

BIFENTHRIN

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EXPLANATION

Bifenthrin is a synthetic pyrethroid insecticide and acaricide that was reviewed for the first time by the present Meeting.

EVALUATION FOR ACCEPTABLE DAILY INTAKE**BIOLOGICAL DATA****Biochemical aspects**Absorption, distribution, excretion and biotransformation

Absorption, distribution, excretion and biotransformation of bifenthrin was investigated in hens, rats and goats. Alcohol (phenyl)- and acid (cyclopropyl)-¹⁴C-bifenthrin were utilized.

Hens

Laying hens (20/group) were dosed with encapsulated ¹⁴C-labelled bifenthrin for 10 days at a level equal to 40 ppm. Excreta and eggs were collected on specified days and prepared for analysis. The hens in the control and treatment groups were sacrificed for tissue collection within 24 h of the final dose. Measurable ¹⁴C-residues were found in all treated group's tissues, excreta, egg white and egg yolk. Maximum residues in egg yolk were about 3 ppm, in egg white 0.04 ppm. The highest tissue concentration was found in fat and liver with values of about 2 ppm. ¹⁴C-bifenthrin was eliminated primarily via the excreta (Jameson *et al.*, 1986).

White Leghorn laying hens were dosed orally with either acid-¹⁴C or alcohol-¹⁴C-bifenthrin for 10 days with doses of 2 mg/kg bw. Residues in livers of acid-¹⁴C-bifenthrin treated hens consisted mainly of hydroxymethyl-bifenthrin and fatty acid conjugates (palmitate, oleate), TFP acid¹, hydroxymethyl TFP acid and the parent

¹ *Cis, trans*-3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl-cyclopropanecarboxylic acid

compound. A similar metabolic pattern was identified from hens treated with alcohol-¹⁴C-bifenthrin. Hydroxylation of the 2-methyl group of the cyclopropyl ring is the major metabolic pathway in poultry. The presence of fatty acid conjugates of the hydroxymethyl-bifenthrin represents a new process in the biotransformation of this pyrethroid (Singer *et al.*, 1987).

Laying hens were orally dosed with ¹⁴C-bifenthrin for 10 days at dose levels of 4 mg/animal. Analysis of tissues and eggs from treated laying hens showed that unchanged bifenthrin (40-50%) and the fatty acid conjugates with palmitic or oleic acid (20-40%) are the major constituents of the residues in the tissues. A minor metabolite is the unconjugated hydroxymethyl-bifenthrin (Tullman *et al.*, 1987).

The metabolism of bifenthrin in poultry appears to start by hydroxylation of the 2-methyl carbon of the cyclopropane ring, followed by fatty acid conjugation (Wu, 1987).

Rats

Rats were treated with a single oral dose of 5 mg/kg bw alcohol (phenyl)-¹⁴C-labelled bifenthrin. About 76%-79% of the administered radioactivity was eliminated via the faeces and 6-7% via urine within the first 48 h. A total of about 90% was recovered in excreta after 7 days. Radiocarbon residues in most tissues were < 0.1 ppm, except for liver (up to 0.1 ppm), skin (up to 0.4 ppm) and fat (up to 1.7 ppm). A significant portion of parent chemical was excreted unchanged in the faeces (El Naggar *et al.*, 1983).

Excretion of bifenthrin following oral administration of a single dose of 2.7 mg/kg bw to female or 5.2 mg/kg bw to male bile duct-cannulated rats was investigated in urine, faeces and bile. Signs of stress, evidenced by low biliary volume, decreased defecation and a high fatality rate as a consequence of intoxication, was noticed among the male rats. Therefore the bifenthrin dose was reduced in female rats. In female rats an average of about 30% of the radioactivity was excreted in bile, about 15% in the urine and about 49% in the faeces. In male rats excreted radioactivity averaged 19%, 11% and 25% of the ¹⁴C-dose in bile, urine and faeces, respectively. Over 90% of the excreted ¹⁴C-residue in the bile was in form of polar conjugates and less than 1% could be attributed to the parent compound. Total absorption of bifenthrin using the sum of average biliary and urinary excretion and tissue concentrations determined in this study yields a value of about 50% in females and 36% in males, respectively (El Naggar *et al.*, 1991).

Male and female rats were dosed with ¹⁴C-bifenthrin in one of the following dose regimens: control (vehicle only), a single low-dose of 4 mg/kg bw, multiple low-doses of 4 mg/kg bw/day of non-radiolabelled test material over a two-week period, followed by a single radiolabelled dose of 4 mg/kg bw or a single high-dose of 35 mg/kg bw. In a preliminary study total recovery in expired air was less than

1% of the dose administered; thus expired air was not collected during the definitive study. The majority of the radioactivity was found in faeces ranging from about 71%-84% of the total dose while 9%-15% of the applied radioactivity was eliminated in the urine. After application of low-doses the majority of radioactivity in urine and faeces was eliminated within 36 h after treatment, whereas after application of the high-dose the majority of the applied dose was eliminated after only 72 h.

Tissues and carcass contained a total of about 3%-5% of the dose. Highest residues were found in fat with values of slightly more than 1 ppm after low-dose application and 8 and 16 ppm in males and females, respectively, after application of the high-dose. Residue levels in other organs were in most cases < 0.2 ppm after low-dose administration and \leq 1 ppm after high-dose administration (Cheng *et al.*, 1988).

Male and female rats were orally dosed with acid- and alcohol- ^{14}C -labelled bifenthrin at single dose levels of 4 mg/kg bw or 35 mg/kg bw. Additional groups of rats were dosed once daily with unlabelled bifenthrin for 14 days at 4 mg/kg bw/day followed by a single low dose of radiolabelled bifenthrin. A majority of ^{14}C -radioactivity was excreted in faeces and ranged from about 66%-73% (alcohol- ^{14}C -label) and 69-83% (acid- ^{14}C -label). In the urine, elimination ranged from 20-25% and 13-22% for both ^{14}C -labels, respectively. Total tissue residues amounted to about 3%. The majority of ^{14}C -residue was eliminated within 12-72 h after dosing. Analysis of the ^{14}C -residues showed that the parent compound was the major product. Faecal metabolites were mainly derived from hydroxylated (on either the biphenyl and/or cyclopropyl part of the molecule) parent compound. Urinary metabolites were the result of hydrolytic and oxidative-hydrolytic processes. Slight sex differences and differences between the various dosing regimens were observed in metabolite distribution. The amount of parent compound eliminated in the excreta was lower in females (17%-26%) than in males (25%-44%). Multiple low-doses when compared with a single low-dose showed a decrease in the amount of parent chemical within the same ^{14}C -label, and a noticeable increase in hydrolytical degradates indicating a significant inductive effect on esterase activities (El Naggar *et al.*, 1986; Selim, 1986a).

Female and male rats were dosed with acid- ^{14}C and alcohol- ^{14}C -bifenthrin, respectively, using the following dose regimens: single oral low-dose of 5.4 mg/kg bw; single oral high-dose of 36-43 mg/kg bw depending on sex; multiple oral low-doses of 4.9 mg/kg bw. For the multiple oral low-dose regimen, rats were dosed once daily with unlabeled bifenthrin for 14 days followed by a single low-dose of ^{14}C -labelled chemical on the 15th day. A majority of ^{14}C -residues were excreted in faeces and urine within 48-72 h. Faecal metabolites were excreted primarily as non-conjugates while urinary metabolites were eliminated in both conjugated and non-conjugated form. Metabolic profiles appeared to be similar among the three dosing regimens, while excretion rate appeared to be slower in high dose rats.

Analyses of metabolite fractions indicated that the major faecal metabolites were primarily derived from hydroxylated parent compound, such as: hydroxymethyl bifenthrin, 4'-OH bifenthrin, 3' or 4'-OH-hydroxymethyl bifenthrin. Hydrolytic products related to mono- and dihydroxylated intact parent chemical were also detected including 4'-OH BP acid¹, 4'-OH BP alcohol², dimethoxy BP acid and dimethoxy BP alcohol. Analyses of metabolites from urine fractions indicated that the majority of ¹⁴C-residues were also from hydrolytic or oxidative degradation resulting in metabolites such as: 4'-OH BP acid, BP acid, 4'-OH BP alcohol, dimethoxy BP acid, 4'-Methoxy BP acid, dimethoxy BP alcohol, BP alcohol, TFP acid, *cis*- and *trans*-hydroxymethyl TFP acid (Wu *et al.*, 1988).

¹⁴C-labelled bifenthrin was administered orally to female rats for 70 days at a dose level of 0.5 mg/kg bw/day. Animals were sacrificed daily during the dosing period and radiocarbon levels were measured in blood, tissues and organs. Average peak concentrations of radioactivity were 9.6 ppm in fat, 1.7 ppm in skin, 0.4 ppm in liver, 0.3 ppm in kidney, 1.7 ppm in ovaries, 3.2 ppm in sciatic nerve, 0.06 ppm in whole blood and 0.06 ppm in plasma. Analyses were extended for an additional 85 days following cessation of dosing (depuration phase). Half-lives of 51 days (fat), 50 days (skin), 19 days (liver), 28 days (kidney), and 40 days (ovaries and sciatic nerve) were estimated from ¹⁴C-depuration. Plasma concentrations of radioactivity were similar from days 21 to 70 (0.04-0.06 ppm) and decreased to 0.01 ppm at 78 days and to < 0.01 ppm thereafter. Whole blood levels were similar to plasma indicating no specific accumulation. Analysis of fat revealed that parent chemical accounted for a majority (65%-85%) of the ¹⁴C-residues in fat. Three metabolites accounted for the remaining radiocarbon residues (Hawkins *et al.*, 1986).

Bifenthrin was administered once orally to male rats at dose levels of 4 or 35 mg/kg bw using alcohol-¹⁴C-labelled compound. Mean peak concentrations of ¹⁴C in blood of about 0.6 and 3 µg/ml for the low- and high-dose, respectively, were reached 4-6 h after dosing. Twenty-four hours after dosing about 0.2 µg/ml and 2 µg/ml were measured in the plasma at the two dose levels, respectively (Selim *et al.*, 1986b).

Male rats were given either a single oral low dose of 4 mg/kg bw or a high-dose of 35 mg/kg bw of alcohol-¹⁴C-bifenthrin. Plasma samples were analyzed for parent compound and metabolites. The major products found were parent compound, the hydrolysis product BP alcohol and the oxidized hydrolysis product, BP acid each representing about 20-30% of the total radioactive residues (Tullman and Robinson, 1986).

¹ BP acid = 2-methyl-3-phenylbenzoic acid

² BP alcohol = 2-methyl-3-phenylbenzyl alcohol

Bifenthrin (aqueous emulsion) was dermally administered to a shaved area on the back of rats at a dose of 36 µg/rat. A mean of about 4% of the administered dose remained on the washed dosed skin site following treatment. Concurrently a mean of about 97% of the dose was recovered in the skin wash. After a contact time of 24 h, 19% of the dose was recovered on the skin and about 73% in the skin wash. Radioactivity in the residual carcass was less than 2%. About 1.4% was excreted in the urine and 1.8% in the faeces 24 h post-dose. Thus dermal absorption is low (Braun *et al.*, 1990).

Rats were treated dermally with single doses of 49.2, 514 or 5253 µg ¹⁴C-labelled bifenthrin/rat (proposed dosage levels: 0.05, 0.5 and 5.0 mg/rat). The average amount of test material eliminated in the urine and faeces within 24 h was less than 1% of the applied dose. Measurable amounts of 0.01 µg/ml were only detected in blood 4 h after application of the highest dose of 5253 µg bifenthrin. Twenty-four hours after application the concentration had increased to 0.02 µg/ml. The amount of bifenthrin present in the carcasses, 24 h after application, corresponded to about 0.4% for the highest dose group and 0.8% for the other dose groups. Average amounts absorbed into and through the skin 24 h after application varied between 45 and 71% for the different dose groups (Craine *et al.*, 1986).

Goats

Lactating goats were orally dosed with ¹⁴C-labelled bifenthrin for 7 consecutive days at a dose level of 2 mg/kg bw/day. About 90%-98% of the ¹⁴C-residue in milk samples were found to be the parent compound. Milk also contained about 4-5 minor degradates (El Naggar *et al.*, 1984).

Analysis of tissues and milk from goats administered ¹⁴C-labelled bifenthrin at dose levels of 2 mg/kg bw/day for seven consecutive days showed the parent compound to be the major product in milk, contributing about 75%-82% of total ¹⁴C-residues (ca. 1 ppm). Fat contained 78%-80% (ca. 1.7 ppm) parent compound, muscle 74%-88% (ca. 6.2 ppm), heart 77% (ca. 0.4 ppm), kidney 16%-22% (0.1 ppm) and liver 19%-44% (0.8 ppm). Biphenyl acid was the major metabolite identified in kidney and liver amounting to 42% (0.2 ppm) and 31% (0.6 ppm), respectively, and was a minor metabolite in milk. Biphenyl alcohol was detected in milk, fat, kidney and liver at lower levels (< 1-3%). Other metabolites, including 4'-hydroxy-bifenthrin, hydroxymethyl-bifenthrin, hydroxymethyl-TFP acid³ and BP aldehyde⁴ were detected in minor amounts. A majority of the ¹⁴C-residues were

³ *Cis, trans*-3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2-methyl, *trans*-hydroxymethyl-(1-¹⁴C)-cyclopropanecarboxylic acid

⁴ 2-Methyl-3-phenylbenzaldehyde

isolated as organosoluble, non-conjugated products. Certain hydrolytic and intact ester metabolites of the parent chemical were found to be conjugated with polar and nonpolar substrates (El Naggar *et al.*, 1986a).

Lactating goats were orally dosed with acid (cyclopropyl)-¹⁴C or alcohol (phenyl)-¹⁴C-bifenthrin at 2 mg/kg bw/day for 7 consecutive days. ¹⁴C-Residues from acid-¹⁴C and alcohol-¹⁴C were comparable. Steady state concentration in milk was reached within 4 days from the beginning of dosing and ranged from about 0.8-1.5 ppm. Maximum residues in liver, fat, kidneys and heart were 3.9 ppm, 2.8 ppm, 1.0 ppm and 0.6 ppm, respectively. About 40%-52% of the dose was excreted in faeces and 8%-17% in the urine (Predmore *et al.*, 1984).

Toxicological studies

Acute toxicity studies

The predominant clinical signs in the animal species tested were clonic convulsions, tremors and oral discharge. The results are summarized in Table 1. Bifenthrin has moderate acute toxicity and is classified as moderately hazardous by WHO (WHO, 1992).

Table 1: Acute toxicity of bifenthrin

Species	Sex	Route	LD ₅₀ (mg/kg bw)	Reference
Mouse	M,F	oral	43	Freeman (1983)
Rat	M,F	oral	56	Freeman <i>et al.</i> (1982) Freeman <i>et al.</i> (1983a)
Rabbit	M,F	ip dermal	799 > 2000	Freeman <i>et al.</i> (1986) Freeman <i>et al.</i> (1983b)

Irritation and sensitization

Instillation of 0.1 ml in the eyes of rabbits caused slight irritation reactions (Freeman *et al.*, 1983c). No irritation was observed after dermal application on abraded and intact skin of rabbits (Freeman *et al.*, 1983d). After dermal treatment of guinea-pigs with undiluted material no sensitization reaction was noted (Freeman *et al.*, 1983e).

Short-term toxicity studies

Mice

Two sequential 28-day dietary studies were conducted with groups of mice (Swiss Webster 10/sex/group). In the first study bifenthrin was administered in the diet at concentrations of 0, 50 (500), 100, 200 or 300 ppm. Since there were no significant treatment-related adverse effects in the 50 ppm group, it was changed to a dietary concentration of 500 ppm for the last 2 weeks of the study. Therefore a second study was initiated with dosage levels of 0, 500, 600, 750 or 1000 ppm. Tremors and clonic convulsions were the most consistent clinical signs of intoxication noted in males and females of the 750 and 1000 ppm groups prior to death. Tremors were also prevalent in males and females surviving dietary treatment of 500 and 600 ppm.

In the 1000 ppm, 7/10 males and all females died. Deaths occurred also at 750 and 600 ppm in females only. No consistent influence on body-weight was noticed among the treatment groups. Food consumption was depressed in males at 1000 and 750 ppm during most of the study and in females in all dose groups in the first study week. Changes in mean organ weights were slight and showed no dose-response relationship. The NOAEL was 300 ppm equal to 69 mg/kg bw/day for males and 84 mg/kg bw/day for females (Rand *et al.*, 1983a).

Rats

In a 28-day range-finding study, groups of rats (Sprague-Dawley, 10/sex/group) were fed dietary levels of 0, 50, 100, 200, 300 or 400 ppm. All rats in the 400 ppm group died by day 15 of the study. Clinical signs consisting of clonic convulsions and tremors were observed at dose levels of 200 ppm and higher. Deaths occurred also at 300 ppm (6/10 males and 1/10 females). No further results are recorded for the study group at 400 ppm. Body-weight gain was reduced in the 300 ppm dose group and at 200 ppm in males at the beginning of the study. Food consumption was depressed at 200 and 300 ppm particularly during the first study weeks. Changes in the organ weights usually did not follow a dose-related pattern with the exception of an increase in adrenal weight and depressed testes weight in males at 300 ppm. At 300 ppm in males relative organ weights of the brain and kidney were elevated; in females at this dose level an elevation of the relative brain, kidney and liver weights were observed. No other parameters were investigated. The NOAEL was 100 ppm equal to about 11 mg/kg bw/day (Rand *et al.*, 1983b).

Technical bifenthrin (90% *cis*/10% *trans*-isomer) was continuously administered in the diet of rats (Sprague-Dawley: 15/sex/dose) for at least 90 days at concentrations of 0, 12, 50, 100 or 200 ppm. For this study only a summary report was available. An additional 10 animals in the control and 200 ppm group were observed for a period of 28 days without treatment to discover reversibility

or appearance of delayed effects. The only significant treatment-related effect consisted of tremors in all test animals of the 200 ppm group. This effect was reversible and was not observed during the 28-day post treatment period. The treatment did not cause effects on mortality, body-weight development, food consumption, ophthalmologic examination, haematology, clinical chemistry, organ weights or gross and histopathological examination. The NOAEL in this study was 100 ppm equivalent to 5 mg/kg bw/day (Rand *et al.*, 1984).

Rabbits

Technical bifenthrin was applied to the shaved skin of rabbits (New Zealand white; 6/sex/group) for at least 6 h/day at dosages of 0, 25, 50, 100 or 500 mg/kg bw/day for 21 consecutive days. One female at 500 mg/kg bw/day died on day 19 most probably due to ingestion of the test material. The other animals at 500 mg/kg bw/day showed tremors and loss of muscle control as the most consistent sign of intoxication. The treatment did not influence body-weight gain, food consumption, values of haematology and clinical chemistry with the exception of an increased platelet count in males at 500 mg/kg bw/day and elevated kidney- and liver-weights in females at this dose level. The NOAEL in this study was 100 mg/kg bw/day (De Prosopo *et al.*, 1984).

Dogs

In a 13-week subchronic oral capsule study, groups of dogs (beagle: 4/sex/dose) were treated with technical bifenthrin (purity 88.4%) at levels of 0, 2.5, 5.0, 10 or 20 mg/kg bw/day. There were no treatment-related effects on survival, food consumption, ophthalmologic examination, haematology, clinical chemistry, organ weights, gross and microscopic pathology. Compound-related tremors were observed at doses of 5 mg/kg bw/day and above. Signs of ataxia and languid appearance were noted at 20 mg/kg bw/day with single findings at 10 and 5 mg/kg bw/day. Less frequent or isolated signs of compound-related effects included salivation, lacrimation or mydriasis. Slightly reduced body-weight gain was observed at 20 mg/kg bw/day in females. The NOAEL in this study was 2.5 mg/kg bw/day (Serota *et al.*, 1984).

In a 52-week oral capsule study, groups of dogs (beagle;4/sex/dose) were treated with technical bifenthrin (purity 88.4%) at dose levels of 0, 0.75, 1.5, 3.0 or 5.0 mg/kg bw/day. No treatment-related effects concerning survival, food consumption, ophthalmology, haematology, clinical chemistry, urinalysis, organ weights, gross pathology and histopathology were observed. Dose-related tremors appeared at doses of 3 and 5 mg/kg bw/day after 15 weeks of treatment disappearing again following 29 weeks of treatment. The body-weight gain was decreased in males at 5 mg/kg bw/day. The NOAEL in this study was 1.5 mg/kg bw/day (Serota *et al.*, 1985).

Long-term toxicity/carcinogenicity studies

Mice

In a lifetime feeding study technical bifenthrin (purity 88.4%) was administered continuously over at least 20 months in the diet of mice (Swiss Webster; 50/sex/dose) at concentrations of 0, 50, 200, 500 or 600 ppm (these levels refer to concentrations of pure bifenthrin). The treatment did not affect significantly the survival rate of the animals although single early deaths after 1-2 weeks of study occurred at 500 and 600 ppm. The predominant clinical sign of toxicity consisted of tremors occurring at 500 and 600 ppm. Single males at 200 ppm exhibited also minimal clinical signs of toxicity. Body-weight gain was reduced in all dose groups in males and in the 500 and 600 ppm group in females, but no distinct dose-effect relationship was observed. A treatment-related depression in food consumption was observed in the first week of the study only in the two highest dose groups. The treatment did not affect the haematological parameters and organ-weights. Histopathological examination revealed an increase in urinary bladder tumours in high-dose males. The tumours were originally described as leiomyosarcoma of the urinary bladder wall by the study author with incidences of 2/48 (4%), 6/50 (12%), 8/50 (16%), 7/50 (14%) and 14/49 (29%), in the control, 50, 200, 500 and 600 ppm groups respectively. The tumours were also noted in females including one control animal, but no dose-effect relationship was present. The data have been reassessed by a panel of pathologists who concluded that the tumours were of vascular origin. The panel reported incidences of 10, 14, 16, 16, and 27% in control through the high-dose group, respectively. So far lesions of this morphology have only been reported infrequently in the literature probably due to variations in diagnoses. They are described only in the mouse and predominantly in males. The historical control incidence is not known, furthermore, no lesions of this morphological type have been reported in the human urinary bladder. According to the reassessment of the histological data the tumours occurring in the submucosa of the mouse bladder are of low malignant potential (slow growth, no metastasis). Statistical analysis of the data produced equivocal results leading to the conclusion of the study reviewers (Butler *et al.*, 1991) that the results do not provide persuasive evidence of a compound-related effect. Although the statistical analysis of the tumour data does not indicate unambiguous significance of the increase in incidence of bladder tumours, the lack of such significance being used as the only criterion to rebut tumorigenic potential is not sufficient to exclude a possible tumorigenic potential of the compound. In addition, an increased incidence of liver hyperplasia/adenoma/carcinoma was observed in the high dose males. A significant trend was noted for carcinoma incidence which occurred in 0/49, 0/50, 1/50, 2/49 and 2/49 at 0, 50, 200, 500 and 600 ppm respectively. The NOAEL in this study was 50 ppm equal to 7.6 mg/kg bw/day concerning clinical effects in males and 200 ppm equal to 37 mg/kg bw/day in females, respectively (Geiger *et al.*, 1986).

Rats

In a two-year feeding study in rats (Sprague-Dawley; 50/sex/dose) technical bifenthrin (purity 88.4%) was administered at dietary concentrations of 0, 12, 50, 100 or 200 ppm. The treatment did not influence mortality, parameters of clinical chemistry, urinalysis, organ weights, gross and microscopic examination. Numerous instances of tremors were observed in all males and females of the 200 ppm group between day 4 through about day 30, in single animals and at single instances also in the other dose groups. Due to the low number of animals and incidences and the lack of a dose-relationship, the tremors observed at lower dose levels are not considered treatment-related. A treatment-related decrease in body-weight gain was observed in females at 200 ppm. Erythrocyte counts were reduced in males at 200 ppm. In this study, bifenthrin did not show any tumorigenic potential. The NOAEL in this study was 100 ppm equal to 4 mg/kg bw/day in males and 7.5 mg/kg bw/day in females (McCarty *et al.*, 1986).

Reproduction studies

Rats

Only a summary report was available for evaluation of this study. Bifenthrin (technical) was administered in the diet at concentrations of 0, 30, 60 or 100 ppm to groups of rats (25/sex/group) over two consecutive generations. The dietary levels represent concentrations of bifenthrin after correcting for purity. There was no influence on mortality. At 100 ppm tremors were observed in lactating dams of the P₁ and F₁ generation. Females of the P₁ generation showed reduced body-weight gain on days 7 and 14 of the lactation period. Food consumption was depressed in the F₁ group at 100 ppm in the males during a single week of exposure. The treatment did not have any effects on the reproductive performance or litter size, litter weight or survival of the progeny. Changes in organ weights at 100 ppm consisted of an elevation of the brain weights of P₁ females. No histomorphologic alterations were observed in tissues from parental or weanling animals. A NOAEL of 60 ppm equivalent to 3 mg/kg bw/day is proposed (DeProspo *et al.*, 1986).

Special studies on delayed neurotoxicity

Rats

Groups of rats (COBS/Wistar; 3 males/dose group) were orally treated with dose levels of 0, 1, 3, 10 or 30 mg/kg bw/day for 5 consecutive days. Parameters investigated included alertness, locomotor activity, apathy, tremor and abnormal gait. Rats at 30 mg/kg bw/day showed tremor, abnormal gait, respiratory depression and signs of CNS depression (apathy, paralysis). Deaths occurred after

developing convulsions. No effects were recorded during the 7-day period after termination of dosing with 1, 3 and 10 mg/kg bw/day (Algate *et al.*, 1985).

The minimum effective dose of 30 mg/kg bw/day which caused neurological signs such as paralysis as determined in the Irwin dose-range test (Algate *et al.*, 1985) was used in a tilting-plane test. The test compound was administered orally to groups of rats (5/sex) on two consecutive days. The tilting-plane test (parameter: angle of inclination at which the animals began to slide down a tilted platform) was performed every second day from days 2-16 of the study. The results did not reveal impairment of performance by the treatment and this gave no indication of a delayed neurotoxic effect (Algate *et al.*, 1985).

Hens

In a neurotoxicity study, female domestic hens were orally treated with a single dose of 5000 mg/kg bw followed by a repeat dose after 21 days in birds showing negative response at this dose level ($LD_{50} > 5000$ mg/kg bw). The second dose was followed by a 22-day observation period. Clinical signs of toxicity consisting of unsteadiness and trembling appeared within about 22 h after dosing. Some mortalities occurred in all groups. Surviving birds had recovered from the clinical signs a few days after second dosing. The treatment did not produce clinical signs of delayed neurotoxicity. No histological examination of the nervous tissue was performed (Roberts *et al.*, 1984).

Special studies on embryotoxicity and teratogenicity

Rats

In a teratogenicity study, groups of rats (25 females/dose/group) were orally treated (gavage) on days 6 through 15 of gestation with doses of 0, 0.5, 1 or 2 mg/kg bw/day. Estimation of dose levels were based on a previous pilot teratology study, where doses of 2.5 mg/kg bw/day resulted in the death of some dams (DeProspero *et al.*, 1983b). An aqueous aspirin suspension (250 mg/kg bw/day) served as positive control. Tremors were observed as the predominant sign of toxicity among animals receiving 2 mg/kg bw/day. Body-weight gain did not differ between the different groups. No treatment-related effects were observed concerning the reproduction parameters (pregnancy, number of corpora lutea, implantations, resorptions or litter size). Malformations occurred only sporadically in all groups and without dose relationship. The study did not reveal any teratogenic activity of bifenthrin at the dose levels tested. The NOAEL in this study was 1 mg/kg bw/day for maternotoxicity and > 2 mg/kg bw/day for embryo fetotoxicity (Freeman *et al.*, 1984b).

Rabbits

In an oral teratology study groups of rabbits (20 females/dose/group) were treated with doses (stomach tube) of 0, 2.7, 4 or 8 mg/kg bw on days 7 through 19 of gestation. The recommended dose levels were estimated from a previous dose range finding study (DeProspero *et al.*, 1983a). Observations of tremors were noted for most of the animals receiving 8 mg/kg bw/day and head and fore limb twitching were observed during the second half of the dosing period among most of the animals receiving 4 or 8 mg/kg bw. The application of the test material did not affect the body-weight of the dams, the reproduction parameters, viability or body-weight of the pups, nor the incidence of external and visceral anomalies. The study therefore gave no indication for a teratogenic potential at the dose-levels administered. The NOAEL was 2.7 mg/kg bw/day for maternotoxicity and > 8 mg/kg bw/day for embryo-fetotoxicity (Freeman *et al.*, 1984a).

Special studies on genotoxicity

Based on the results of genotoxicity essays given in Table 2, the Meeting concluded that bifenthrin was unlikely to present a genotoxic hazard.

COMMENTS

After oral administration of bifenthrin to rats the compound was absorbed and eliminated mainly via faeces (70-80% within 48 h). Urinary excretion amounted to 5-10% of the administered doses. Biliary excretion was shown to range from 20-30%. Hydrolysis and hydroxylation were the major steps in the biotransformation.

Bifenthrin has moderate acute toxicity and is classified as moderately hazardous by WHO (WHO, 1992).

Following dietary administration to rats for 90 days at concentrations of 0, 12, 50, 100 or 200 ppm bifenthrin, tremors were the only treatment-related effect occurring at 200 ppm. The NOAEL was 100 ppm, equivalent to 5 mg/kg bw/day.

In a 13-week oral toxicity study in dogs at doses of 0, 2.5, 5.0, 10 or 20 mg/kg bw/day administered in capsules, the NOAEL of 2.5 mg/kg bw/day was based on the occurrence of tremors at 5.0 mg/kg bw/day and higher. In a one-year oral toxicity study in dogs at doses of 0, 0.75, 1.5, 3.0, or 5.0 mg/kg bw/day administered in capsules, the NOAEL of 1.5 mg/kg bw/day was based on the appearance of the same clinical signs.

In a lifetime feeding study with mice at dietary concentrations of 0, 50, 200, 500 or 600 ppm over at least 20 months, a NOAEL (based on tremors at 200 ppm in males and 500 ppm in females) was 50 ppm, equal to 7.6 mg/kg bw/day in

males, and 200 ppm, equal to 37 mg/kg bw/day, in females. Treatment at 600 ppm equal to 103 mg/kg bw/day caused an increased incidence of submucosal tumours (hemangiomas) in the urinary bladder in male animals. This finding was of marginal statistical significance, but tumorigenic potential for bifenthrin in mice cannot be excluded.

In a two-year feeding study with rats at concentrations of 0, 12, 50, 100 and 200 ppm, the NOAEL was 100 ppm equal to 4 mg/kg bw/day in males and 7.5 mg/kg bw/day in females. Higher dose levels caused tremors and a reduction in body-weight gain. Bifenthrin was not carcinogenic in rats.

In a multigeneration study in rats at dietary concentrations of 0, 30, 60 or 100 ppm, the NOAEL was 60 ppm equivalent to 3 mg/kg bw/day, based on changes in brain weight at 100 ppm. Reproduction was not impaired by treatment.

In a teratogenicity study in rats at gavage dose levels of 0, 0.5, 1 or 2 mg/kg bw/day, the NOAEL was 1 mg/kg bw based on the occurrence of tremors at 2 mg/kg bw in the dams. There was no evidence of teratogenicity.

In a teratogenicity study in rabbits at gavage dose levels of 0, 2.7, 4 or 8 mg/kg bw/day, the NOAEL was 2.7 mg/kg bw/day. Doses of 4 and 8 mg/kg bw/day caused tremors and twitching. No teratogenic, foetotoxic or embryotoxic effects were found.

After reviewing the available genotoxicity data, the Meeting concluded that bifenthrin was unlikely to present a genotoxic hazard.

The results of the long-term studies in rats and mice and a series of studies designed to evaluate genotoxicity indicated that bifenthrin is unlikely to pose a carcinogenic hazard to humans.

An ADI was allocated on the basis of the NOAEL of 1.5 mg/kg bw/day in the one-year study in dogs using a 100-fold safety factor. This result was supported by the same NOAEL in the rat teratology study, although in the latter study gavage, rather than dietary administration, was used.

Table 2. Results of genotoxicity assays on bifenthrin

Test system	Test object	Concentration (purity)	Results	Reference
Ames assay	<i>S. typhimurium</i>	75 - 7500 µg/plate ± activation (techn. mat.)	negative	Haworth (1983)
Ames assay	<i>S. typhimurium</i>	8 - 5000 µg/plate 5000 µg/plate , ± activation (88.4%)	precipitation at negative	Kennelly <i>et al.</i> (1988)
Mouse lymphoma assay (TK +/- locus)	L 5178 Y mouse lymphoma cells	non-activated: 0.018 - 0.24 µl/ml activated: 0.0075 - 0.1 µl/ml (88.3%)	positive ¹	Kirby (1983)
Mouse lymphoma assay (HGPRT locus)	L 5178 Y mouse lymphoma cells	15.8 - 500 µg/ml ± activation (purity not specified)	negative	Kennelly (1986)
CHO/HGPRT mutation assay	Chinese hamster ovary cells	without activation: 250 - 1000 µg/ml with activation: 20 - 50 µg/ml (88.3%)	negative inconclusive ²	Thilagar (1984a)
CHO/HGPRT	Chinese hamster ovary cells	10 - 100 µg/ml ± activation (90.6%)	negative	Heidemann <i>et al.</i> (1989)
Chromosome aberration assay	Chinese hamster ovary cells	1000 - 10 000 µg/ml ± activation (techn. mat.)	negative	Thilagar (1984b)
DNA repair test (UDS)	rat primary hepatocytes	0.01 - 2.0 µl/ml (techn. mat.)	positive ³	Thilagar (1983a)

Test system	Test object	Concentration (purity)	Results	Reference
DNA repair test (UDS)	rat primary hepatocytes	0.5 - 2.5 μ l/ml (techn. mat.)	negative	Thilagar (1983b)
DNA repair test (UDS)	rat primary hepatocytes	1 - 100 μ g/ml (90%)	negative	Fautz <i>et al.</i> (1989)
Sister chromatid exchange	Chinese hamster ovary cells (CHO)	1 - 60 μ g/ml \pm activation (90.6%)	negative	Heidemann (1989)
Transformation test	BALB/3T3 mouse embryo cells	3 - 100 μ g/ml without activation (techn. mat.)	negative	Putman (1983a)
5 day Cytogenetics assay (<i>in vivo</i>)	rat	3, 10, 30 mg/kg oral (techn. mat.)	negative	Putman (1983b)
Recessive lethal assay (<i>in vivo</i>)	<i>Drosophila melanogaster</i>	50 and 100 μ g/ml (88.4%)	negative	Benson (1984)

¹ After metabolic activation: positive answer at the highest concentration of 0.1 μ l/ml without metabolic activation in most concentration positive, no distinct dose-effect relationship.

² In the activation system at the lowest dose of 20 μ g/ml positive response; no dose-response relationship.

³ Slightly positive answer at the highest dose level of 2 μ g/ml.

TOXICOLOGICAL EVALUATION

Level causing no toxicological effect

Mouse:	50 ppm, equal to 7.6 mg/kg bw/day (20-month feeding study)
Rat:	100 ppm, equal to 4 mg/bw/day (two-year feeding study) 1 mg/kg bw/day (teratogenicity study) 60 ppm, equivalent to 3 mg/kg bw/day (multi-generation reproduction study)
Rabbit:	2.7 mg/kg bw/day (teratogenicity study)
Dog:	1.5 mg/kg bw/day (one-year study)

Estimate of acceptable daily intake for humans

0-0.02 mg/kg bw

Studies which will provide information valuable in the continued evaluation of the compound

Observations in humans.

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* FMC 54800 = Bifenthrin

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