5.2 BIFENTHRIN (178)

TOXICOLOGY

Bifenthrin is the International Organization for Standardization (ISO) approved name for 2-methyl-3-phenylphenyl) methyl (1RS, 3RS)-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 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 the JMPR. Bifenthrin was reviewed by the present Meeting within the periodic review programme of the Codex Committee on Pesticide Residues (CCPR). All pivotal studies with bifenthrin were certified as complying with good laboratory practice (GLP).

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 5.0 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; $t_{1/2}$, 51 days) and skin (1.75 ppm; $t_{1/2,}$ 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 was 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 (median lethal dose, 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 and 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 75.0 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 polypnea. 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 temors 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 and 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 bronchioalveolar 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 were 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 unscheduled DNA synthesis 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 and the absence of carcinogenicity in rats and the fact that the carcinogenic effects observed in mice were not considered

to be relevant to humans, 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 functional observation battery (FOB) findings and differences in motor activity was observed at the LOAEL of 75 mg/kg bw. In a published study by Wolansky et al. (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 dose 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 convusions 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 paresthaesia (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 based on 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 identified on the basis of effects on motor activity 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 the 1-year study of toxicity in dogs, a 2-year combined study of toxicity/carcinogenicity in rats and a 90-day study of neurotoxicity in rats, all with NOAELs in the range of 1.5 to 2.9 mg/kg bw per day.

The Meeting established an 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 male rats treated by gavage and using a safety factor of 100. Although this study was conducted with males only, it was considered appropriate since 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.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Two-year study of toxicity and carcinogenicity[a]	Toxicity	50 ppm, equal to 7.6 mg/kg bw per day	200 ppm, equal to 29.0 mg/kg bw per day
		Carcinogenicity	600 ppm, equal to 92.0 mg/kg bw per day[c]	—
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[c]	—
	Acute motor activity assessment[b]	Neurotoxicity	Threshold dose, 1.28± 0.31 mg/kg bw[e]	3.21 ± 0.32 mg/kg bw[e] (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[c]
		Offspring toxicity	60 ppm, equivalent to 3.0 mg/kg bw per day	100 ppm, equivalent to 5.0 mg/kg bw per day[c]
	Developmental toxicity[b]	Maternal toxicity	1 mg/kg bw per day	2 mg/kg bw per day[c]
		Embryo and fetal toxicity	1 mg/kg bw per day	2 mg/kg bw per day[c]
	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[c]
		Embryo and fetal toxicity	200 ppm, equal to 16.3 mg/kg bw per day[c]	—

Species	Study	Effect	NOAEL	LOAEL
	Developmental Neurotoxicity[a]	Maternal toxicity	50 ppm, equal to 3.6 mg/kg be per day	100 ppm, equal to 7.2 mg/kg be per day
		Offspring toxicity	50 ppm, equal to 3.6 mg/kg be per day	100 ppm, equal to 7.2 mg/kg be per day
Rabbit	Developmental toxicity[b]	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[c]	__
Dog	90-day toxicity[b]	Toxicity	2.5 mg/kg bw per day	5.0 mg/kg bw per day
	1-year toxicity[b]	Toxicity	1.5 mg/kg bw per day	3.0 mg/kg bw per day

[a] Dietary administration.

[b] Gavage administration.

[c] Highest dose tested.

[e] The threshold dose is defined as an estimate of the highest no-effect dose level at which treated rats did not display any decreases in motor activity. ED_{30} is defined as the dose associated with a 30% decrease in motor activity. From: Wolansky MJ, Gennings C, Crofton, KM (2006) Relative potencies for acute effects of pyrethroids on motor function in rats. Toxicol Sci 89: 271–277.

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 and in 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	Decreased 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

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

[a] The threshold dose is defined as the highest no-effect level at which treated rats would respond with 100% performance of the controls.

DIETARY RISK ASSESSMENT

Deferred to 2010, when residue re-evaluation is scheduled

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