 and 24 h post-application. Based on the results of this study, it can be concluded that the dermal absorption (sum of the radioactivity in excreta, blood, plasma and carcass) of aqueous emulsion CAPTURE 2EC containing 36.2 µg of bifenthrin was 1.01%, 1.30% and 4.90% at 4, 10 and 24 h after dermal application (Braun, 1990).

(c) In vitro

An in vitro comparative metabolism study was conducted to evaluate species differences in metabolism of radiolabelled bifenthrin between male and female Swiss-Webster mice and male Sprague-Dawley rats. Bifenthrin labelled with ^{14}C in the cyclopropyl ring (acid-labelled) or in the phenyl ring (alcohol-labelled) was incubated for up to 60 min with liver microsomal metabolizing S9 mix obtained from male and female Swiss-Webster mice or male Sprague-Dawley rats. The reactions were quenched with methanol, the incubates were centrifuged to remove protein and the supernatant was analysed by HPLC. In order to accentuate any differences in metabolism between the incubates, 60 min supernatants were adjusted to pH 10 and extracted with hexane to remove the majority of unmetabolized bifenthrin. Analysis of the 60 min incubates revealed that more than 60% of the radioactivity was present as the unmetabolized bifenthrin. Those metabolites that were observed indicated that bifenthrin had undergone hydroxylation and scission reactions with each liver S9 mix at 60 min. Extractions of the supernatants revealed the presence of up to nine metabolites of bifenthrin, most of which remained unidentified. Comparison of chromatograms from each of the S9 types indicated that one metabolite was found uniquely in male mouse and another only in female mouse.

When incubated with liver S9 mixes, bifenthrin was metabolized by scission and hydroxylation. The extent of metabolism with each liver was in the order male mouse > female mouse > rat. However, the overall rate of in vitro metabolism was low (Kennelly, 1989).

2. Toxicological studies

2.1 Acute toxicity

The acute toxicity of bifenthrin is summarized in Table 7.

(a) Oral administration

Mice

Groups of male and female young adult Swiss-Webster mice (10 of each sex per dose) were given bifenthrin (purity 91.4%) as a single dose at 0, 25, 35, 42 or 50 mg/kg bw by gavage in corn oil. Treated mice were subjected to gross necropsy after 14 days. Animals were observed for mortality and clinical signs of toxicity at 0.5, 1, 2, 3, 4 and 6 h on the day of dosing and twice daily thereafter for 13 days. Body weights were recorded on days 0, 7 and 14 of the study. Clinical signs commonly observed during the study included clonic convulsions, tremors and oral discharge. The onset of these signs began approximately 2 h after dosing and continued to be observed until day 1 of the study, at which time all surviving mice had returned to normal. All survivors gained weight by the end of the study. All deaths occurred within 24 h of dosing. There were no significant treatment-related effects noted at necropsy. The oral median lethal dose (LD_{50}) for bifenthrin in mice was 43.5 (36.2–50.7) mg/kg bw and 42.5 (37.1–47.9) mg/kg bw for males and females, respectively (Rand, 1983a).

Rats

Groups of male and female young adult Sprague-Dawley (Tac:N(SD)fBR) rats (10 of each sex per dose) were given bifenthrin (purity 92.0%) as a single dose at 0, 34, 40, 44, 48, 55 or 67 mg/kg bw by gavage in corn oil. Animals were observed for mortality and clinical signs at 0.5, 1, 2, 3, 4 and 6 h after administration and twice daily thereafter for 13 days. Body weights were recorded on days 0, 7 and 14. A gross necropsy was performed on all animals. No treatment-related effects on body weight were observed. The clinical signs generally observed at all dose levels included clonic convulsions, tremors and chromorhinorrhoea. The onset of these signs began approximately 3 h after dosing and continued to be observed throughout the day. In addition, animals

Table 7. Acute toxicity of bifenthrin

Species	Strain	Sex	Route	LD_{50} (mg/kg bw)	LC_{50} (mg/l)	Reference
Mouse	Swiss-Webster	M, F	Oral	M: 43.5 (36.2–50.7) F: 42.5 (37.1–47.9)		Rand (1983a)
Rat	Sprague-Dawley (Tac:N(SD)fBR)	M, F	Oral	M: 55.5 (49.7–61.3) F: 53.4 (46.8–60.0)		Norvell (1982)
Rat	Sprague-Dawley (Tac:N(SD)fBR)	M, F	Oral	M: 70.1 (44.5–95.6) F: 53.8 (44.2–63.5)		Freeman (1983)
Rat	Sprague-Dawley CD	M, F	Oral	M: 168.4 (111.4–225.4) F: 210.4 (129.3–291.6)		Watt (1997)
Rat	Sprague-Dawley (Tac:N(SD)fBR)	M, F	Intraperitoneal	M: 770.9 (364.5–1177.4) F: 822.4 (432.8–1212.1)		Kedderis (1985)
Rabbit	New Zealand White	M, F	Dermal	>2000		DeProspo (1983a)
Rat	Sprague-Dawley	M, F	Dermal	>2000		Kedderis (1985)
Rat	Crl:CD(SD)IGS BR	M, F	Inhalation (4 h, nose only)		F: 0.8 (0.5–1.5) M: 1.1 (0.94–1.29)	Kiplinger (2003)
Rabbit	New Zealand White	M, F	Dermal irritation	Non-irritating		DeProspo (1983b)
Rabbit	New Zealand White	M, F	Ocular irritation	Non-irritating		DeProspo (1983c)
Guinea-pig	Dunkin-Hartley	M	Dermal sensitization	Not sensitizing		DeProspo (1983d)
Guinea-pig	Ibm: GOHI; SPF	F	Dermal sensitization	Skin sensitizer		Arcelin (2003)

F, female; LC_{50}, median lethal concentration; LD_{50}, median lethal dose; M, male

at all dose levels appeared to have abdominal pain following dosing. By day 3, all surviving rats had returned to normal. All deaths occurred within 24 h after dosing. There were no internal gross lesions noted in any animal dying after treatment. Gross signs observed in rats dying after dosing included chromorhinorrhoea, chromodacryorrhoea and abdominogenital staining. The external signs correlate with the clinical observations prior to death. The oral LD_{50} of bifenthrin in rats was 55.5 (49.7–61.3) mg/kg bw and 53.4 (46.8–60.0) mg/kg bw for males and females, respectively (Norvell, 1982).

In a second study, groups of male and female young adult Sprague-Dawley (Tac:N(SD)fBR) rats (10 of each sex per dose) were given bifenthrin (purity 91.4%) as a single dose at 0, 20, 40, 60, 80, 90 or 100 mg/kg bw by gavage in corn oil. Animals were observed for mortality and clinical signs at 0.5, 1, 2, 3, 4 and 6 h after administration and twice daily thereafter for 13 days. Body weights were recorded on days 0, 7 and 14. A gross necropsy was performed on all animals. No treatment-related effects on body weight were observed. Clinical signs commonly observed during this study included clonic convulsions, tremors, ataxia, loss of muscle control, decreased locomotion, chromorhinorrhoea, chromodacryorrhoea and oral discharge. These signs started approximately 3 h after dosing and continued until day 5. At that time, the surviving animals returned to normal. At necropsy of rats that died during the study, blood in the intestines of three animals and red intestinal lining in one animal were observed. The necropsy of the rats that survived until study termination appeared normal.

The oral LD_{50} of bifenthrin was 70.1 (44.5–95.6) mg/kg bw and 53.8 (44.2–63.5) mg/kg bw for males and females, respectively (Freeman, 1983).

In a third study, groups of male and female young adult Sprague-Dawley CD rats (five of each sex per dose) were given bifenthrin (purity 93.7%) as a single dose at 0, 75, 100, 150, 200 or 300 mg/kg bw by gavage, undiluted. Animals were observed for mortality and clinical signs at 0.5, 1, 2, 3, 4 and 6 h after administration and twice daily thereafter for 14 days. Body weights were recorded on days 0, 7 and 14. A gross necropsy was performed on all animals. No treatment-related effects on body weight were observed. The most significant clinical signs observed during the study were tremors, vocalization, clonic convulsions, twitching, abdominal gripping and hypersensitivity to touch. Other clinical signs noted included abdominal staining, oral discharge, chromorhinorrhoea, chromodacryorrhoea, diarrhoea and broken tooth. All signs of toxicity ended by day 3 of the study. There were no gross internal lesions noted in any animal during necropsy. The oral LD_{50} of bifenthrin in rats was 168.4 (111.4–225.4) mg/kg bw and 210.4 (129.3–291.6) mg/kg bw for males and females, respectively (Watt, 1997).

(b) Intraperitoneal administration

Groups of male and female young adult Sprague-Dawley (Tac:N(SD)fBR) rats (10 of each sex per dose) were given bifenthrin (purity 88.35%) as a single intraperitoneal dose at 0, 100, 250, 500, 900 or 1500 mg/kg bw in corn oil. Animals were observed for mortality and clinical signs at 0.5, 1, 2, 3, 4 and 6 h post-dosing and twice daily thereafter. Body weights were recorded on day 0 and weekly thereafter. A gross necropsy was performed on all animals. Clinical signs such as tremors, clonic convulsions, chromorhinorrhoea, abdominogenital staining and hypersensitivity to touch were observed 4–6 days post-dosing and continued to be observed for up to 4–5 weeks (500 mg/kg bw) or 6–8 weeks (900 mg/kg bw). Minimal or no clinical signs were observed at 100 or 250 mg/kg bw. Deaths occurred in some animals after dosing but were delayed (1–2 weeks) in most animals. Most animals had white nodules throughout the liver, spleen, diaphragm, stomach or mesentery. These lesions were histologically diagnosed as focal foreign body granulomata, apparently induced by precipitation of the test substance following injection. The intraperitoneal LD_{50} of bifenthrin in rats was 770.9 (364.6–1177.4) mg/kg bw and 822.4 (432.8–1212.1) mg/kg bw for males and females, respectively (Kedderis, 1986).

(c) Dermal application

Rats

Five male and five female young adult Sprague-Dawley rats were exposed dermally to bifenthrin (purity 88.35%) at 2000 mg/kg bw applied undiluted to a Hilltop chamber, then allowed to set for approximately 15 min. The Hilltop chamber was then placed over the intact test site and secured by latex tape. The test substance was maintained in contact with the skin for 24 h. The test site was then washed with a clean gauze pad moistened with acetone, followed by a wipe with tap water. The rats were observed for 14 days. Animals were observed for mortality and clinical signs at 0.5, 1, 2, 3, 4 and 6 h after administration and twice daily thereafter for 13 days. Body weights were recorded on days 0, 7 and 14. A description of the local irritation was recorded on days 1, 3, 7 and 14. A gross necropsy was performed on all animals. There were no deaths. All rabbits lost weight by day 14 of the study. No irritation was observed. Male rats exhibited staggered gait on days 2 and 3. Female rats exhibited staggered gait, decreased locomotion and abdominogenital staining between study days 2 and 4. At necropsy, no gross lesions were observed in any animal. The dermal LD_{50} of bifenthrin in rats was >2000 mg/kg bw for males and females (Kedderis, 1985).

Rabbits

Five male and five female young adult New Zealand White rabbits were exposed dermally to bifenthrin (purity 88.35%) at 2000 mg/kg bw applied to approximately 10% of the (shaved) intact

body surface area. The test substance was maintained in contact with the skin for 24 h using an occlusive wrap. The rabbits were observed for 14 days. Animals were observed for mortality and clinical signs at 0.5, 1, 2, 3, 4 and 6 h after administration and twice daily thereafter for 14 days. Body weights were recorded on days 0, 7 and 14. A description of the local irritation was recorded on days 1, 3, 7 and 14. A gross necropsy was performed on all animals. There were no deaths. All rabbits lost weight by day 14 of the study. All rabbits remained healthy throughout the study. The only signs of irritation observed were erythema in all rabbits 24 h after application and desquamation in four rabbits on day 14 of the study. Postmortem examination revealed pitted kidneys in one rabbit. The dermal LD_{50} of bifenthrin in rabbits was >2000 mg/kg bw for males and females (DeProspo, 1983a).

(d) Exposure by inhalation

Rats

Groups of five male and five female young adult Crl:CD(SD)IGS BR rats were exposed nose only to bifenthrin (purity 94.8%) for 4 h at mean measured (gravimetric method) particulate concentrations of 0.56, 0.99 or 2.33 mg/l. Rats were observed for 14 days. Atmospheres generated had mean aerodynamic particle sizes of 2.0, 2.3 and 2.1 µm. Mortality occurred at 0.56 mg/l (two females), 0.99 mg/l (one male and two females) and 2.33 mg/l (five males and five females). All deaths occurred within 1 day of exposure. At 2.33 mg/l, varying degrees of central nervous system effects, ranging from tremors to convulsions, were noted in the surviving animals immediately after exposure. Three males in this group were euthanized. At 0.99 mg/l, abnormal gait, convulsions, hypothermia, laboured respiration and rales were noted immediately following exposure. There were no other toxicologically relevant clinical findings immediately following exposure. Abnormal gait and tremors were noted in the 0.56 mg/l group immediately following exposure. During the 14-day post-exposure, abnormal gait, convulsions, decreased defecation/urination, increased respiration rate, tremors, unkempt appearance and red/yellow staining on various body parts were noted in the 0.56 mg/l and 0.99 mg/l dose groups. No treatment-related effects on body weight were observed. No effects were noted in animals during the necropsy. The median lethal concentration (LC_{50}) of bifenthrin at 4 h in rats was calculated to be 0.8 mg/l (0.5–1.5 mg/l) for females and 1.1 mg/l (0.94–1.29 mg/l) for males (Kiplinger, 2003).

(e) Dermal irritation

In a study of primary dermal irritation, three young adult male and female New Zealand White rabbits were dermally exposed to 0.5 ml of bifenthrin (purity 88.35%). Eight test sites (intact and abraded) were covered with gauze patches (5 cm × 5 cm) under which 0.5 ml of bifenthrin technical was applied per test site. The trunk of the animal was then wrapped with an elastic gauze bandage. The test material was in contact with the skin for 4 h, after which the animals were unwrapped. Dermal irritation was scored according to the Draize method after 30 min and then daily for 3 days. Clinical signs were recorded daily. No irritation was observed on any rabbits following application of bifenthrin on intact or abraded sites. Under the conditions of this study, it is concluded that bifenthrin is non-irritating to the skin of rabbits (DeProspo, 1983b).

(f) Ocular irritation

In a study of primary eye irritation, 0.1 ml of bifenthrin (purity 88.35%) was instilled into the conjunctival sac of one eye of each of three male and six female young adult female New Zealand White rabbits. The eyes of six of the rabbits remained unwashed, and the eyes of three of the rabbits were gently washed with 100 ml of tap water approximately 20–30 s after treatment. Irritation was scored by the method of Draize at 1 h and 1, 2 and 3 days after exposure. The primary irritation scores for the unwashed eyes were 6.0, 1.0, 0 and 0 at 1, 24, 48 and 78 h post-instillation. The primary irrita-

tion scores for the washed eyes were 8.0, 0, 0 and 0 at 1, 24, 48 and 78 h post-instillation. One hour after dosing, all of the eyes had severe discharge (grade 3), and all of the washed eyes had slight conjunctival redness. At the 24 h reading, two of the unwashed eyes had slight conjunctival redness, one of which also had slight discharge. Within 48 h after instillation, all eyes had returned to normal, and the test was terminated following the 72 h scoring. Under the conditions of this study, it is concluded that bifenthrin is non-irritating to the eyes (washed and unwashed) of rabbits (DeProspo, 1983c).

(g) Dermal sensitization

In a study of dermal sensitization with bifenthrin (purity 88.35%), 10 young male Dunkin-Hartley guinea-pigs were tested using the closed patch technique (Buehler method). One half millilitre of bifenthrin was applied to each of 10 Hilltop chambers. The chambers were applied to the test sites on the left shoulder and secured by a bandage. After 6 h, the bandage and chambers were removed, and the test sites were cleaned. The guinea-pigs were dosed in this manner 3 times a week for a total of 10 treatments. Fourteen days after the tenth treatment, the animals were challenged with the test material at a virgin skin site. Observations for skin reactions (Draize method) were recorded at 24 h after each application. Body weights were recorded at study initiation and termination. 1-Chloro-2,4-dinitrobenzene (0.15% weight by volume in ethanol) was used as the positive control. All animals gained weight by the end of the study. The guinea-pigs that received the test material had tremors within 48 h after the first application. Sporadic incidences of tremors continued to be observed in many of the animals during the dosing period. No irritation was observed in any test animals after induction or challenge application. All of the positive control animals had moderate to severe erythema (nine of which also had necrosis) at challenge. Based on these results, it is concluded that bifenthrin is not a skin sensitizer in guinea-pigs as determined by the closed patch technique (DeProspo, 1983d).

In another study of dermal sensitization with bifenthrin (purity 94.8%), 10 young female SPF guinea-pigs were tested using the maximization method of Magnusson & Kligman. For the main study, 10 female guinea-pigs were assigned to a control group, and 10 to the treatment group. In this study, the test concentrations chosen were 5% for intradermal induction, 5% for topical induction and 3% for the challenge. Polyethylene glycol 300 was used as the vehicle. Skin reactions at the challenge sites were observed at 24 h and 48 h after removal of the patch. One animal was found dead on test day 18. At necropsy, no macroscopic findings were reported. The cause of death was not attributed to the treatment. One animal of the test group was noted with slight tremor on test day 10. Body weights were normal except for the animal that was found dead. Discrete/patchy erythema was observed in eight out of nine animals at the 24 and 48 h readings in the treated animals. No skin reactions were noted in the controls. Based on the results of this study, bifenthrin is a potential sensitizer in guinea-pigs (Arcelin, 2003).

2.2 Short-term studies of toxicity

(a) Oral administration

Mice

In a 28-day dose range–finding study of toxicity, groups of 10 male and 10 female Swiss-Webster mice were given diets containing bifenthrin (purity 88.35%) at a dietary concentration of 0, 50, 100, 200 or 300 ppm (equivalent to 0, 7.5, 15, 30 and 45 mg/kg bw per day) for 28 days. The low dose of 50 ppm was changed to 500 ppm after 2 weeks. In a separate study, groups of 10 male and 10 female Swiss-Webster mice were given diets containing bifenthrin (purity 88.35%) at a concentration of 0, 500, 600, 750 or 1000 ppm (equivalent to 0, 75, 90, 112.5 and 150 mg/kg bw per day) for

28 days. Diets were prepared at the initiation of the study and biweekly thereafter. Diets were kept at room temperature. Mice were inspected daily for signs of toxicity and mortality. Body weight and food consumption were measured weekly. At termination, surviving mice were subjected to a gross necropsy, and organ weights were obtained for the brain, heart, liver, gonads, adrenals and kidneys.

In this study (doses up to 300 ppm), there were no significant treatment-related effects. Slightly decreased absolute brain weights were observed at the 200 and 300 ppm dose levels. At doses up to 1000 ppm, all female mice died by day 12, and 7 of 10 males died by day 7. At 750 ppm, five females died by day 6, and at 600 ppm, two females died by day 7. There was no mortality in males in the 600 and 750 ppm dose groups. No mortality was observed in the 500 ppm dose group and below. Prior to death, the most consistent clinical signs of intoxication were clonic convulsions and tremors. Tremors were also consistently observed in the three surviving 1000 ppm males until termination. Food consumption was also significantly lower in these three males compared with controls for the first 3 weeks of the study. However, in the final week, their food consumption was less than that of the controls, but not significantly. In the 600 ppm group, mean body weight was significantly greater in males compared with controls during the last 2 weeks of the study. Body weight gain and brain and liver weights of males were also significantly greater. The only marked aberrant clinical observation noted in males and females of the 500 ppm group was tremors. Under the study conditions utilized, the NOAEL for mice is 300 ppm, equivalent to 45 mg/kg bw per day, based on clinical signs, mortality, body weight changes and organ weight changes seen at 500 ppm, equivalent to 75 mg/kg bw per day, and above (Rand, 1983b).

Rats

In a 28-day study of toxicity, groups of 10 male and 10 female Sprague-Dawley rats were given diets containing bifenthrin (purity 91.4%) at a concentration of 0, 50, 100, 200, 300 or 400 ppm (equivalent to 0, 5, 10, 20, 30 or 40 mg/kg bw per day) for 28 days. Diets were prepared at the initiation of the study and at two other times during the study and stored at room temperature. Dietary concentrations were confirmed analytically. Rats were inspected daily for signs of toxicity and mortality. Body weight and food consumption were measured weekly. At termination, surviving rats were subjected to a gross necropsy, and organ weights were obtained for the brain, heart, liver, gonads, adrenals and kidneys.

All rats in the 400 ppm group died by day 15 of the study. In the 300 ppm group, 6 of 10 males died by day 12, and 1 of 10 females died by day 20 of the study. Prior to death, the most consistent clinical signs of intoxication were clonic convulsions and tremors. Mean body weight was significantly depressed for males and females during weeks 1, 2, 3 and 4. Furthermore, the overall gain in weights of males and females throughout the study was significantly less than that of the controls. Adrenal weights were significantly elevated, whereas testicular weights were depressed among males. Organ weights of the females were similar to those of controls. Relative organ to body weight ratios were significantly elevated for the adrenals, brain and kidneys of males and for the brain, kidneys and liver of females. In the 200 ppm group, mean food consumption was significantly depressed during week 1 in females, and mean body weight was depressed in males during week 1. Tremors in males and in females were the most consistent treatment-related observation noted. There were no treatment-related effects observed in rats in the 50 or 100 ppm groups.

Under the conditions of this study, it may be concluded that the NOAEL for bifenthrin in rats is 100 ppm, equivalent to 10 mg/kg bw per day, based on clinical signs seen at the lowest-observed-adverse-effect level (LOAEL) of 200 ppm, equivalent to 20 mg/kg bw per day (Rand, 1983c).

In an oral study of toxicity in rats, bifenthrin (91.4% active ingredient [ai]) was administered for 90 days in the diet to Sprague-Dawley rats (15 of each sex per dose) at dose levels of 0, 12, 50, 100 and 200 ppm (equal to 0, 0.88, 3.8, 7.5 and 15 mg/kg bw per day for males; 0, 1.04, 4.3, 8.5 and

17.2 mg/kg bw per day for females). An additional 10 rats of each sex were administered the diet containing bifenthrin at 0 or 200 ppm for 90 days and then fed a recovery (control) diet for an additional 28 days. Diets were prepared at the initiation of the study and stored at room temperature. Stability, homogeneity and dietary concentrations were confirmed analytically. All rats were examined daily for signs of toxicity and mortality. Body weight and food consumption were measured weekly. At termination, blood was taken for haematological and clinical chemistry analysis from 10 rats of each sex per dose. Ophthalmoscopic examinations were performed on all rats at initiation of the study and during the last week of the study. Animals were then subjected to a gross necropsy, and organ weights were obtained for the brain, gonads, heart, kidneys, liver and adrenals. Histopathological examination of selected tissues was conducted on all animals in the control and the 200 ppm groups. In addition, histopathological examination was performed on the lungs, liver and kidneys of animals in all dose groups.

There was no mortality during the study. There were no treatment-related changes noted in haematological, clinical chemistry, organ weight or gross and microscopic data. In addition, there were no ophthalmological changes observed that were related to dietary levels of bifenthrin. Tremors were noted in 3 out of 15 males and females during the first 2 weeks of the study at 100 ppm and throughout the study at 200 ppm. At 200 ppm, the tremors were reversible within 3 days after discontinuation of dosing. Sporadic changes in body weight and food consumption were noted initially, but these were considered not treatment related, as a dose–response relationship was not apparent and changes were within biological variability. Slightly decreased blood urea nitrogen in the high-dose males and females and higher serum potassium levels in high-dose females were minor and lacked any histopathological correlates.

Under the study conditions utilized, the LOAEL for this 90-day study is 100 ppm, equal to 7.5 mg/kg bw per day for males and 8.5 mg/kg bw per day for females, based on the increased incidence of tremors in both sexes. The NOAEL is 50 ppm, equal to 3.8 mg/kg bw per day for males and 4.3 mg/kg bw per day for females. The study author set the NOAEL at 100 ppm (7.5 mg/kg bw per day for males; 8.5 mg/kg bw per day for females) because the author did not consider tremors seen in 3 out of 15 animals of both sexes at 100 ppm as adverse (Rand, 1984).

Dogs

In a 90-day study of toxicity, groups of four male and four female Beagle dogs were given gelatine capsules containing bifenthrin (purity 88.35%) at a dose of 0, 2.5, 5.0, 10 or 20 mg/kg bw per day for 13 weeks. The dogs were inspected twice per day for mortality, moribundity and clinical signs. Eyes were examined by indirect ophthalmoscopy prior to initiation of dosing and at week 13. Body weight and food consumption were measured weekly. Blood for measurement of haematological and clinical chemistry parameters was collected from all dogs before the test and after 4, 8 and 13 weeks of treatment. At the end of the study, a complete gross postmortem was done. Selected organs were weighed, and a comprehensive range of tissues were preserved and examined microscopically. Stability of the test material was analysed at weeks 5, 9 and 13, and homogeneity was measured during week 7.

There was no mortality during the study. There were no treatment-related changes noted in food consumption, haematology, clinical chemistry, organ weights or gross and microscopic parameters, except for 41.1% and 58.8% reductions in mean absolute ovary weights in the 10 and 20 mg/kg bw per day group females, respectively, relative to controls, presumably because estrus did not occur. In addition, there were no treatment-related ophthalmological changes, although one high-dose male had bilateral epiphora (overflow of tears) at week 13 that may have been treatment related. Tremors were noted in three dogs of each sex at 5.0 mg/kg bw per day and in four dogs of each sex at 10 and 20 mg/kg bw per day. There was a definite increase in the incidence of tremors as the study continued, indicating a cumulative effect. Ataxia was noted in four dogs of each sex at 10 and 20 mg/kg bw per

day and in one female at 5.0 mg/kg bw per day. Languidness occurred primarily at 20 mg/kg bw per day in both sexes, with isolated findings at 5.0 and 10 mg/kg bw per day. All of these symptoms occurred more frequently during the last 3 weeks of the study. Other dose-related clinical signs included blinking, mydriasis, nystagmus, lacrimation and polypnoea (increased rate of respiration) in the two highest dose groups. One high-dose female appeared thin or dehydrated during the final weeks of the study. A non-statistically significant, but possibly treatment-related, reduction in mean body weight gain was noted in females at 20 mg/kg bw per day (0.6 kg) relative to the controls (1.3 kg). None of the females at 10 or 20 mg/kg bw per day showed cyclic activity or signs of estrus, but cyclic activity was observed in two, two and one female at 0, 2.5 and 5.0 mg/kg bw per day, respectively, and four of five showed signs of estrus. A minor decrease in the red blood cell mass was observed, especially in the 10 and 20 mg/kg bw per day dose groups, whereas slight decreases in sodium and potassium levels were noted in some treated groups at selected intervals during the study. The effects were of a subtle nature and were considered to be of little biological importance.

The LOAEL for this 13-week study is 5.0 mg/kg bw per day, based on the increased incidence of tremors in both sexes. The NOAEL is 2.5 mg/kg bw per day (Serota, 1984).

In a 1-year study of oral toxicity, groups of four male and four female Beagle dogs were given gelatine capsules containing bifenthrin (purity 88.35%) at a dose of 0, 0.75, 1.5, 3.0 or 5.0 mg/kg bw per day for 52 weeks. The dogs were inspected twice per day for morbidity or mortality, with clinical signs being checked daily. Body weight and food consumption were recorded weekly through week 13 and every 4 weeks thereafter beginning in week 16. Eyes were examined by indirect ophthalmoscopy at the start of the study and during week 52. Clinical chemistry parameters were measured at week 26 and week 52. Haematology parameters were measured and urinalysis was performed prior to treatment and at weeks 13, 26 and 52. At the end of the study, a complete gross postmortem was done. Selected organs were weighed, and a comprehensive range of tissues were preserved and examined microscopically. Samples were taken at weeks 14, 16, 24, 32, 40 and 52 and sent to the sponsor for stability testing.

No mortality occurred during the study, and there were no treatment-related effects on food consumption, organ weights, ophthalmology, urinalysis or gross and microscopic pathology. Mean body weight gains in the 5.0 mg/kg bw per day males were 42% lower than those of controls during weeks 0–24 and 56% lower than those of controls during weeks 0–52. The decreased body weight gain in the high dose group males, generally observed following 11 weeks of treatment, is suspected to be treatment related, as the timing was consistent with the timing of delayed response of tremors observed in this group. Tremors were noted in all males and females at 5.0 mg/kg bw per day during weeks 15–29 and in one of four males and two of four females at 3.0 mg/kg bw per day during weeks 16–23, with the effects somewhat more pronounced in the males. The lack of tremors after 29 weeks suggests that dogs may have developed a tolerance to treatment. In seven of the dogs (two from the 3.0 mg/kg bw per day group and five from the 5.0 mg/kg bw per day group), tremors were noted prior to the daily dose, indicating a persistent effect from the previous day's dose. There was a slight, non-significant decrease in red blood cells, haematocrit and haemoglobin at 26 and 52 weeks in the 5.0 mg/kg bw per day males and females. A significant increase in platelets was noted at 52 weeks in the 5.0 mg/kg bw per day males. Serum sodium levels were significantly increased in males at 3.0 and 5.0 mg/kg bw per day, and serum chloride was increased in males at 5.0 mg/kg bw per day. There was a significant increase in creatinine phosphokinase in the 1.5 and 5.0 mg/kg bw per day females, which was considered to be of questionable biological significance: no clear effect was seen in the 3.0 mg/kg bw per day females, there was considerable variation in individual values, there were a limited number of dogs per group and there was no histological correlate.

The LOAEL for this 52-week study is 3.0 mg/kg bw per day, based on the increased incidence of tremors in both sexes. The NOAEL is 1.5 mg/kg bw per day (Serota, 1985).

(b) Dermal application

Rats

In a repeated-dose dermal toxicity study, groups of 10 male and 10 female Charles River Sprague-Dawley CD rats received dermal applications of undiluted bifenthrin (purity 93.2%) at doses of 0, 25, 50, 100 or 1000 mg/kg bw per day for 6 h/day, 5 days/week, for 3 weeks. The control group animals were wrapped but received no vehicle or other treatment. An area of approximately 10% of the total body surface area on the back of each rat was clipped free of hair prior to study initiation and as necessary thereafter. The appropriate volume of liquefied bifenthrin was applied neat to the skin under a four-ply 5 cm × 5 cm gauze pad using a syringe or microlitre pipette. The gauze patch was held in place with hypoallergenic tape and was wrapped with a self-adhesive bandage. After 6 h, the dressings were removed, and the treated sites were rinsed with acetone, followed by tap water. Animals received treatments for 5 consecutive days per week over a 3-week period. Animals were examined for mortality and signs of toxicity twice daily. Animals were weighed pretest and weekly throughout the study. Individual food consumption was calculated weekly. Ophthalmoscopic examination was performed on all rats before the start of dosing and prior to termination. At termination, animals underwent functional observational battery (FOB) and motor activity testing. At termination of the dosing period, haematological and clinical chemistry determinations were performed, and each animal was examined externally and internally for macroscopic changes. Selected organs were weighed, and a comprehensive range of tissues were preserved and examined microscopically.

There were no treatment-related deaths and no biologically significant treatment-related effects on body weight, body weight gain, food consumption, motor activity, ophthalmoscopic examination or organ weights. Slight haematological and clinical chemistry effects were considered toxicologically insignificant because of small magnitude and the lack of a dose–response relationship. Treatment-related dermal effects included desquamation and eschar on 25 mg/kg bw per day males and females and on 50 mg/kg bw per day females; eschar on 50 mg/kg bw per day males; eschar and erythema on 100 mg/kg bw per day males; and eschar, desquamation and ulceration on 100 mg/kg bw per day females. Eschar, erythema and ulceration were noted in 932 mg/kg bw per day males and females. Hyperplasia and hyperkeratosis were observed at the treatment sites of all groups, including controls, compared with untreated skin. The severity was similar between controls and groups treated with 25, 50 and 100 mg/kg bw per day; however, in 1000 mg/kg bw per day animals, the hyperplasia was more severe than in controls and was sometimes associated with ulceration and secondary dermal inflammation. Dermal effects appeared to be more frequent and more severe in females than in males. Clinical signs suggestive of systemic toxicity occurred in 100 mg/kg bw per day males and females and in 1000 mg/kg bw per day females and included tremors, staggered gait and exaggerated hind limb flexion. Effects were noticeably more prevalent in females than in males. One male treated with 100 mg/kg bw per day exhibited staggered gait, and one female treated with 100 mg/kg bw per day exhibited exaggerated hind limb flexion and staggered gait. No significant clinical signs were noted in 1000 mg/kg bw per day males. Exaggerated hind limb flexion was noted in 4 of 10 high-dose females, staggered gait in 1 of 10 high-dose females and tremors in 9 of 10 high-dose females. Decreases in tail flick latency were noted in females dosed with 50 (34%), 93 (22%) and 1000 (25%) mg/kg bw per day, whereas an increase in tail flick latency was noted in the 1000 mg/kg bw per day males (42%) compared with controls. Based on the trend test, only the 100 and 1000 mg/kg bw per day female results and 1000 mg/kg bw per day male results were statistically significant. Clinical signs attributed to cutaneous paraesthesia from synthetic pyrethroids included vocalization, thrashing in the cage and lying on the back. These effects were noted in one female each at 25, 50 and 100 mg/kg bw per day and in 5 of 10 females at 1000 mg/kg bw per day. Vocalization was observed in one male each at 100 and 1000 mg/kg bw per day.

The systemic NOAEL for bifenthrin in rats is 50 mg/kg bw per day, and the systemic LOAEL is 100 mg/kg bw per day, based on staggered gait and exaggerated hind limb flexion. The dermal

LOAEL is ≤25 mg/kg bw per day (the lowest dose tested) based on slight eschar and desquamation in both sexes. A dermal NOAEL was not identified (Watt & Freeman, 2000).

Rabbits

In a 21-day study of dermal toxicity after repeated doses, groups of six male and six female New Zealand White rabbits received dermal applications of bifenthrin (purity 88.35%) at a dose of 0, 25, 50, 100 or 500 mg/kg bw per day, 6 h/day, for a total of 21 consecutive days. The hair was clipped from the dorsal trunk of each rabbit before the first application, then periodically as required. The test material was applied neat, then wrapped in occlusive gauze bandage covered by a patch of plastic film, and necks were fitted with an everted plastic collar. After the exposure, the gauze and plastic wrapping were removed, and the application site was cleansed free of any residual test material using an acetone-wetted gauze pad and then a water-wetted pad. The rabbits were observed twice per day for signs of toxicity, mortality and morbidity. Food consumption and body weight were recorded weekly. Blood was taken at the end of the study, and the standard test parameters were examined. At the end of the study, all rabbits were examined grossly postmortem. Histopathological examination of liver, kidney and skin from the control and 500 mg/kg bw per day dose groups was performed.

There were no treatment-related differences in body weights, food consumption, urinalysis, haematology, clinical chemistry, or gross and microscopic pathology. One female rabbit in the 500 mg/kg bw per day dose group died on day 19. This death was attributed to ingestion of the test substance, as this animal was found on the day of death without its everted plastic collar. Tremors were noted in three of six males (days 9–20) and two of six females (day 19) at 500 mg/kg bw per day. Tremors were also noted (on day 17) in one of six females at 100 mg/kg bw per day. Loss of muscle coordination was noted in all males (days 2–21) and females (days 2–21) at 500 mg/kg bw per day. This toxic sign appeared as early as 2 days after dosing began and persisted to the end of the study period. Relative liver and kidney weights were significantly elevated in females of the 500 mg/kg bw per day group without any histopathological correlates.

The systemic LOAEL is 500 mg/kg bw per day, based on the loss of muscle coordination and tremors in both sexes. The systemic NOAEL is 100 mg/kg bw per day (DeProspo, 1984a).

2.3 Long-term studies of toxicity and carcinogenicity

Mice

In a study of carcinogenicity, groups of 50 male and 50 female Swiss-Webster Tac(SW)fBR mice were given diets containing bifenthrin (purity 88.35%) at a concentration of 0, 50, 200, 500 or 600 ppm (equal to 0, 7.6, 29, 74 and 92 mg/kg bw per day for males and 0, 10, 37, 93 and 110 mg/kg bw per day for females) for 87 weeks (males) or 92 weeks (females). The control and treated feeds were sealed in a plastic bag and a closed container and stored at room temperature until distributed to the mice. Stability, homogeneity and dietary concentrations were confirmed analytically. The mice were inspected twice daily for mortality. Changes in clinical condition or behaviour were recorded daily. Body weight and food consumption were measured weekly for the first 13 weeks and then at monthly intervals thereafter. A blood smear was obtained from 10 mice of each sex per dose at 12 and 18 months and also at termination for determining differential blood count data. Clinical chemistry, ophthalmological examination and urinalysis were not performed. All mice that died and those that were sacrificed on schedule were subjected to gross pathological examination. At termination, organ weights were obtained for brain, kidneys, liver and gonads from 10 animals of each sex per group. Histopathological examination of selected tissues was conducted on all animals in the control and high dose groups and also on animals that died or were sacrificed during the study. In addition, histopathological examination was performed on the lungs, liver, sciatic nerve, spinal cord, kidneys, urinary bladder and stomach of animals in the 50, 200 and 500 ppm groups.

Table 8. Non-neoplastic findings in a carcinogenicity study in mice

	Males					Females				
	Dietary concentration (ppm)									
	0	50	200	500	600	0	50	200	500	600
Stomach										
Total evaluated (*N*)	49	50	50	50	49	50	50	50	50	48
Glandular hyperplasia (*N*)	6	8	7	9	8	5	6	5	5	9
% of total	12	16	14	18	16	10	12	10	10	19
Eye										
Total evaluated (*N*)	48	29	25	36	49	49	37	35	29	49
Retinal atrophy (*N*)	14	12	8	11	24	14	12	11	8	23
% of total	29	41	32	31	49*	29	32	31	28	47*
Testes										
Total evaluated (*N*)	49	32	26	38	49	—	—	—	—	—
Bilateral germinal epithelial degeneration (*N*)	4	8	8	8	12	—	—	—	—	—
% of total	8	25*	31*	21	24*	—	—	—	—	—

Data extracted from Geiger (1986), Vol. 1, Table B, p. 28
* $P \leq 0.05$ (Fisher's exact test)

Stability, homogeneity and dietary concentrations were within acceptable ranges. There were no statistically significant differences in survival; however, two females and two males in the high dose group and one female in the 500 ppm group died after 1–2 weeks with compound-related symptoms. Tremors were noted in all males and females at 500 ppm and 600 ppm during the first 3 months of the study. Tremors were also noted in two males and two females at 200 ppm and in one male at 50 ppm. However, tremors in the 50 ppm male occurred late in the study, and this animal died soon after, with fluid detected in the lungs. Tremors in 500 ppm and 600 ppm animals occurred mostly during the first 60 days of the study. Tremors in the 200 ppm males were observed on days 37–39, a period when tremors were quite frequent in the 500 and 600 ppm mice. High-dose males and females also displayed clonic convulsions, jerks and twitching. The mean body weight of males was significantly reduced in the 600 ppm group from weeks 2 to 20 and also in the 500 ppm group on weeks 5, 8, 9, 12 and 13. The mean body weight of the females was significantly reduced in the 500 and 600 ppm groups on weeks 1–6. A treatment-related depression in food consumption was observed for both sexes during the first week of the study only. Differential blood count values were comparable between the 600 ppm dose group and the controls at 12 months, 18 months and study termination. There were no compound-related findings observed at necropsy, and no effects on organ weights were observed. There were slight increases in incidences of glandular hyperplasia of the stomach (not significant by Fisher's exact test) and retinal atrophy (statistically significant by Fisher's exact test) in males and females of the 600 ppm dose group. High-dose (600 ppm) male rats also showed an increased incidence of cortical atrophy of the adrenal gland and bilateral germinal epithelial degeneration of the testes; the latter condition was also significantly elevated in males at 50 ppm and 200 ppm (Table 8).

The incidence of lymphoblastic lymphosarcoma/leukaemia was higher in the high-dose females (22/49 [45%]) than in controls (12/50 [24%]). A pairwise comparison with the controls using Fisher's exact test was statistically significant ($P = 0.24$) at the high dose in females. However, when high-dose female mice with leukaemia were combined with high-dose females with other types of

Table 9. Neoplastic findings in a carcinogenicity study in mice[a]

	Males					Females				
	Dietary concentration (ppm)									
	0	50	200	500	600	0	50	200	500	600
Lymphoblastic leukaemia										
Total evaluated (*N*)	48	50	50	50	49	50	50	50	50	49
Lymphosarcoma/leukaemia (*N*)	—	—	—	—	—	12	14	17	10	22
% of total	—	—	—	—	—	24	28	34	20	44*
Composite lymphosarcoma (*N*)	—	—	—	—	—	7	4	3	6	1
% of total	—	—	—	—	—	14	8	6	12	2
Combined incidence (*N*)	—	—	—	—	—	19	18	20	16	23
% of total	—	—	—	—	—	38	36	40	32	47
Lung										
Total evaluated (*N*)	49	50	50	50	49	50	50	50	50	48
Bronchoalveolar adenocarcinoma (*N*)	21	20	22	17	18	14	25	23	16	22
Bronchoalveolar adenoma (*N*)	4	7	3	1	3	0	1	0	3	1
Combined incidence (*N*)	25	27	25	18	21	14	26	23	19	23
% of total	51	54	50	36	43	28	52*	46*	36	48*
Hepatocellular neoplasms										
Total evaluated (*N*)	49	50	50	50	49	—	—	—	—	—
Adenocarcinoma (*N*)	0	0	1	2	2	—	—	—	—	—
Adenoma (*N*)	2	2	3	2	5	—	—	—	—	—
Combined incidence (*N*)	2	2	4	4	7	—	—	—	—	—
% of total	4	4	8	8	14	—	—	—	—	—
Urinary bladder										
Total evaluated (*N*)	48	50	50	50	49	50	50	50	50	48
Leiomyosarcoma (*N*)	2	6	8	7	14	1	2	4	1	0
% of total	4	12	16	14	29**	—	—	—	—	—

Data extracted from Geiger (1986), Vol. 1, Table A, p. 23
* $P \leq 0.05$; ** $P \leq 0.01$ (Fisher's exact test)

lymphoreticular neoplasms, the overall incidence of lymphoreticular neoplasms was not unlike that experienced by control females (Table 9). A pairwise comparison with the controls using Fisher's exact test indicated increased incidences of bronchoalveolar adenocarcinomas and adenomas in females in the 50, 200 and 600 ppm dose groups. However, time-to-tumour tests for positive trend and heterogeneity indicated that there was no significant trend and that the incidence rates were not significantly different between groups. The hepatocellular tumour incidence rate was elevated in high-dose males (Table 9); however, no predisposing hepatic changes were present in the livers of treated animals. The combined incidence of adenomas and adenocarcinomas in male livers shows that none of the treatment groups were significantly different from the control group as judged by pairwise comparisons with the control using Fisher's exact test. Time-to-tumour tests showed a significant positive trend ($P = 0.022$) in conjunction with a non-significant ($P = 0.354$) test for heterogeneity. Considering other historical control data using CD-1 Swiss-Webster mice in which the incidence of hepatocellular carcinomas ranged from 6% to 28% and the incidence of hepatocellular adenomas

ranged from 0% to 16%, it was concluded that the hepatocellular neoplasms were unlikely to have been treatment induced.

Treated male mice exhibited a dose-related increase in the incidence of leiomyosarcomas in the urinary bladder. Time-to-tumour tests for positive trend and heterogeneity were also significant and support the conclusion that the prevalence and onset of this neoplasm were increased in male mice by administration of bifenthrin in the diet. Female mice did not exhibit this pattern of response.

The LOAEL in this study is 200 ppm, equal to 29 mg/kg bw per day, based on the incidence of tremors in both sexes. The NOAEL in this study is 50 ppm, equal to 7.6 mg/kg bw per day (Geiger, 1986).

The mouse urinary bladder tumours (leiomyosarcomas) from the Geiger (1986) study were further evaluated by transmission electron microscopy (TEM) by Wilborn, Hyde & McConnell (1988). In this evaluation, six small formalin-fixed specimens supposedly of urinary bladders from male mice that were believed to contain tumours were evaluated by the TEM technique. Two urinary bladders were free of tumour cells. They exhibited the three histological layers characteristic of normal bladder: mucosa, muscularis and adventitia. Ultrastructurally, smooth muscle cells of the muscularis in tumour-free bladders and in bladders with tumours appeared to be uninvolved in tumour histogenesis and exhibited the usual features of smooth muscle, including parallel arrays of myofilaments, dense bodies into which myofilaments inserted, surface pinocytotic vesicles and attachment plaques. Most myofilaments were of the actin (thin) type. They were swollen due to the fixative employed, and myosin (thick) myofilaments were difficult to distinguish. A basal lamina rich in collagen microfibrils and sometimes discontinuous focally surrounded individual smooth muscle cells. Nuclei, mitochondria, polyribosomes and segments of rough endoplasmic reticulum were recognizable, but not well preserved by formalin fixation. Tumour cells occupied, and sometimes filled or even distended, the lamina propria. They had unequivocal features of smooth muscle. It is generally agreed that only two features are essential for the diagnosis of smooth muscle tumours—bundles of myofilaments and dense bodies. These and other features are observed in the tumour cells that are characteristic of smooth muscle, and it is evident that the tumour is of smooth muscle origin.

The study authors concluded that evaluation of the formalin-fixed specimens of mouse urinary bladder by TEM has shown that the tumour cells in the lamina propria are derived from smooth muscle (Wilborn, Hyde & McConnell, 1988).

Increased incidences of leiomyosarcomas of the urinary bladder in male mice, combined hepatocellular adenomas and adenocarcinomas, also in male mice, and combined bronchoalveolar adenomas and adenocarcinomas in female mice were observed in the carcinogenicity study by Geiger (1986). These tumours in mice were re-evaluated by an expert panel of three pathologists. This panel of three pathologists found five additional bladder lesions in control mice and concluded that the mouse bladder tumour was not a leiomyosarcoma but rather that the tumour arose in the submucosa, has an unknown pathogenesis, may arise from the vascular mesenchyme, has low malignant potential, occurs predominantly in males and apparently occurs only in mice. The panel considered that the top dose response was equivocal and failed to provide persuasive evidence of a compound-related effect. In a review of liver tumours in male mice, the panel also identified four additional lesions (one each in controls and the 500 ppm dose group, and two in the 50 ppm dose group). Statistical evaluation of adenoma/hyperplasia and carcinoma, both separately and combined, showed no significant difference between control and any treated group on a pairwise comparison and no evidence of a statistically significant trend for adenoma/hyperplasia. While the trend analysis of carcinoma alone showed a significance of $P = 0.024$, the level of significance did not achieve the $P = 0.01$ that would be required for statistical significance of a common tumour in the absence of a

significant pairwise comparison. There was no effect in female mice. The effect in male mice was not considered to be related to the treatment with bifenthrin. The panel reclassified lung adenomas and carcinomas in accordance with widely accepted historical diagnostic criteria. The incidence of adenomas and adenocarcinomas, whether considered separately or in combination, showed no evidence of a significant trend or significant pairwise comparison between controls and the highest dose group. Based upon re-evaluation of the liver and lung pathology, the panel found no evidence of a compound-related effect on the incidence of either benign or malignant liver or lung tumours. The panel found equivocal evidence of bladder tumours in male mice. The panel concluded that the bladder tumour is predominantly benign, is probably vascular in origin and has no relevance to humans (Butler, 1991a).

Additionally asked questions by the USEPA on the histopathological review of the oncogenicity lifetime feeding study in mice were answered by the reviewer (Butler, 1991b) in the addendum, as follows:

- There is no evidence of increased size of bladder tumours in mice exposed to bifenthrin.
- It is generally considered that size alone is not pathognomonic for increased severity of a tumour.
- Concurrent historical control data show that vascular tumours of the lamina propria of the bladder are common in this strain of mouse.
- The histology of leiomyosarcoma is remarkably different from the vascular lesions in the lamina propria of the bladder observed in this study.
- There is no evidence of a compound-related effect on the incidence of lesions of the liver (hyperplasia, adenoma and carcinoma).

In a published study by Butler, Cohen & Squire (1997), members of the pathology review panel for bifenthrin suggested that the initially reported urinary bladder tumours in bifenthrin-treated male Swiss-Webster mice showed a pattern of both epithelial cells and spindle cells forming irregular vascular channels, which appeared to arise from the region of the bladder and, in some cases, invaded the bladder wall. No metastases were recorded. The tumour (leiomyosarcoma) is rare; however, in this study, it was commonly observed in all groups, but predominantly in males. The histogenesis of the tumour is uncertain, but from its pleomorphic histological features, including smooth muscle and vascularity, it is probably derived from vascular mesenchyme (Butler, Cohen & Squire, 1997).

A summary of pathological evaluations of urinary bladder tumours in bifenthrin-treated male Swiss-Webster mice was prepared by Wells (2006). Based on the conclusions of the experts cited in this review and the European Union criteria for classification of carcinogens, Wells (2006) concluded that bifenthrin does not meet the criteria for classification as a carcinogen.

Rats

In a long-term combined study of toxicity and carcinogenicity, groups of 50 male and 50 female Sprague-Dawley (Tac(SD)fBR) rats were given diets containing bifenthrin (purity 88.35%) at a concentration of 0, 12, 50, 100 or 200 ppm, equal to 0, 0.6, 2.3, 4.7 and 9.7 mg/kg bw per day for males and 0, 0.7, 3.0, 6.1 and 12.7 mg/kg bw per day for females, for 24 months. Prepared diets were sealed in plastic bags and closed containers and stored at room temperature. Stability, homogeneity and dietary concentrations were confirmed analytically. All rats were observed twice a day for mortality and daily for clinical signs and morbidity. Individual body weights and food consumption

were measured weekly for the first 13 weeks of the study and at monthly intervals thereafter. An ophthalmoscopic examination was performed on all animals prior to treatment and at termination of the study. Haematological, clinical chemistry and urinalysis determinations were conducted on 10 animals of each sex per dose at 6, 12, 18 and 24 months (termination) after the treatment. A gross necropsy was conducted on all animals. At termination, organ weights were obtained for brain, kidneys, liver and gonads from 10 animals of each sex per group. Histopathological examination of selected tissues was conducted on all animals in the control and 200 ppm groups. In addition, histopathological examination was performed on the lungs, liver, kidneys, sciatic nerve and spinal cord of animals of the other groups.

Stability, homogeneity and dietary concentrations of bifenthrin were within acceptable ranges. There were no treatment-related differences in survival. At termination, the survival of the males ranged from 34% to 48%, and the survival of the females ranged from 56% to 70%. Tremors were noted in all males at 200 ppm during days 4–28 and in all females at 200 ppm during days 4–30 and days 36–38. At 100 ppm, one female displayed tremors for 3 days (days 3–5). The incidence of tremors decreased during the middle portion of the study and increased towards the termination of the study. Other clinical signs in the 200 ppm males and females included increased incidences of abrasion, alopecia and tail laceration. Mean body weights of females at 200 ppm were significantly lower (↓8–10%, $P < 0.05$ or 0.01) during weeks 13–96. The 200 ppm females also exhibited a significant reduction in total body weight change (↓17%). Mean body weights of the 200 ppm males were decreased (non-significantly) relative to controls from weeks 1 to 92. There were changes in food consumption in male and female rats in various treatment groups, but there was no clear dose–response pattern to the changes in food consumption. No treatment-related changes in the clinical chemistry, urinalysis or ophthalmological examinations were observed. No treatment-related changes in haematological parameters were observed, except for a decrease in red blood cells in the 200 ppm males at 24 months. The decrease in red blood cells was not considered to be toxicologically relevant, as the magnitude of change was small and other red blood cell parameters were not affected. Males at 200 ppm had higher, although not statistically significant, mean liver (↑11%) and kidney (↑28%) weights at 24 months. Males and females at 200 ppm and males at 100 ppm also had higher, although not statistically significant, liver to body weight and kidney to body weight ratios. Three of 28 females at 200 ppm had retinal atrophy, compared with 0 of 40 (controls), 0 of 7 (12 ppm), 0 of 4 (50 ppm) and 0 of 6 (100 ppm). The incidences of pancreatic islet cell adenoma and fibrosarcoma in males at 200 ppm were increased (3/50 versus 1/47 for the controls and 3/50 versus 0/50 for the controls, respectively), but statistical significance was not achieved, and historical control data indicated that these are not rare tumours in this strain. There were no treatment-related findings noted at necropsy. There were no gross or histopathological lesions noted in any animal that could be attributed to the treatment. There were no biologically significant differences between treated groups with respect to histological findings in the sciatic nerve.

The LOAEL is 100 ppm, equal to 4.7 and 6.1 mg/kg bw per day for males and females, respectively, based on the increased incidence of tremors in females. The NOAEL is 50 ppm, equal to 2.3 and 3.0 mg/kg bw per day for males and females, respectively. Under the conditions of this study, there was no conclusive evidence of carcinogenic potential of bifenthrin in rats (McCarty, 1986).

2.4 Genotoxicity

Bifenthrin gave negative responses in various in vitro and in vivo genotoxicity tests except for the test on mouse lymphoma cells at low concentrations and a weak positive response in the unscheduled deoxyribonucleic acid (DNA) synthesis (UDS) assay (Table 10). As the second in vitro test did not replicate the results of the in vitro test and negative findings in the in vivo UDS assay, bifenthrin is

considered to be negative in the UDS assay. Based on the overall weight of evidence, it is concluded that bifenthrin is unlikely to be genotoxic.

Table 10. Results of studies of genotoxicity with bifenthrin

End-point	Test system	Concentration or dose	Purity (%)	Result	Reference
In vitro					
Reverse mutation (Ames test)	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538	75–7500 µg/plate ± metabolic activation in acetone	91.4	Negative	Haworth (1983)
	S. typhimurium strains TA98, TA100, TA1535 and TA1537	8–5000 µg/plate ± metabolic activation in DMSO (experiment 1) 500–4000 µg/plate ± metabolic activation in DMSO (experiment 2)	88.34	Negative	Kennelly (1988)
	S. typhimurium strains TA98, TA100, TA1535 and TA1537 *Escherichia coli* WP2 uvrA	50–5000 µg/plate ± metabolic activation in DMSO	95.7	Negative	Wagner & VanDyke (2006)
Forward mutation	Mouse lymphoma L5178Y cells	0.018–0.24 µg/ml without metabolic activation in acetone 0.0075–0.1 µg/ml with metabolic activation in acetone	88.35	Positive	Kirby (1983)
	Mouse lymphoma L5178Y cells	15.8–500 µg/ml ± metabolic activation in DMSO (test 1) 50–200 µg/ml ± metabolic activation in DMSO (test 2)	88.35	Negative	Kennelly (1986)
CHO/HGPRT mutation assay	CHO/HGPRT (CHO-K_1-BH_4)	250–1000 µg/ml without metabolic activation in DMSO 20–50 µg/ml with metabolic activation in DMSO	88.35	Negative (without metabolic activation) Inconclusive (with metabolic activation)	Thilagar (1984a)
	CHO/HGPRT (CHO-K_1-BH_4)	10–100 µg/ml ± metabolic activation in DMSO	90.58	Negative	Heidemann (1989a)
Chromosomal aberration	CHO cells	100–10 000 µg/ml ± metabolic activation in acetone	88.35	Negative	Thilagar (1984b)
Sister chromatid exchange	CHO cells	1–60 µg/ml ± metabolic activation in DMSO	88.35	Negative	Heidemann (1989b)
Morphological transformation assay	BALB/3T3 mouse embryo cells	3–100 µg/ml without metabolic activation in DMSO	88.35	Negative	Putman (1983a)
UDS	Rat primary hepatocytes	0.01–2 µg/ml in acetone	88.35	Weak positive	Thilagar (1983a)
	Rat primary hepatocytes	0.5–2.5 µg/ml in acetone	88.35	Negative	Thilagar (1983b)
	Rat primary hepatocytes	1–100 µg/ml in acetone	90	Negative	Fautz (1990)

Table 10 (contd)

End-point	Test system	Concentration or dose	Purity (%)	Result	Reference
In vivo					
UDS	Sprague-Dawley rats (male)	10–150 mg/kg bw single gavage dose in acetone (pilot study) 7.5–30 mg/kg bw single gavage dose in corn oil	94.7	Negative	Pant & Sly (2005)
Cytogenetic assay (chromosomal aberrations)	Sprague-Dawley rats (male)	3–30 mg/kg bw per day gavage in corn oil for 5 days	88.35	Negative	Putman (1983b)
Sex-linked recessive lethal assay	*Drosophila melanogaster*	50 and 100 µg/ml in unsalted butter	88.35	Negative	DeGraff & Sky Benson (1984)
Micronucleus formation	ICR mice (male and female, 6–8 weeks old)	50–400 mg/kg bw (single oral dose in corn oil, dose range study) 8.75–35 mg/kg bw (single oral dose in corn oil, definitive study)	94.7	Negative	Krsmanovic & Huston (2005)

CHO, Chinese hamster ovary; DMSO, dimethyl sulfoxide

2.5 Reproductive toxicity

(a) Multigeneration studies

Rats

In a two-generation study of reproductive toxicity, groups of 25 male and 25 female Sprague-Dawley TAC(SD)fBR rats were given diets containing bifenthrin (purity 88.35%) at a concentration of 0, 30, 60 or 100 ppm (equivalent to 0, 1.5, 3.0 and 5.0 mg/kg bw per day). The amount of test material added to the diet was adjusted to account for purity. Dosing began 8 weeks prior to mating for the F_0 generation and 11 weeks prior to mating for the F_1 generation. F_0 generation animals were bred twice, and F_1 parental animals were selected from the F_{1b} pups. All animals were observed daily for signs of toxicity and twice daily for mortality. Body weights were recorded weekly except during mating for P_1 males. All dams were weighed on gestation days (GDs) 0, 6, 15 and 20 and on lactation days (LDs) 0, 7, 14 and 21. Individual food consumption was measured weekly except during mating (both sexes) and lactation. At birth, the number of pups born, the number of pups born alive or stillborn, sex anomalies and individual body weights were recorded. Body weights were also recorded on LDs 4, 7, 14 and 21. Daily observations were made throughout lactation for mortality and signs of toxicity. On LD 21, F_{1a} and F_{2a} litters were sacrificed and discarded. Shortly thereafter, mating for the F_{1b} and F_{2b} litters was initiated. After all F_{1b} litters were weaned (LD 21), 25 males and 25 females were randomly chosen from each group to continue on study as the F_1 parents. All adults and selected weanlings (10 of each sex per dose) were subjected to a complete necropsy. Organ weights were obtained for brain, heart, liver, kidneys, adrenals and gonads. Microscopic examination of selected tissues was conducted for parental animals in the 0 ppm and the 100 ppm groups and for all weanlings.

There was no treatment-related mortality in either the F_0 or the F_1 generation. Tremors were noted only in females of both generations at 100 ppm, with one F_0 generation rat observed to have clonic convulsions. The tremors occurred during days 9–35 following delivery in the F_0 generation and during days 3–35 following delivery in the F_1 generation. Premating body weights were

comparable to those of the controls for both sexes of both generations at all dose levels. F_0 generation females at 100 ppm had lower mean body weights (↓4%, $P < 0.05$) at week 17 (after gestation and lactation), significantly lower body weights during the first lactation (days 7 and 14) period, and lower body weight gains during the second gestation and lactation periods (statistically significant only on LD 14, ↓5% for body weight and ↓34% for body weight gain, $P < 0.01$). There was no correlation between lower body weight and frequency of tremors. Lower body weights in females at 60 ppm, although not statistically significant, frequently paralleled body weight depression at 100 ppm. There were no clinical signs or effects on body weight at 30 ppm. There were no significant differences in mean body weights between treated F_1 animals and controls. In the high-dose F_0 generation females, there was a statistically significant increase in absolute and relative brain weights. Mean absolute ovary weights were slightly decreased (↓9%, $P < 0.05$, or ↓12%, $P < 0.01$) at 60 and 100 ppm, respectively, in the F_1 parental generation; however, ovary to body weight ratios were unaffected. In the 100 ppm group F_{1b} female progeny, absolute adrenal and heart weights were statistically elevated compared with control values. Significantly elevated absolute ovary weights and ovary to brain weight ratios were also observed in these animals. There were no treatment-related gross or microscopic findings in either adults or progeny. In either the F_0 or F_1 generations, there were no treatment-related effects on reproductive parameters (mating, male fertility, female fertility and gestation indices), and there were no treatment-related gross or microscopic findings in either sex.

The systemic and developmental toxicity LOAEL is 100 ppm, equivalent to 5.0 mg/kg bw per day, based on the incidence of tremors and marginally lower body weights in F_0 and F_1 generation females during gestation and lactation. The systemic and developmental toxicity NOAEL is 60 ppm, equivalent to 3.0 mg/kg bw per day. A reproductive LOAEL was not observed. The reproductive NOAEL is 100 ppm, equivalent to 5.0 mg/kg bw per day (DeProspo, 1986).

(b) Developmental toxicity

Rats

In a study of developmental toxicity, groups of 25 pregnant Sprague-Dawley rats were given bifenthrin (purity 88.35%) at a dose of 0, 0.5, 1.0 or 2.0 mg/kg bw per day by gavage in corn oil (dosing volume, 5 ml/1000 g bw) from day 6 to day 15 of gestation, inclusive. An additional group of 25 pregnant rats was administered aqueous aspirin solution at a dosage of 250 mg/kg bw per day by gavage from GD 6 to GD 15 to serve as a positive control. The dosing solutions were prepared daily. All rats were observed twice daily for clinical signs of toxicity, mortality and moribundity. Maternal body weights were recorded on days 0, 6–15 and 20 of gestation. Individual food consumption was calculated on a weekly basis. On day 20 of gestation, all surviving dams were sacrificed and subjected to gross necropsy. Examinations at sacrifice comprised uterine weight, number and positions of implantations, number of corpora lutea in each ovary, individual fetal weights, percentage preimplantation loss, percentage postimplantation loss, and early and late intrauterine deaths. All fetuses were weighed, sexed and examined for external malformations/variations. Approximately half of the fetuses from each litter were preserved in Bouin's fixative, sectioned and examined microscopically using a variation of Wilson's technique for visceral anomalies. The remaining fetuses were necropsied and eviscerated, then stained with Alizarin Red-S and examined for skeletal variations.

There were no deaths during the study, and no significant differences between groups or dose-related trends with respect to mean maternal body weight gains or food consumption were noted. Maternal toxicity was characterized as tremors in 18 of 25 dams at 2.0 mg/kg bw per day during days 10–19. At necropsy, blood clots in the uterus were observed in one rat at 2.0 mg/kg bw per day, and a subcutaneous abdominal mass was observed in one rat in the control group.

There were no group differences or dose-related trends with respect to pregnancy rates, numbers of corpora lutea, implantation sites and resorptions, litter sizes, sex ratios, fetal body weights or viability. Slight fetotoxicity was noted at 2.0 mg/kg bw per day and was characterized as an increased

Table 11. Incidence of hydroureter with and without hydronephrosis in the study of developmental toxicity in rats

Effects	Incidences	Dose group (mg/kg bw per day)				
		0 (vehicle)	0.5	1.0	2.0	0 (positive control)
Hydroureter with hydronephrosis	Fetal incidence	3/146 (2.5)[a]	2/142 (1.41)	3/148 (2.03)	2/141 (1.42)	5/52 (9.61)
	Litter incidence	3/23[b] (13)	2/24 (8.3)	2/24	2/23	
Hydroureter without hydronephrosis	Fetal incidence	0/146 (0)	0/142 (0)	0/148 (0)	5/141 (3.55)	0/52 (0)
	Litter incidence	0/23 (0)	0/24 (0)	0/25 (0)	5/23 (21.74)	
Hydronephrosis without hydroureter	Fetal incidence	0/146 (0)	0/142 (0)	2/148 (1.35)	0/141 (0)	2/52 (3.85)

Data extracted from DeProspo (1984c)

[a] Values are expressed as number of occurrences per number of fetuses examined, and values in parentheses are expressed as percentages.

[b] Values are expressed as number of occurrences per number of litters examined, and values in parentheses are expressed as percentages.

Table 12. Incidence of hydronephrosis and hydroureter in the study of developmental toxicity in rats[a]

Effects	Incidences	Dose (mg/kg bw per day)			
		0	0.5	1.0	2.0
Hydronephrosis	Litter incidence	2/23 (8.7)[a]	2/24 (8.3)	4/25 (16)	2/23 (8.7)
	Fetal incidence	3/146 (2.1)[b]	2/142 (1.4)	5/148 (3.4)	2/141 (1.4)
Hydroureter	Litter incidence	2/23 (8.7)	2/24 (8.3)	3/25 (12)	6/23 (26.1)
	Fetal incidence	3/146 (2.1)	2/142 (1.4)	3/148 (2.0)	7/141 (5.0)

Data extracted from DeProspo (1984c)

[a] Values are expressed as number of occurrences per number of litters examined, and values in parentheses are expressed as percentages.

[b] Values are expressed as number of occurrences per number of fetuses examined, and values in parentheses are expressed as percentages.

fetal and litter incidence of "hydroureter without hydronephrosis" (Table 11). This finding that five fetuses from five different litters had "hydroureter without hydronephrosis" is considered treatment related because it was not present in controls or any of the other exposure groups, including positive controls. Although not statistically significant, the incidence of hydroureter was doubled in the high dose group (Table 12). Also, there were no other treatment-related malformations or variations noted at any dose level. The positive control gave the appropriate responses of increased early resorptions, depressed fetal body weights and external, visceral and skeletal malformations and variations.

The maternal LOAEL is 2.0 mg/kg bw per day, based on the incidence of tremors observed in dams between GD 10 and GD 19. The developmental LOAEL is 2.0 mg/kg bw per day, based on the increased fetal and litter incidence of "hydroureter without hydronephrosis". The maternal and developmental NOAEL is 1.0 mg/kg bw per day (DeProspo, 1984c).

In a second study of developmental toxicity, groups of 25 pregnant Sprague-Dawley rats were administered bifenthrin (purity 95.3%) in the diet at concentrations of 0, 30, 60, 90 or 200 ppm (equal to 0, 2.5, 5.0, 7.4 and 16.3 mg/kg bw per day) from days 6 to 20 of gestation, inclusive. Homogeneity, stability and dietary concentrations were measured analytically. All rats were observed daily for clinical signs of toxicity, mortality and moribundity. Maternal body weights were recorded on days 0, 6, 9, 12, 15, 18 and 20 of gestation. Food consumption was calculated for GDs 0–6, 6–9, 9–12, 12–15, 15–18 and 18–20. On day 20 of gestation, all surviving dams were sacrificed and subjected to gross necropsy. The uterus was removed from each dam and weighed. All fetuses were removed

by caesarean section and examined. The number and distribution of implantation sites, early and late resorptions, live and dead fetuses and corpora lutea were recorded. All fetuses were weighed, sexed and examined for external malformations/variations. Approximately half of the fetuses from each litter were preserved in Bouin's fixative, sectioned and examined microscopically using a variation of Wilson's technique for visceral anomalies. The remaining fetuses were necropsied and eviscerated, then stained for skeletal variations.

The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the study animals was acceptable. No animals died during the study. When compared with concurrent controls, no treatment-related changes were observed in gross pathology, number of corpora lutea, number of implantations, number of live and dead fetuses, number of resorptions, fetal weights, sex ratios or postimplantation losses. At 200 ppm, clinical signs indicative of neurotoxicity were observed. These signs included tremors (22/25), observed from days 9 to 20; hypersensitivity to sound (5/25), observed from days 18 to 20; splayed hind limbs (1/25), observed from days 15 to 20; and piloerection (1/25), observed at day 19. None of these findings were observed in any control animal or any other treatment groups. A negative trend ($P \leq 0.05$) in body weight gain was observed during GDs 6–9, 15–18 and 18–20, with a decrease of 44%, 17% and 14%, respectively, at 200 ppm relative to controls. In addition, a negative trend ($P \leq 0.001$) was observed in adjusted (for gravid uterine weight) body weight gain, with a 22% decrease at 200 ppm when compared with controls. Food consumption was decreased at 200 ppm at the beginning (GDs 6–9) and end (GDs 18–20) of treatment (↓11–12%, relative to controls). In addition, a negative trend ($P \leq 0.05$) was observed during GDs 6–9, 9–12 and 18–20 and for the overall treatment interval (GDs 6–20). Dose-dependent ($P \leq 0.05$ for negative trend) decreases in food consumption were observed; however, the decreases that were noted at doses below 200 ppm did not result in decreased body weight gains and were considered not to be toxicologically important. No treatment-related developmental findings were noted at any dose tested.

The maternal LOAEL is 200 ppm, equal to 16.3 mg/kg bw per day, based on clinical signs and decreased food consumption, body weight gain and adjusted (for gravid uterine weight) body weight gain. The maternal NOAEL is 90 ppm, equal to 7.4 mg/kg bw per day. A developmental toxicity LOAEL was not observed. The developmental toxicity NOAEL is 200 ppm, equal to 16.3 mg/kg bw per day, the highest dose tested (Watt & Freeman, 2001).

Rabbits

In a study of developmental toxicity, groups of 20 pregnant New Zealand White rabbits were given bifenthrin (purity 88.35%) at a dose of 0, 2.67, 4.0 or 8.0 mg/kg bw per day by gavage in corn oil on days 7–19 of gestation, inclusive. An additional group of 20 pregnant rabbits was administered 6-aminonicotinamide in 2% carboxymethyl cellulose via intraperitoneal injection at a dosage level of 3 mg/kg bw on GD 12 to serve as a positive control. Test substance formulations were prepared daily. All rabbits were observed twice per day for mortality or clinical signs of toxicity. Maternal body weights were recorded on days 0, 7 through 19, 21, 28 and 29. Food consumption was not measured. On day 29 of gestation, all surviving does were killed and subjected to gross necropsy. The uterus and ovaries were excised, and the number of corpora lutea on each ovary was recorded. Gravid uteri were weighed and opened, and the location and number of viable and non-viable fetuses, the number of early and late resorptions, and the total number of implantations were recorded. All fetuses were weighed and examined for external malformations/variations. Each fetus was examined viscerally by fresh dissection and the sex determined by the Staples technique. All carcasses were eviscerated and processed for skeletal examination.

There were no treatment-related deaths in the does; however, 10 rabbits died during the study, and 9 of these deaths (including 3 vehicle control animals) were attributed to *Pasteurella multocida*. One death occurred on day 10 of the study from an unknown cause.

Maternal toxicity was characterized at 8.0 mg/kg bw per day as tremors in 17 of 20 rabbits (observed during days 12–23) and twitching of the head and forelimbs in 14 of 20 rabbits (observed during days 13–20). In addition, one rabbit in the 8.0 mg/kg bw per day group displayed clonic convulsions and loss of muscle control during days 17 and 18. At 4.0 mg/kg bw per day, head and forelimb twitching was noted in 4 of 20 rabbits (observed during days 8–16). There were no apparent treatment-related differences in mean body weight gains in the does or pregnancy rates; data excluded those with infection. There were no gross or microscopic findings attributable to exposure to the test material. There were no treatment-related effects on the number of live fetuses, fetal weights, implantations, resorptions, or external, visceral or skeletal malformations and variations. The positive control gave the appropriate responses of increased early resorptions, reduced number of live fetuses, and increased external, visceral and skeletal malformations and variations.

The maternal LOAEL is 4.0 mg/kg bw per day, based on the treatment-related incidence of head and forelimb twitching. The maternal NOAEL is 2.67 mg/kg bw per day. There was no developmental toxicity demonstrated at any dose level. The developmental NOAEL is 8.0 mg/kg bw per day, the highest dose tested (DeProspo, 1984b).

2.6 Special studies

(a) Acute neurotoxicity

Rats

In a study of acute neurotoxicity, four groups of 10 male and 10 female Sprague-Dawley rats were given a single dose of bifenthrin (purity 93.7%) at 0, 10, 35 or 75 mg/kg bw by gavage (undiluted) and observed for the following 14 days. All the rats were evaluated in FOB and motor activity tests on days –7, 1 (6–8 h after dosing; time of peak effects), 7 and 14. All rats were observed before the study start and daily throughout the study for any changes in clinical condition. Body weights were measured on study days 0, 7 and 14. Food consumption was not monitored during the study. Five males and five females per group were perfused in situ for neurohistological examination. Microscopic neuropathological examination was performed on the control and high-dose animals.

Two control males and two control females were removed from the study due to an unspecified dosing error. At 75 mg/kg bw, two females died on day 0, shortly after dosing. No other premature deaths occurred. Body weights and body weight gains were similar in all groups. No treatment-related gross lesions were observed in any animal during necropsy. There were no treatment-related microscopic neuropathological differences in any treated groups relative to controls. The following clinical signs were observed in high-dose males after dosing: decreased faeces, staggered gait, tremors and twitching. High-dose females displayed the following clinical signs following dosing: abdominogenital staining, clonic convulsions, chromorhinorrhoea and tremors. Most of these clinical signs were seen in two females that died. All clinical signs of toxicity were resolved in survivors by study day 2. No findings were observed in the 10 or 35 mg/kg bw animals at any day. The following FOB home cage observations were noted on day 0 at 6–8 h post-dosing: whole-body tremors (1 male and 1 female [later died] versus 0 control); abnormal mobile posture (1 male versus 1 control); uncoordinated movement/ataxia (1 male versus 0 control); splayed hind limbs (1 male versus 0 control); convulsions (2 females [later died] versus 0 control); tense/rigid during handling (1 male, 4 females [2 later died] versus 0 controls); and unusual posture (immobile; 1 female [later died] versus 0 control). Day 0 FOB open field observations included the following: localized spasms/twitching (2 males versus 0 control); whole-body tremors (2 males, 2 females [1 later died] treated versus 0 control); staggered gait (1 male versus 0 control); abnormal posture (mobile; 1 male versus 0 control); uncoordinated movement/ataxia (1 male versus 0 control); splayed hind limbs (1 male versus 0 control); increased activity (1 female versus 0 control); decreased activity (1 female [later died] versus 0

control); convulsions (2 females [1 later died] versus 0 control); walking on toes (1 female versus 0 control); and unusual immobile posture (1 female [later died] versus 0 control). Landing foot splay values were decreased in males during the day 0 FOB (↓15%, $P \leq 0.05$). No treatment-related differences from controls were observed in the FOB assessment in survivors on study days 7 and 14. Mean motor activity was decreased in males on day 0 (↓36%, not statistically significant), whereas motor activity in the females was increased on days 0 and 14 (↑23% and ↑18%, respectively; not statistically significant), although the day 14 increase was not considered biologically significant. No treatment-related findings were observed at 10 or 35 mg/kg bw.

The LOAEL for this study is 75 mg/kg bw, based on mortality (females only), clinical and FOB findings and differences in motor activity. The NOAEL for this study is 35 mg/kg bw (Watt, 1998a).

In a published acute neurotoxicity study involving several compounds, including bifenthrin, by Wolansky, Gennings & Crofton (2006), male Long-Evans rats were exposed to bifenthrin (purity 89.0%) at single gavage doses ranging from 0.03 to 28 mg/kg bw in corn oil (1 ml/kg bw). Control rats received only vehicle. Generally, 6–11 doses per compound and 8–18 rats per dose were treated; for bifenthrin, nine doses were tested. Motor activity was measured for 1 h 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 time of peak effects for bifenthrin was determined to be 4 h post-dosing. The motor activity data were analysed using a non-linear exponential threshold activity model (Casey et al., 2004). Bifenthrin 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 ED_{30} is defined as the dose associated with a 30% decrease in motor activity. The threshold dose for bifenthrin was 1.28 mg/kg bw, with 95% confidence intervals of 0.67–1.88 mg/kg bw. The ED_{30} for bifenthrin was 3.21 ± 0.32 mg/kg bw (Wolansky, Gennings & Crofton, 2006).

(b) Delayed neuropathy

Hens

In an acute oral toxicity (LD_{50}) study in female domestic hens (*Gallus gallus domesticus*), bifenthrin (purity 88.3%) was administered as a single dose to 10 animals per dose at 0 (group 1), 1250 (group 2), 2500 (group 3) or 5000 (group 4) mg/kg bw by gavage in corn oil. The treated birds were observed for clinical signs and mortality for 14 days after dosing. For neurotoxicity determination, 10 animals per dose were administered bifenthrin (purity 88.3%) as a single gavage dose of 0 (vehicle control) or 5000 (two groups of bifenthrin treatment) mg/kg bw in corn oil. A separate group of 10 animals received tri-*ortho*-cresyl phosphate (TOCP; positive control) by gavage as a single dose of 500 mg/kg bw in corn oil. The treated birds were observed for clinical signs and mortality for 21 days. On day 22, each group received a single oral gavage dose of the appropriate dose regime as described above. The treated birds were observed for another 21 days for clinical signs and mortality. For the acute lethality study, body weights were measured weekly for 2 weeks prior to treatment and also during a 14-day observation period. For neurotoxicity determination, body weights and food consumption were recorded twice per week. Gross necropsy was performed on all birds at the end of the observation period. Neural tissues (brain, spinal cord, peripheral nerves) were examined microscopically from all birds in the neurotoxicity determination study.

In the acute lethality study, approximately 21 h following dosing, a number of test birds (one in group 2, two in group 3 and three in group 4) showed clinical signs of toxicity, which included unsteadiness or inability to walk, wing-dropping and twitching of the head and neck. Within 48 h following dosing, the observed signs of toxicity were diminishing; by the end of day 3, test birds appeared to have recovered. The few mortalities that occurred following dosing were apparently the

result of bullying by other birds. During the pretreatment period, birds in all groups tended to experience a decrease in body weight. All groups showed decreased body weights during the first week of the treatment, except group 3, which showed slight body weight gain. During the second week of the observation period, all groups gained body weight.

In the neurotoxicity study, approximately 20 h after the first dose, birds dosed with test compound became unsteady, and within a few hours, all test birds were eliciting jerking movements of the head. By the end of day 3, most birds appeared to have recovered. Within approximately 21 h after the second dose, test birds showed varying degrees of unsteadiness, accompanied by jerking head movements or trembling. By the end of day 22, test birds were making violent movements of the head and legs, and 11 out of 18 were unable to stand. Over the next few days, the clinical signs of toxicity were generally less severe, and by day 28, surviving birds appeared to have recovered. No clinical signs of ataxia were noted in the treatment group. One bird from the positive control group (TOCP) demonstrated ataxia following the first dose, and five birds following the second dose. After the first dose, birds treated with test compound showed overall weight losses, followed in general by weight increases over days 3–17. Following the second dose on day 21, marked weight decreases were observed over days 21–24, but, again, test birds generally increased in weight over days 24–43. Food consumption was reduced in the treatment groups. No treatment-related changes in the nerve tissue were found in negative control and bifenthrin-treated groups. The positive control group showed significant degenerative changes in the spinal and peripheral nerves.

In conclusion, the LD_{50} of bifenthrin to adult female hens appeared to be greater than 5000 mg/kg bw. An oral administration of a single dose of bifenthrin at 5000 mg/kg bw followed by a repeated dose after 21 days did not produce any clinical signs of neurotoxicity in adult hens (Roberts et al., 1984).

Rats

In an investigation of possible delayed neurological effects using the tilting plane test, COBS/Wistar rats were dosed with bifenthrin (purity 88.35%) via single oral gavage dose daily for 2 or 5 consecutive days. For the Irwin dose range–finding study, three male rats per dose were dosed orally for 5 consecutive days at 0 (corn oil, group 1), 30 (group 2), 10 (group 3), 3 (group 4) or 1 (group 5) mg/kg bw per day. For the tilting plane test, five male and five female rats per dose were dosed orally for 2 consecutive days at 0 (corn oil) or 30 (group 2) mg/kg bw per day. Detailed clinical observations were performed before dosing, at 2 and 6 h after each dose and at 24, 48, 72, 96 and 120 h after the final oral dose. The tilting plane test was performed every second day from day 2 to day 16. This study was not conducted according to GLP.

In the Irwin dose range–finding study, no notable behavioural or autonomic effects were noted in groups 4 and 5, except for one rat in group 4, which exhibited salivation on day 2. Behavioural and autonomic effects were most notable in groups 2 and 3. No notable effects were recorded at the 2 and 6 h observation period on day 1. All rats in the 30 mg/kg bw per day group exhibited moderate tremor by 24 h post-dosing. All rats in the 30 mg/kg bw per day dose group exhibited tremor, gait, abnormal body carriage and respiratory depression by 2 h after the second dose. In addition, two of the three rats also exhibited signs of central nervous system depression, such as apathy, decreased touch response and paralysis. One rat at this dose level subsequently developed clonic convulsions and died approximately 4 h after dosing. Two animals in the 10 mg/kg bw per day treatment group exhibited signs of possible weak central nervous system stimulation. Prior to dosing on day 3, the fur of surviving rats at 30 mg/kg bw per day had a greasy appearance. During the 2 h post-dose observation period on day 3, these rats were showing effects, which included tremor, paralysis and abnormal body carriage and gait. A similar pattern of effects was seen at 30 mg/kg bw per day on day 4. One rat was found dead at the pre-dose observation on day 5. Another rat died by 24 h after the last dose. No

effects were noted in the 10, 3 or 1 mg/kg bw per day dose groups during the last 7-day observation period after the last dose.

The minimum effective dose at which severe neurological signs such as paralysis were apparent in the Irwin dose range–finding test was 30 mg/kg bw. This dose level was therefore used in the tilting plane test. The results of the tilting plane test indicate that the treatment with bifenthrin at 30 mg/kg bw per day did not produce delayed neurological effects. There was no significant impairment of performance of bifenthrin-treated rats compared with vehicle controls. However, on day 2, some impairment of performance was observed for three rats that received 30 mg/kg bw per day. The toxic effects were most notable after administration of the second dose. Approximately 6 h after the second dose, four of the five female rats showed a stereotypical grooming behaviour. In addition, the fur of these rats had a greasy appearance. No overt toxic signs were recorded in any of the treated males at this stage of the study. Two male and two female rats were found dead 24 h after the second dose. The body weights of the female rats were decreased on days 4–14 of the study. No effects on body weights were observed in male rats. In conclusion, the results of the tilting plane test indicate that treatment with bifenthrin at 30 mg/kg bw per day did not produce delayed neurological effects (Algate et al., 1985).

(c) Short-term studies of neurotoxicity

Rats

In a short-term study of neurotoxicity, groups of male and female Sprague-Dawley rats were given diets containing bifenthrin (purity 93.7%) at a concentration of 0 or 50 ppm (10 rats of each sex per dose) or 100, 200 or 300 ppm (5 rats of each sex per dose) for 28 days. Clinical signs were recorded daily. Body weights were recorded weekly. Low-dose and control animals underwent motor activity testing following 28 days of treatment. All survivors underwent gross necropsies on study day 31.

One 300 ppm female died on day 25. Decreased ($P \leq 0.05$ or 0.01) body weights (8–11%) and body weight gains (16% at day 28) were observed in the 300 ppm males throughout the study. Males receiving doses of 200 ppm and above displayed tremors, twitching, dehydration and unthriftiness. In addition, chromorhinorrhoea, hypersensitivity to sound and splayed hind limbs were observed in the 300 ppm males. No treatment-related clinical signs were observed in males receiving 100 ppm or less. All females receiving doses of 100 ppm or higher displayed tremors, whereas the 200 ppm females displayed twitching and unthriftiness. Abdominogenital staining, chromorhinorrhoea, dehydration, hypersensitivity to sound, splayed hind limbs and unthriftiness were observed in the 300 ppm females. Body weights and body weight gains were also reduced in females at 300 ppm (8.6–10%; gain 25% at day 28), although these decreases were not statistically significant. No treatment-related clinical signs were observed in the 50 ppm females. No gross lesions were noted during necropsy.

The NOAEL for this study was 50 ppm based on tremors at 100 ppm. Based on the results of this study, 0, 50, 100 and 200 ppm dose levels were selected for the 90-day neurotoxicity study in rats (Watt, 1998b).

In a short-term study of neurotoxicity, groups of 10 male and 10 female Sprague-Dawley rats were given diets containing bifenthrin (purity 93.7%) at a concentration of 0, 50, 100 or 200 ppm (equal to 0, 2.9, 6.0 or 11.8 mg/kg bw per day in males and 0, 3.7, 7.2 or 14.6 mg/kg bw per day in females) for 13 weeks. All rats were evaluated in FOB and motor activity tests prior to treatment and following treatment weeks 4, 8 and 13. All rats were observed before the study start and daily throughout the study for any changes in clinical condition. Body weight and food consumption were measured weekly throughout the study. Five male and five female rats from the control group and at the highest dose were perfused in situ and evaluated for microscopic neuropathology. Homogeneity, stability and dietary concentrations were confirmed analytically.

Analysis of the dietary preparations showed that diets were stable at room temperature and the test article was homogeneously distributed in the diet. The analytical data indicated that the variations between nominal and actual dosage to the study animals were acceptable. No treatment-related differences were observed at any dose level in body weights, body weight gains, food consumption, home cage FOB examination, motor activity measurements or gross and neuropathological examinations. No treatment-related findings were observed in the 50 ppm group. At 100 ppm, tremors were observed during clinical examinations in 8 of 10 (28 incidences) males and 10 of 10 (119 incidences) females. Twitching was observed in 4 of 10 (4 incidences) males and 2 of 10 (5 incidences) females. These signs were first observed on day 21 in males and day 20 in females. During the open field portion of the FOB, tremors were observed in all females following 4 weeks of treatment. In addition, females displayed decreased ($P \leq 0.05$) hind limb grip strength during weeks 8 and 13 (22–25%). One female died on day 52 as a result of kidney inflammation; however, this death was not considered treatment related.

At 200 ppm, tremors were observed during clinical examinations in 10 of 10 (311 incidences) males and 10 of 10 (336 incidences) females. Twitching was also observed in 10 of 10 (76 incidences) males and 10 of 10 (96 incidences) females. These signs were first observed on day 8 in males and day 9 in females. During the open field FOB, tremors were observed in all males and females following 4 weeks of treatment. In addition, females displayed increased arousal when compared with concurrent controls (3 treated versus 1 control). Females displayed decreased ($P \leq 0.05$ or 0.01) forelimb grip strength (20–31%) and hind limb grip strength (18–36%) and increased landing foot splay values (21–28%) during weeks 4, 8 and 13. In addition, decreased forelimb grip strength was observed in males at week 4 (27%, not statistically significant), but not at later times.

Under the study conditions utilized, the LOAEL for this study is 100 ppm, equal to 6.0 mg/kg bw per day, based on neuromuscular findings (tremors, changes in grip strength and landing foot splay). The NOAEL is 50 ppm, equal to 2.9 mg/kg bw per day (Freeman, 1998).

(d) Developmental studies of neurotoxicity

Rats

In a range-finding study for the developmental neurotoxicity study, bifenthrin (purity 94.8%) was administered in the diet to 10 female Crl:CD(SD)IGS BR rats per group at concentrations of 0, 50, 65, 80, 100 and 125 ppm (equal to 0, 3.6, 4.6, 6.0, 7.4 and 9.3 mg/kg bw per day, respectively, during gestation; 0, 9.2, 11.7, 14.3, 17.2 and 22.5 mg/kg bw per day, respectively, during lactation) from GD 6 through LD 22. All animals were observed twice daily, and clinical observations were recorded at appropriate intervals. Maternal body weight and food consumption were measured on GDs 0, 6, 9, 12, 15, 18 and 20 and on LDs 1, 4, 7, 11, 14, 17 and 22. Females were allowed to deliver and rear their offspring until postnatal day (PND) 22. On PND 4, litters were culled to yield four males and four females (as closely as possible). Pups were observed for morbidity and moribundity; other clinical observations were also recorded. Body weight was measured on PNDs 1, 4, 7, 11, 14, 17 and 22. Locomotor activity was assessed on one pup of each sex per litter on PND 22. On LDs 5, 11 and 17, milk samples were collected from all dams (following subcutaneous injection of oxytocin) and analysed for the presence of bifenthrin. Blood was collected from five dams per group on LDs 4 and 22, and brain samples were collected on LD 22 from these same animals to analyse for the test material. The culled pups from these five dams were used for blood and brain collection on PND 4; blood and brain samples were pooled by litter. On PND 22, blood and brains were collected and necropsy was performed on one pup of each sex per litter from the five selected litters; the remaining pups and all dams were discarded without examination. Brain weights in dams and offspring were recorded but unreported.

One female in the 50 ppm group delivered on GD 20 and was euthanized along with her pups. All other dams survived to scheduled termination. Slight to moderate whole-body tremors were observed in 8 of 10 dams (beginning as early as LD 5 and extending until LD 22) at 125 ppm. The

finding of whole-body tremors was not observed in any other bifenthrin-treated dose groups. Body weight, food consumption, pregnancy rates and gestation length were unaffected by treatment. No treatment-related clinical effects, macroscopic changes or differences in motor activity were observed in the offspring. Bifenthrin was detected in maternal milk and plasma and in offspring plasma on all sampling days. The highest mean concentration detected in milk occurred on LD 11 for all dietary levels (range of means: 6.01–10.4 ppm). Residue levels increased with increasing dietary concentration in a somewhat linear fashion. Mean maternal plasma levels were almost identical on LDs 4 and 22 and showed a more robust increase with increasing dose than did milk concentrations. Offspring plasma levels were similar to maternal levels, as were the dose–response and time course profiles.

The results of this range-finding study in rats demonstrated that the plasma and milk samples from dams exposed via diet to bifenthrin confirmed that pups were adequately exposed to the test article. Based on whole-body tremors at 125 ppm, the doses of 0, 50, 100 and 125 ppm were selected for a dietary developmental neurotoxicity study of bifenthrin in rats described below (Nemec, 2006a).

In a developmental neurotoxicity study, bifenthrin (purity 94.8%) was administered in the diet to 25 female Crl:CD(SD) rats per dose at dose levels of 0, 50, 100 and 125 ppm (equal to 0, 3.6, 7.2 and 9.0 mg/kg bw per day, respectively, during gestation; 0, 8.3, 16.2 and 20.7 mg/kg bw per day, respectively, during lactation) from GD 6 through LD 21. Maternal animals were checked twice daily for mortality or moribundity and daily for cage-side observations. Individual maternal body weight was recorded on GDs 0, 6, 9, 12, 15 and 20 and on LDs 1, 4, 7, 11, 14, 17 and 21. Food consumption was determined on GDs 0, 6, 9, 12, 15 and 20 and on LDs 1, 4, 7, 11, 14, 17 and 21. An FOB was performed on all dams on GDs 10 and 15 and on LDs 10 and 21. On PND 4, litters were culled to yield four males and four females (as closely as possible). Offspring were allocated for detailed clinical observations (FOB) and assessment of motor activity, auditory startle reflex habituation, learning and memory (water maze testing) and neuropathology at termination (PND 72). On PND 21, the whole brain was collected from 10 pups of each sex per group for micropathological examinations and morphometric measurements. Pup physical development was evaluated by body weight. The age of sexual maturation (vaginal opening in females and preputial separation in males) was assessed. Homogeneity, stability and dietary concentrations were confirmed analytically.

The analytical data indicated that the mixing procedure was adequate and that the difference between nominal and actual dosage to the study animals was acceptable. No dams died during the study. Maternal body weight, body weight gain and food consumption were unaffected by treatment. Tremors were observed during the daily examinations in 8 of 25 females at 100 ppm beginning on LD 14 and in 23 of 25 females in the 125 ppm group beginning on LD 4. In the 100 ppm group, the tremors were graded as slight and resolved in 4 of 8 females after one occurrence; slight tremors were observed in the remaining 4 of 8 females 3–7 times. In the 125 ppm group, the tremors were graded slight to moderate and continued on multiple occasions (2–18 consecutive days) during lactation. Additional test article–related effects consisted of piloerection, noted for up to 4 females in the 125 ppm group during the daily examinations and lactation FOB assessments, and increased mean grooming counts at 125 ppm during the FOB assessments on GD 10 and LDs 10 and 21. Clonic convulsions (limb tremors) and tremors were noted in 2 of 25 and 7 of 25 females, respectively, in the 125 ppm group on LD 10. On LD 21, the number of females with clonic convulsions (limb tremors) and tremors at 125 ppm increased to 10 of 25 and 13 of 25, respectively. Clonic convulsions and tremors were noted in 2 of 23 and 3 of 23 females, respectively, in the 100 ppm group on LD 21. Reproductive performance was unaffected by treatment.

No treatment-related changes were observed at gross necropsy. There were no test article–related effects on the mean number of offspring born per dam, percentage of liveborn and stillborn pups or sex ratio on the day of birth. Offspring postnatal growth and survival were unaffected by maternal

test diet consumption at any dietary concentration. The mean day for reaching sexual maturation (vaginal opening in females and balanopreputial separation in males) was not affected by treatment. No treatment-related changes were observed at gross necropsies of F_1 animals. At 125 ppm, 2 of 20 female offspring had slight tremors during the detailed physical examinations conducted on PND 28, which was 7 days after the last exposure of the dams to the test diet. During the FOB, an increase in the incidence of tremors and clonic convulsions (limb tremors) was observed in males (4/20) at 125 ppm on PND 21. A significant increase in mean grooming counts was noted in females at 100 and 125 ppm on PND 21. No treatment-related changes in forelimb or hind limb grip strength were observed. No treatment-related effects on motor activity, acoustic startle response or learning and memory testing were observed. Brain weight, length and width and macroscopic findings were not affected by treatment. In brain morphometry, a slight increase (3.5%) in the height of the hemisphere (Level 1) that was observed at 125 ppm was not considered toxicologically significant.

The maternal LOAEL for bifenthrin in rats was 100 ppm, equal to 7.2 mg/kg bw per day during gestation and 16.2 mg/kg bw per day during lactation, based on clinical signs of neurotoxicity (tremors, clonic convulsions and increased grooming counts). The maternal NOAEL is 50 ppm, equal to 3.6 mg/kg bw per day during gestation and 8.3 mg/kg bw per day during lactation.

The offspring LOAEL for bifenthrin in rats is 100 ppm, equal to 7.2 mg/kg bw per day during gestation and 16.2 mg/kg bw per day during lactation (maternal dose), based on clinical signs of neurotoxicity (increased grooming counts). The offspring NOAEL is 50 ppm, equal to 3.6 mg/kg bw per day during gestation and 8.3 mg/kg bw per day during lactation (Nemec, 2006b).

(e) Studies on metabolites

No studies on metabolites were submitted by the sponsor, because the metabolites formed in the plants are also formed in animals, and therefore the toxicity of metabolites was assessed in the submitted toxicological studies.

3. Observations in humans

FMC Corporation has been manufacturing bifenthrin technical at FMC's plant in Baltimore, Maryland, USA, since the winter of 1988. Employees are working with bifenthrin about 20% of the time. No significant harmful effects except for mild and temporary paraesthesia (skin tingling) resulting from skin contact were reported in 21 current chemical/raw material operators, supervisors and/or engineers who, since start-up, have worked in the bifenthrin area for any significant period of time. All FMC Baltimore employees, including those who work in the bifenthrin production unit, participate in the medical surveillance programme. Particular attention is given to liver and kidney function, as these would be most likely affected by an overexposure to organic chemicals, including bifenthrin. All employees with potential exposure receive an annual examination, which includes spirometry, audiometric testing, electrocardiogram and a hands-on examination by an occupational health physician, as well as complete haematological, clinical chemistry and urinalysis testing. Based on the medical surveillance programme, FMC concluded that no unexplained or significant changes from the baseline or values falling outside the reference ranges have been noted for employees working in the synthetic pyrethroids business unit, nor have these employees experienced harmful effects as a result of their 14 years of work in this production unit. In addition, an industrial hygiene monitoring programme is also in place at the plant. The results of the industrial hygiene monitoring programme indicated that the airborne levels of the product in the plant are minimal and generally less than the analytical detection limit (O'Grodnick & Niedbalski, 2008).

FMC Corporation emergency calls in 2002 included 58 calls involving formulations containing bifenthrin. Most of these calls were from individuals applying products containing bifenthrin and accidental exposures. The predominant finding was dermal sensations of burning/tingling, which mostly resolved within 24 h. The second most common complaint was eye irritation. No reports

of symptoms from exposure in the general population were found in the open literature search (O'Grodnick & Niedbalski, 2008).

Smith, Thompson & Edwards (2002) developed an extraction and HPLC-ultraviolet method to measure the urinary excretion of 2-methyl-3-phenylbenzoic acid (MPA), a metabolite of bifenthrin, to detect the exposure of workers applying bifenthrin as a termiticide. The results of this biomonitoring of workers applying bifenthrin as a termiticide indicate that the levels of MPA in the urine of workers applying bifenthrin ranged from 1.8 to 31.9 µg/g creatinine (Smith, Thompson & Edwards, 2002). Another article in the literature discusses the development of methods for the analysis of 61 pesticides in human biological matrices. The procedures were used to help diagnose intoxication with bifenthrin (Lacassie et al., 2001).

Comments

Biochemical aspects

In a toxicokinetic study, groups of male and female Sprague-Dawley rats were given bifenthrin labelled with ^{14}C in either the alcohol (phenyl) or acid (cyclopropyl) ring as a single dose at 4 or 35 mg/kg bw or as 14 repeated doses at 4 mg/kg bw per day followed by a single oral dose of radiolabelled bifenthrin at 4 mg/kg bw. There were no significant differences in the results for the different doses and durations. All female rats received alcohol-labelled bifenthrin, and all male rats received acid-labelled bifenthrin. Most of the radiolabel was excreted in the faeces (66–88%) and to some extent in the urine (13–25%) in the first 48 h. Approximately 3% of the administered dose was retained in the body. Fat contained the highest concentrations of bifenthrin-derived radioactivity. In bile duct–cannulated female rats receiving a dose of 2.7 mg/kg bw, mean excretion of radioactivity was 30.0%, 15.0% and 48.7% of the administered dose in the bile, urine and faeces, respectively, 72 h after dosing. Approximately 4.8% of the administered dose was recovered in the gastrointestinal tract, skin and liver in female rats. In male rats at 5.2 mg/kg bw, mean excretion of radiolabel was 18.6%, 10.7% and 24.9% of the administered dose in the bile, urine and faeces, respectively, 72 h after dosing. Approximately 6.3% of the administered dose was recovered in the gastrointestinal tract, skin and liver in male rats. The oral absorption of bifenthrin is estimated to be about 50%. In a study of distribution and bioaccumulation, rats were exposed to bifenthrin for 70 days and 15 days for the depuration phase. Maximum concentrations of radiolabel were detected in the fat (9.62 ppm; half-life 51 days) and skin (1.75 ppm; half-life 51 days). The estimated half-lives were 19 days for liver and 28 days for kidneys. Bifenthrin was metabolized via hydrolysis, oxidation and subsequent glucuronide conjugation. In the faeces, unchanged bifenthrin was the major component (17–45% of the administered radiolabel). Twelve other products derived from hydrolysis and oxidation of the parent compound were also detected in the faeces. Almost no parent compound was detectable in the urine. Nine metabolites derived from hydrolysis and hydrolysis–oxidation products of bifenthrin were detected in the urine.

Toxicological data

Bifenthrin was moderately toxic when administered orally to mice and rats. Data from the studies of acute toxicity in rats suggested that bifenthrin is more toxic when given by gavage in diluted solution (LD_{50} 53 mg/kg bw) than undiluted (melted) (LD_{50} 168 mg/kg bw). In addition, data from the studies of developmental toxicity in rats suggest that bifenthrin is more toxic when given via gavage (the NOAEL for maternal toxicity was 1.0 mg/kg bw) than when given in the diet (the NOAEL for maternal toxicity was 7.4 mg/kg bw). The LD_{50} in rats treated dermally was >2000 mg/kg bw. The LC_{50} in rats treated by inhalation (nose only) was 0.8 mg/l air. Bifenthrin was not irritating to the eyes or skin of rabbits. Bifenthrin was a skin sensitizer as determined by the Magnusson & Kligman (maximization) test in guinea-pigs, but gave a negative response for sensitization in the Buehler test.

Bifenthrin produces characteristic type I pyrethroid neurotoxicity in short- and long-term studies. Clinical signs of neurotoxicity such as tremors were observed in many studies. No reports of histopathological findings in the nervous system were found in the data submitted.

In a 28-day dietary study of toxicity in mice, clinical signs (tremors and convulsions) were observed at 500 ppm, equivalent to 75 mg/kg bw per day, and above, and there were mortalities at 600 ppm and above. The NOAEL was 300 ppm, equivalent to 45 mg/kg bw per day. In a 28-day dietary study of toxicity in rats, tremors were observed at dietary concentrations of 200 ppm, equivalent to 20 mg/kg bw per day, and above. The NOAEL was 100 ppm, equivalent to 10 mg/kg bw per day. In a 90-day dietary study of toxicity in rats, the NOAEL was 50 ppm, equal to 3.8 mg/kg bw per day, on the basis of tremors observed at the LOAEL of 100 ppm, equal to 7.5 mg/kg bw per day.

In a 90-day study of toxicity in dogs fed capsules containing bifenthrin, clinical observations included tremors, ataxia, blinking, mydriasis, nystagmus, lacrimation and polypnoea. The NOAEL was 2.5 mg/kg bw per day on the basis of tremors seen at the LOAEL of 5.0 mg/kg bw per day. In a 1-year study of toxicity in dogs fed capsules, the NOAEL was 1.5 mg/kg bw per day on the basis of an increased incidence of tremors seen at the LOAEL of 3.0 mg/kg bw per day.

The carcinogenic potential of bifenthrin was studied in mice and rats. In mice, the NOAEL was 50 ppm, equal to 7.6 mg/kg bw per day, on the basis of tremors at the LOAEL of 200 ppm, equal to 29 mg/kg bw per day. In this study, males at the highest dose (600 ppm) showed an increased incidence of urinary bladder tumours (leiomyosarcomas). These lesions were re-evaluated by an expert panel of three pathologists, who concluded that the bladder tumours seen in the study in mice were benign, probably vascular in origin, occurred predominantly in males, apparently occurred only in mice and had no relevance for humans. In the study in mice, there was some indication of increased combined incidences of adenoma and adenocarcinoma of the liver (males only) and increased incidences of bronchoalveolar adenomas and adenocarcinomas of the lung in females, but the results of the re-evaluation suggested that these tumour responses were not treatment related.

In a long-term combined study of toxicity and carcinogenicity in rats, tremors were the most prevalent findings in both sexes. At the highest dose of 200 ppm, equal to 9.7 mg/kg bw per day, a slight decrease in body weights was noted, and there was equivocal evidence for decreased food consumption. At the highest dose, retinal atrophy was noted in 28 females but not in males. The NOAEL was 50 ppm, equal to 2.3 mg/kg bw per day, on the basis of tremors seen at the LOAEL of 100 ppm, equal to 4.7 mg/kg bw per day. There were no treatment-related neoplastic findings in rats.

Bifenthrin gave negative responses in various studies of genotoxicity in vitro and in vivo except for a weakly positive response in vitro but not in vivo in the assay for UDS and at low concentrations in a test in mouse lymphoma cells.

The Meeting concluded that bifenthrin is unlikely to be genotoxic.

In view of the lack of evidence for a genotoxic potential in vivo, the absence of carcinogenicity in rats and the lack of relevant carcinogenic effects in mice, the Meeting concluded that bifenthrin is unlikely to pose a carcinogenic risk to humans.

In a two-generation study of reproductive toxicity in rats, reproductive parameters were not affected at the highest dose tested (100 ppm, equivalent to 5.0 mg/kg bw per day). The NOAEL for parental systemic toxicity and offspring toxicity was 60 ppm, equivalent to 3.0 mg/kg bw per day, on the basis of marginally reduced body weights in F_0 and F_1 females during gestation and lactation and tremors seen at the LOAEL of 100 ppm, equivalent to 5.0 mg/kg bw per day.

There were two studies of developmental toxicity in rats. In a gavage study in rats, the NOAEL for maternal toxicity was 1.0 mg/kg bw per day on the basis of increased incidence of tremors in 18 out of 25 dams during days 10–19 of gestation, seen at the LOAEL of 2.0 mg/kg bw per day. The NOAEL for developmental toxicity was 1.0 mg/kg bw per day on the basis of increased fetal and litter incidences of hydroureter without hydronephrosis seen at the LOAEL of 2.0 mg/kg bw per day. In

the dietary study of developmental toxicity in rats, the LOAEL for maternal toxicity was 200 ppm, equal to 16.3 mg/kg bw per day, on the basis of clinical signs and decreased food consumption, body weight gains and adjusted (for gravid uterine weight) body weight gains. The NOAEL for maternal toxicity was 90 ppm, equal to 7.4 mg/kg bw per day. The NOAEL for developmental toxicity was 200 ppm, equal to 16.3 mg/kg bw per day, the highest dose tested. In a study of developmental toxicity in rabbits treated by gavage, the NOAEL for maternal toxicity was 2.67 mg/kg bw per day on the basis of treatment-related increases in the incidence of head and forelimb twitching seen at the LOAEL of 4.0 mg/kg bw per day. In this study, no developmental toxicity was observed at doses of up to 8.0 mg/kg bw per day, the highest dose tested.

The Meeting concluded that bifenthrin caused developmental toxicity only at doses that were maternally toxic.

The Meeting concluded that bifenthrin is not likely to be teratogenic to humans.

In a study of acute neurotoxicity in rats given undiluted bifenthrin, the NOAEL was 35 mg/kg bw on the basis of mortality (females only), clinical signs and FOB findings and differences in motor activity observed at the LOAEL of 75 mg/kg bw. In a published study by Wolansky, Gennings & Crofton (2006), male rats were given bifenthrin via gavage as nine doses (8–18 rats per dose) ranging from 0.03 to 28 mg/kg bw in corn oil (1 ml/kg bw), and motor activity was assessed for 1 h during the period of peak effects (4 h after dosing). The data were modelled, and a threshold dose was determined to be 1.28 mg/kg bw. The threshold dose is defined as an estimate of the highest no-effect level at which treated rats did not display any significant decreases in motor activity. In a 90-day study of neurotoxicity in rats, the NOAEL was 50 ppm, equal to 2.9 mg/kg bw per day, on the basis of neuromuscular findings (tremors, changes in grip strength and landing foot splay) observed at the LOAEL of 100 ppm, equal to 6.0 mg/kg bw per day. In a study of developmental neurotoxicity in rats given diets containing bifenthrin, the NOAEL for maternal toxicity was 50 ppm, equal to 3.6 mg/kg bw per day, on the basis of tremors, clonic convulsions and increased grooming counts seen at the LOAEL of 100 ppm, equal to 7.2 mg/kg per day. The NOAEL for offspring toxicity was 50 ppm, equal to 3.6 mg/kg bw per day, on the basis of increased grooming counts seen at the LOAEL of 100 ppm, equal to 7.2 mg/kg bw per day. In studies of delayed neurotoxicity in adult hens and rats, no evidence of delayed neurotoxicity was observed.

On the basis of the available data, the Meeting considered that bifenthrin was neurotoxic.

Workers in a bifenthrin manufacturing plant reported mild and temporary paraesthesia (skin tingling) resulting from skin contact. Of emergency calls received by the manufacturer during 2002 from individuals applying products containing bifenthrin, the most common complaints were dermal sensations of burning/tingling and eye irritation, which mostly resolved within 24 h.

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

Toxicological evaluation

The Meeting established an ADI of 0–0.01 mg/kg bw on the basis of a NOAEL of 1.0 mg/kg bw per day in a study of developmental toxicity in rats (gavage) based on the increased incidence of tremors in dams during days 10–19 of gestation and increased fetal and litter incidences of hydroureter without hydronephrosis seen at the LOAEL of 2.0 mg/kg bw per day, and using a safety factor of 100. This ADI was supported by a threshold dose of 1.3 mg/kg bw in males in a study of acute toxicity in rats treated by gavage and using a safety factor of 100, as well as several other studies, including a 1-year study of toxicity in dogs, a 2-year combined study of toxicity and carcinogenicity in rats and a 90-day study of neurotoxicity in rats, all with NOAELs in the range of 1.5–2.9 mg/kg bw per day.

The Meeting established an acute reference dose (ARfD) of 0.01 mg/kg bw based on a threshold dose of 1.3 mg/kg bw for motor activity in a study of acute toxicity in rats treated by gavage and

using a safety factor of 100. Although this study was conducted with males only, it was considered appropriate, as there was no evidence of sex-specific differences among the data on bifenthrin. This ARfD was supported by the study of developmental toxicity in rats treated by gavage in which the NOAEL of 1.0 mg/kg bw per day was based on the increased fetal and litter incidences of hydroureter without hydronephrosis seen at the LOAEL of 2.0 mg/kg bw per day and which thereby was also protective for developmental effects.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Two-year study of toxicity and carcinogenicity[a]	Toxicity	50 ppm, equal to 7.6 mg/kg bw per day	200 ppm, equal to 29 mg/kg bw per day
		Carcinogenicity	600 ppm, equal to 92 mg/kg bw per day[b]	—
Rat	Two-year study of toxicity and carcinogenicity[a]	Toxicity	50 ppm, equal to 2.3 mg/kg bw per day	100 ppm, equal to 4.7 mg/kg bw per day
		Carcinogenicity	200 ppm, equal to 9.7 mg/kg bw per day[b]	—
	Acute motor activity assessment[c]	Neurotoxicity	Threshold dose, 1.28 ± 0.31 mg/kg bw[d]	3.21 ± 0.32 mg/kg bw[d] (ED_{30})
	Multigeneration study of reproductive toxicity[a]	Parental toxicity	60 ppm, equivalent to 3.0 mg/kg bw per day	100 ppm, equivalent to 5.0 mg/kg bw per day[b]
		Offspring toxicity	60 ppm, equivalent to 3.0 mg/kg bw per day	100 ppm, equivalent to 5.0 mg/kg bw per day[b]
	Developmental toxicity[c]	Maternal toxicity	1.0 mg/kg bw per day	2.0 mg/kg bw per day[b]
		Embryo and fetal toxicity	1.0 mg/kg bw per day	2.0 mg/kg bw per day[b]
	Developmental toxicity[a]	Maternal toxicity	90 ppm, equal to 7.4 mg/kg bw per day	200 ppm, equal to 16.3 mg/kg bw per day[b]
		Embryo and fetal toxicity	200 ppm, equal to 16.3 mg/kg bw per day[b]	—
	Developmental neurotoxicity[a]	Maternal toxicity	50 ppm, equal to 3.6 mg/kg bw per day	100 ppm, equal to 7.2 mg/kg bw per day
		Offspring toxicity	50 ppm, equal to 3.6 mg/kg bw per day	100 ppm, equal to 7.2 mg/kg bw per day
Rabbit	Developmental toxicity[c]	Maternal toxicity	2.7 mg/kg bw per day	4.0 mg/kg bw per day
		Embryo and fetal toxicity	8.0 mg/kg bw per day[b]	—
Dog	Ninety-day toxicity[c]	Toxicity	2.5 mg/kg bw per day	5.0 mg/kg bw per day
	One-year toxicity[c]	Toxicity	1.5 mg/kg bw per day	3.0 mg/kg bw per day

[a] Dietary administration.
[b] Highest dose tested.
[c] Gavage administration.
[d] 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 ED_{30} is defined as the dose associated with a 30% decrease in motor activity. From: Wolansky, Gennings & Crofton (2006).

Estimate of acceptable daily intake for humans

0–0.01 mg/kg bw

Estimate of acute reference dose

0.01 mg/kg bw

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

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

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

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid and about 50% oral absorption
Dermal absorption	Moderate, 50%
Distribution	Widely distributed in tissues
Potential for accumulation	Low, no evidence of significant accumulation except fat and skin
Rate and extent of excretion	Approximately 82–90% (70–80% in faeces, 5–25% in urine and 20–30% in bile) within 48 h
Metabolism in animals	Moderate; metabolic pathways include hydrolysis, oxidation and conjugation
Toxicologically significant compounds (animals, plants and environment)	Bifenthrin
Acute toxicity	
Rat, LD_{50}, oral	53.4 mg/kg bw
Rat, LD_{50}, dermal	>2000 mg/kg bw
Rat, LC_{50}, inhalation	0.8 mg/l, dust (4 h exposure, nose only)
Rabbit, dermal irritation	Not an irritant
Rabbit, ocular irritation	Not an irritant
Guinea-pig, dermal sensitization	Sensitizer (Magnusson & Kligman test)
	Not a sensitizer (Buehler)
Short-term studies of toxicity	
Target/critical effect	Tremors
Lowest relevant oral NOAEL	1.5 mg/kg bw per day (1-year study in dogs)
Lowest relevant dermal NOAEL	50 mg/kg bw per day (rat)
Genotoxicity	
	Unlikely to be genotoxic
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Tremors
Lowest relevant NOAEL	2.3 mg/kg bw per day (2-year study in rats)
Carcinogenicity	Not carcinogenic in rats or mice
Reproductive toxicity	
Reproduction target/critical effect	No toxicologically relevant effects
Lowest relevant reproductive NOAEL	5.0 mg/kg bw per day (rats; highest dose tested)
Developmental target/critical effect	Developmental toxicity only at maternally toxic dose in rats
Lowest relevant developmental NOAEL	2.0 mg/kg bw per day (rats; highest dose tested)

Neurotoxicity/delayed neurotoxicity	
Acute neurotoxicity	Decrease in motor activity, (threshold dose) 1.28 mg/kg bw (rats)[a]
Short-term study of neurotoxicity	NOAEL: 2.9 mg/kg bw per day (rats)
Developmental neurotoxicity	No neurodevelopmental toxicity observed, NOAEL: 125 ppm, equal to 9.0 mg/kg bw per day (rats), the highest dose tested
Mechanistic data	
	No studies were submitted
Medical data	
	No major effects, and typical symptoms of pyrethroid exposure were reported

[a] 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.

Summary

	Value	Study	Safety factor
ADI	0–0.01 mg/kg bw	Rats, study of developmental toxicity (gavage)	100
ARfD	0.01 mg/kg bw	Rats, acute motor activity assessment	100

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