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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

R 128831

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Registration Action Branch 2 (7509C)

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DATA EVALUATION RECORD
Supplement to DER for MRID No.: 41267801 Beta-cyfluthrin: [90-day oral study in the dog]
This supplement includes a revised executive summary, including changing the NOEL and LOEL to NOAEL and LOAEL.

STUDY TYPE: 90-day oral (feeding) study in the dog
OPPTS Number: 870.3150 OPP Guideline Number: §82-1b

DP BARCODE: N/A SUBMISSION CODE: N/A
P.C. CODE: 128831 TOX. CHEM. NO.: 266E

TEST MATERIAL (PURITY): Beta-cyfluthrin technical (99 % a.i.)

SYNONYMS: FCR 4545, Tempo I, ∝-Cyano(4-fluoro-3-phenoxyphenyl)methyl-3-(2,2-dichloroethenyl)-2,2-dimethyl-cyclopropane carboxylate

CITATION: Von Keutz, E. (1987) FCR 4545: Study of Subchronic Oral Toxicity to Dogs (13-Week Feeding Study): Project ID 98348. Unpublished study prepared by Bayer Ag. 259 p. MRID 41267801.

SPONSOR: Mobay Chemical Corporation, Agricultural Chemicals Division

EXECUTIVE SUMMARY: In an oral toxicity study (MRID 41267801), beta-cyfluthrin (99% a.i.) was administered to beagle dogs (4/sex/dose) at dose levels of 0, 10, 60, or 360 ppm in the diet (achieved doses of 0/0, 0.39/0.39, 2.36/2.5 or 13.9/15.4 mg/kg/day [M/F], respectively) for 13 weeks. The following observations/measurements were conducted: clinical signs, body weights, food consumption, ophthalmological examinations, body temperature, femoral pulse, neurological examinations, hematology, clinical chemistry, urinalysis, organ weights, gross examinations and microscopic examinations.

At 0.39 and 2.36/2.5 mg/kg/day, no treatment-related effects were observed. At 13.9/15.4 mg/kg/day, awkward, staggering gait and occasional buckling of the hind limbs (both sexes, 4/8 dogs); an increase in incidence of vomiting (both sexes); and a suggestive decrease in body weight gain (females: 0.35 kg versus 1.0 kg in controls) were observed. In 3/8 dogs, the gait abnormalities began 6-8 hours after feeding during week 1 (not reported in terms of days; in the fourth dog, the gait abnormalities did not begin until after week 1).

The NOAEL for this 3-month dog feeding study is 2.36/2.5 mg/kg/day for males/females, respectively. The LOAEL is 13.9/15.4 mg/kg/day for males/females, respectively based on gait abnormalities, increased incidence of vomiting, and suggestive decreased body weight gain.

This study is classified as **acceptable guideline** and satisfies the guideline requirements for a subchronic oral study (**§82-1b, 870.3150**) in the dog.

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Reviewed by: Melba S. Morrow, D.V.M. 7/2/91
Section II, Tox. Branch I (H7509C)
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Section II, Tox. Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Subchronic (90 Day) Oral Toxicity - Dogs.

GUIDELINE #: 82-1

TOX. CHEM. #: 266E

MRID #: 412678-01

TEST MATERIAL: FCR 4545

SYNONYMS: Beta Cyfluthrin, Tempo 1

STUDY NUMBERS: 96348

SPONSOR: Mobay

TESTING FACILITY: Bayer, AG
Germany

TITLE OF REPORT: FCR 4545 Study of Subchronic Oral Toxicity to Dogs. (13 - Week Feeding Study)

AUTHORS: Dr. E. Von Keutz

REPORT ISSUED: 11/4/87

CONCLUSIONS: Under the conditions of this study, the NOEL of FCR 4545 was 60 ppm (3.9 mg/kg) and the LEL was 360 ppm (13.9 mg/kg for males and 15.4 mg/kg for females) based on the occurence of motor disturbances which included awkward, staggering gait and occasional buckling of the hind limbs in dogs treated at this level. A decrease in body weight gain in females was also reported at doses of 360 ppm.

CLASSIFICATION: Minimum

The study satisfies the requirements set forth in Subdivision F Guidelines for a subchronic toxicity study in non-rodents.

MATERIALS: The test material was FCR 4545 (beta cyfluthrin) which contained 99% active ingredient. The test animals were beagles which were 27 to 31 weeks of age and weighed between 7.6 and 9.7 kg and were obtained from Winkelmann, a breeder in Germany.

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METHODS: Following an acclimation period during which time animals were vaccinated, dewormed, identified with tattoos and metal collars and given an ophthalmoscopic examination, four males and four females were randomly assigned to one of four groups. The groups received daily doses of the test material at the following levels:

Group	Dose (ppm)	Dose (mg/kg)
Group I	0	0
Group II	10 ppm	0.39
Group III	60 ppm	2.35(M), 2.5 (F)
Group IV	360 ppm	13.9 (M), 15.4 (F)

These doses were based on a two-week range finding study conducted in beagles. At the highest dose tested (640 ppm), motor disturbances were present in all dogs. Marked impairment in general physical condition, reduced feed consumption, weight loss, recumbency and death in one male dog were noted at this dose level. At 320 ppm, occasional vomiting, awkward gait involving the hind limbs and conjunctival irritation were reported.

Animals were individually housed and were subjected to a 12 hour light/dark cycle. The kennel temperature was maintained between 20 and 23° C and the relative humidity was between 30 - 50%.

The test compound was uniformly mixed with a dry ration and administered daily for thirteen weeks. Feed was made available to the dogs for a period of 20 to 22 hours. All unconsumed feed was weighed prior to the next feeding in order to determine the amount of test material that each individual consumed.

During the study period, animals were subjected to daily observations for clinical signs of toxicity. Body temperatures were measured and femoral pulse was taken. Feed consumption was measured daily, body weights were recorded weekly, and neurological exams were conducted which consisted of pupillary, corneal, patellar tendon and bending and righting reflexes. Neurological exams were conducted on one occasion prior to the start of the study and again on weeks 4, 7 and 13.

Ophthalmoscopic examinations were conducted on during the acclimation period and on weeks 7 and 13. Hematology, clinical chemistry and urinalysis were conducted prior to the administration of the test material and on weeks 4, 7 and 13.

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The following parameters were measured:

x Hematocrit (HCT)
x Hemaglobin (HGB)
x Leucocyte count (WBC)
x Erythrocyte count (RBC)
x Platelet count
x Leucocyte differential
x Mean corpuscular hemaglobin
x Mean corpuscular hemaglobin concentration
x Mean corpuscular volume
x Reticulocytes

Blood clotting measurements:
Thromboplastin time
Sedimentation rate
Prothrombin time

Electrolytes:
x Calcium
x Chlorine
Magnesium
x Phosphorous
x Potassium
x Sodium

Enzymes:
x Creatinine phophokinase
x Alkaline phosphatase
x Lactic dehydrogenase
x SGPT
x SGOT
Gamma glutamyl transferase
x Glutamate dehydrogenase
Cholinesterase
x Inorganic phosphorus
x Cytochrome P450
x N- demethylase
x Triglyceride

Other Serum Chemistry Values:
x Albumen
x Blood creatinine
x BUN
x Cholesterol
x Globulin
x Glucose
x Total Bilirubin
x Total protein
x Triglycerides
Serum protein electrophoresis

Urinalysis:
x volume
x specific gravity
x pH
x protein
x glucose
x blood
x bilirubin
x ketone bodies

Animals were anesthetized and sacrificed by exsanguination. A full gross necropsy was performed on all animals. Brain, liver, heart, kidneys, spleen, pancreas, prostate, thyroid, adrenals and testes/ovaries were weighed.

Tissues were embedded in paraplast and sections were stained with hematoxylin and eosin. The kidneys were stained with PAS.

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The following CHECKED (x) tissues were collected for histological examination. Weighed organs are designated by (xx)

Digestive system	Cardiovasc./Hemat.	Neurologic
x Tongue	x Aorta	xx Brain
x Salivary glands	xx Heart	xx Periph. nerves
Esophagus	x Bone marrow	x Spinal cord
x Stomach	x Lymph nodes	
x Duodenum	xx Spleen	
x Jejunum	x Thymus	Glandular
x Ileum	x Tonsils	x Parathyroids
x Cecum		xx Adrenals
x Colon	Urogenital	xx Thyroid
x Rectum	xx Kidneys	x Pituitary
	x Urinary bladder	
xx Liver	xx Testes	
xx Gall bladder	x Epididymides	Other
xx Pancreas	xx Prostate	x Bone
	x Seminal vesicle	x Skin
Respiratory	xx Ovaries	x Skel. muscle
x Trachea	x Uterus	x All gross lesions
x Lung	x Vagina	x Eyes/ Optic N.
Nose		
Pharynx		
Larynx		

At the end of the study, flouride levels were determined in the bones (femur) and teeth of all animals in the study.

Test Compound Analysis

The active ingredient was extracted from dog food with ethyl acetate. The quantitative determination of the test compound was made by using gas chromatographic detection. Peak areas of the analytical solutions were determined and compared to those of external standard solutions. Recoveries of the test compound were determined by recovery tests.

QUALITY ASSURANCE: A statement of Quality Assurance dated 10/30/87 was included in the submission.

STATISTICAL ANALYSIS: Descriptive statistical analysis was performed. Calculations included determination of the arithmetic mean and of the standard deviations. Levels of significance were not identified.

RESULTS: Clinical signs of toxicity were observed with the most frequency in the high dose group. Motor disturbances affecting 4 dogs in the 360 ppm group were observed on 41 occasions and consisted mainly of alterations in normal gait with occasional buckling of the hind limbs. These motor disturbances were

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observed approximately 6 to 8 hours after feeding. Vomiting was reported for 4 dogs and pasty feces and diarrhea were reported in 2 and 5 dogs, respectively. Observations in the high dose group are considered compound related.

In the mid dose group (60 ppm), vomiting was reported on two occasions in one dog. Pasty feces were observed on two occasions and diarrhea was reported 5 times and affected four animals. No motor disturbances were observed in animals in this treatment group.

Motor disturbances and vomiting were not reported in the 10 ppm group. Diarrhea and pasty feces were reported in two dogs. Pasty feces were observed on two occasions and diarrhea was observed on three occasions.

In the control animals, one dog vomited and one dog had diarrhea on two occasions. (See Table I, extracted from the study report for information on the frequency of clinical signs).

In males feed intake was lowest in the 10 ppm group when compared to controls; however, in females the high dose group had the lowest feed consumption (9% lower than controls). When both sexes were combined, there did not appear to be a significant difference between groups.

Body weight was affected in females in the high dose group and was consistent with the decrease in feed intake. There was a 65% difference in body weight gain when these animals were compared to controls. An average weight gain of 0.35 kg was reported for females receiving 360 ppm and an average weight gain of 1.0 kg was reported for the control females at the end of the study. Decreased weight gain appeared to be associated with lower feed efficiency as calculated by the reviewer. Statistical significance was not determined in the report; however, the observed decrease in body weight gain appears to be biologically significant. No significant differences in average body weight gains were reported for males; treated males gained slightly more weight than controls. (See Table II for information on body weight gain and food intake in females).

FCR 4545 had no affect on hematology, serum chemistry or urinalysis. Positive tests for blood in the urine were reported for one dog in group I and for two dogs in group II. Repeat collections did not yield the same results; this finding was not considered to be treatment related and may have been the result of trauma.

No differences were observed in relative and absolute organ weights when treated animals were compared to controls. No compound related gross or microscopic lesions were observed and no significant differences were reported in the flouride content

of bones and teeth from treated and control animals.

With regard to the test compound analysis, the mean recovery of active ingredient was 104% of nominal with a standard deviation of 3.9%.

DISCUSSION: Based on the results of this study, the NOEL was 60 ppm and the LEL was 360 ppm based on the occurence of motor disturbances and a decrease in weight gain reported in high dose females. The observed motor disturbances are associated with pyrethrin intoxication and no gross or microscopic lesions were present that could be associated with these disturbances.

Feed efficiency was lower in the high dose females when compared to controls. This is indicative of the toxic effects of the compound and is reflected in the differences observed in the over all body weight gains for high dose females.

When the number of animals affected in the mid dose group is considered, the incidence of diarrhea appears to be dose related. However, it would be difficult to attribute this clinical observation to the test compound for the following reasons:

- Diarrhea occured on two occasions in one animal in the control group; one time in one animal and twice in another in the low dose group; one time in three animals and twice in one animal in the mid dose group. One or two episodes of diarrhea in individual animals over a three month period is not unusual in a laboratory setting.

- The time at which diarrhea was observed varied in each of the affected animals and with the exception of one animal in the mid dose group, diarrhea is followed by complete recovery.

- There are no additional clinical findings or pathological lesions that can be correlated to the occurence of diarrhea in these mid dose animals.

In the high dose group, the observed increase in incidence of diarrhea may be treatment related in that it occured on three or more occasions in two of the five animals that were affected. Additionally, the diarrhea occured in animals that had a high frequency of observed motor disturbances which indicates that compound related toxicity was present.

If doses between 60 and 360 were investigated a more accurate assessment of the LEL could be determined. The study is therefore classified as core minimum.

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TABLE I - FREQUENCY OF CLINICAL SIGNS

Clinical signs (f/#)[a]	Dose Group (ppm)			
	0	10	60	300
Motor disturbance	0	0	0	41x/4
Vomiting	1x/1	0	2x/1	9x/4
Pasty feces	0	2x/2	2x/2	5x/2
Diarrhea	2x/1	3x/2	5x/4	14x/5

a = frequency of observation of symptoms / # of animals with symptoms

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TABLE II - BODY WEIGHT GAINS, FOOD INTAKE and FEED EFFICIENCY for HIGH DOSE FEMALES[a]

	Dose Group (ppm)			
	0	10	60	360
Week	Body Weight Gain (kg)			
2	0.00	0.20	0.10	0.10
3	0.05	0.15	0.12	0.00
4	0.10	0.10	0.08	0.10
5	0.15	0.15	0.18	0.05
6	0.08	0.13	0.08	-0.10
7	0.18	0.18	0.08	0.08
8	0.13	0.05	0.08	0.05
9	-0.05	0.08	0.10	0.00
10	0.08	0.18	0.00	0.10
11	0.20	0.23	0.08	0.08
12	0.03	0.03	0.05	-0.02
13	0.05	0.15	0.18	-0.08
Total kg (% of control)	1.00	1.48(148)	1.13(113)	0.35(35)
	Food Intake (kg)			
1	2.45	2.45	2.45	2.27
2	2.45	2.45	2.45	2.41
3	2.45	2.45	2.45	2.45
4	2.66	2.66	2.66	2.45
5[b]	2.66	2.66	2.66	2.66
13	2.66	2.66	2.66	2.40

a = table derived from data provided by sponsor.
b = from weeks 6 thru 12, the food intake was the same as week 5.

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