EPA Reviewer: Anna P. Bearden _____, Date ___
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DATA EVALUATION RECORD

STUDY TYPE: 3 Month Oral Toxicity in Dog; OPPTS 870.3151 §82-1 (b)

DP BARCODE: D244009
P.C. CODE: 129112

SUBMISSION CODE: S-53879
TOX. CHEM. NO.: N/A

TEST MATERIAL (96.4%): CGA 279202 (Trifloxystrobin)

SYNONYMS: Not given

CITATION: Altman, B. (1994) 3 month subchronic oral toxicity study in beagle dogs. Short/Long-term Toxicology; Novartis Crop Protection, AG (Formerly Ciba-Geigy Limited) Stein, Switzerland. Laboratory test number 94300. June 26, 1994. MRID [44496642]. Unpublished.

SPONSOR: Novartis Crop Protection, Inc.

EXECUTIVE SUMMARY:

In a subchronic toxicity study (MRID 444966-42) trifloxystrobin, (purity=96.4%) was administered to 4 beagle dogs/sex/dose by capsule at dose levels of 0 (empty capsule), 5, 30, 150, and 500 mg/kg/day for 91 days. Dogs were dosed 7 days a week and were observed daily in addition to weekly weighing and urine and blood analysis at pretest, week 7 and at termination. At termination gross and microscopic pathology were observed. Due to poor palatability of trifloxystrobin in the diet, route of administration was in capsule. Doses were based on a range-finding test (MRID 4496642) in which 2 dogs/dose/sex were dosed at 0, 5, 50, and 150 mg/kg/day for 28 days with additional dosing of the high dose group for 21 days at 500 mg/kg/day. Vomiting and increased liver weights in the high dose group were observed.

During this study one male beagle dog in the 500 mg/kg/day group was moribund and had to be sacrificed on day 66. All other dogs survived the study. Treatment with trifloxystrobin at 500 mg/kg/day significantly effected the animals in almost all parameters assayed including body weight, food consumption, gross pathology, hematology, clinical chemistry, and clinical signs. Treatment with trifloxystrobin at 5, 30, and 150 mg/kg/day did not affect body weight gain, hematology, urinalysis, and gross pathology. Clinical signs observed in the 150 mg/kg/day group included "moderate" diarrhea and vomiting in both sexes. Dogs in the 150 mg/kg/day group exhibited an increased liver organ to body weight ratio (+33% in males; +18% in females). Hypertrophy of liver hepatocytes was observed in 3/4 males in the 150 mg/kg/day group.

Reduction in creatine was observed in males at week 7 and 13 (-39%) and in females at week 13 (-34%). At termination an increase in triglycerides was observed in males of the 30 mg/kg/day group (+53) and both sexes in the 150 mg/kg/day groups (+79 males; +78 females). Increases in triglycerides are considered incidental since triglycerides levels at termination were the same as their pretest levels. Reductions in levels of aspartate aminotransferase were observed in the 30 (-29%) and 150 mg/kg/day (-36%) female dose groups but are not toxicologically significant due to unusually high control levels at termination.

The NOAEL was determined to be 30 mg/kg/day. The LOAEL is 150 mg/kg/day based on increased liver weights in both sexes and corresponding observations of hepatocyte hypertrophy in males.

This subchronic oral toxicity study is classified acceptable and does satisfy the guideline requirement for a subchronic oral study (82-1; 870.3150) in dogs.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: CGA 279202 tech. (Trifloxystrobin)
   Description: brown powder
   Lot/Batch #: P.405009
   Purity: 96.4%.
   Stability of compound: not given
   CAS #: not given

2. Vehicle control: Empty gelatin capsule; Capsules supplied by Torpac Limited, Canada;

3. Test animals: Species: Dog
   Strain: pedigree beagle
   Age and weight at study initiation: Age ranged from 28-33 weeks. The average male age was 28.5 weeks old and the average female age was 31.4 weeks old at beginning of dosing; Weight ranged from 9.3 to 12.1 kg for males and 9.5 to 13.6 kg for females. Weight averaged 10.70 kg for males and 10.50 kg for females.
   Source: Animal production CIBA-GEIGY Limited, 4332 Stein/Switzerland
   Housing: Two/kennel. Fastened with chain during feeding.
   Diet: Certified pelleted standard diet NAFAG 9405 Tox 350g/animal/day
   Water: Tap water was given ad libitum; Water quality fulfilled Switzerland water quality regulations.

Environmental conditions: Temperature: Temperature not controlled. Minimum temperature of 15°C.
Humidity: Monitored, not given
Air changes: not given
Photoperiod: 12hr light/12hr dark
Acclimation period: 27 days between delivery and treatment

B. STUDY DESIGN:

1. In life dates - start: November 7, 1994 end: February 6-9, 1995

2. Animal assignment

Animals were assigned by a randomized complete block design to the test groups in table 1 using the Statistical Analysis System software. Each animal was given an identifying number.

TABLE 1: STUDY DESIGN

Test Group	Dose to Animal (mg/kg)	Male	Female
Control	0	4	4
Group 1	5	4	4
Group 2	30	4	4
Group 3	150	4	4
Group 4	500	4	4

3. Dosing rational:

Doses were selected during an exploratory test followed by a 28-day range finding test (MRID no. 933163). In the range finding test, 2 dogs/dose/sex were dosed at 0, 5, 50, and 150 mg/kg/day for 28 days. At the end of treatment, laboratory parameters did not indicate significant toxicity at 150 mg/kg/day. At day 29, dogs in control, 5, and 30 mg/kg/day groups were sacrificed and necropsied. Dogs in the 150 mg/kg/day group were not sacrificed but instead the dosage was increased to 500 mg/kg/day for 21 more days. At day 50, dogs in this high group were sacrificed. Results of this range finding study were vomiting of dogs at both the 150 and 500 mg/kg/day dose levels. At day 50, liver weights of dogs in the 150/500 mg/kg/day group were increased relative to control dogs although there were not effects in blood parameters or microscopic examination. Due to poor palatability of trifloxystrobin in the diet,

route of administration was in capsule.

3. Statistics.
The following statistical evaluations were used for the results: For each time point and parameter, univariate statistical analysis was performed using nonparametric methods. The Wilcoxon test was used to compare dose groups to control ($p < 0.05$). Dose groups were tested for increasing or decreasing trends from control group by Jonckheere's test for ordered alternatives. These tests are appropriate for this data.

C. METHOD:

1. Administration of test agent.
In this study dogs in the 5, 30, and 150 mg/kg/day groups were dosed once a day in capsules for 91 days. The method of oral capsule administration was not described.

Dogs in the 500 mg/kg/day were dosed with capsules once daily up to day 10. Because of significant vomiting and decreased food consumption, beginning with day 11, dogs in the 500 mg/kg/day were given two capsules (250 mg/kg/day per capsule) a day. In addition, dosing was suspended in 2 males from day 38 to 47 and another male from day 49 to 60. Concentrations in the capsule were adjusted to maintain appropriate dosage level upon weight gain/loss of animals.

2. Diet:
Dogs in the control, 5, 30, and 150 mg/kg/day groups were fed 350g/animal/day of certified pelleted standard diet NAFAG 9405 Tox. 150 and 500 mg/kg/day dose levels caused significant vomiting and appetite loss in both sexes. Dogs in the 150 and 500 mg/kg/day groups were also fed powdered diet. Over the course of the study dogs, in the highest group significantly lost weight. Food consumption in males in the highest group was significantly reduced. To prevent excessive weight loss male dogs were force fed for variable periods of the study.

3. Observations:
Animals were inspected twice daily on weekdays and once on the weekend for signs of toxicity and mortality.

4. Body weight: Animals were weighed weekly.

5. Food consumption:
350 g of food was offered to each animal daily during a restricted feeding time. Amount consumed each day was recorded. Food efficiency was not determined. Additionally all males of the 500 mg/kg/day were force fed food for several days

(number of days was dog specific). See above.

6. Ophthalmoscopic examination

Eyes were examined at pretest and at week 13. Following external inspection, the lens, iris and fundus were examined with an opthalmoscope. The fundus was photographed. Mydriaticum[tm] (Dispersa AG) was applied to induce mydriasis. The pupillary reflex was checked in all animals and the third eyelid was examined after local anesthesia using Novesin[tm] 0.4% (Dispersa AG).

7. Blood collection:

Occurred in the mornings at pretest, day 49, and 91. Dogs were fasted for 16 hours prior to collection. Blood was removed from the jugular vein. The CHECKED (X) parameters were examined.

a. Hematology

Table 2. Hematological parameters examined.

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)
X	Platelet count*	X	Reticulocyte count
	Blood clotting measurements*		
	(Thromboplastin time)		
	(Thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time)		

* Required for subchronic studies based on Subdivision F Guidelines

b. Clinical Chemistry

Table 3. Clinical chemistry parameters examined.

	ELECTROLYTES		OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Blood creatinine*
	Magnesium	X	Blood urea nitrogen*
X	Phosphorus*	X	Total Cholesterol
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
	ENZYMES	X	Total bilirubin
		X	Total serum protein (TP)*
X	Alkaline phosphatase (ALK)	X	Triglycerides
	Cholinesterase (ChE)		Serum protein electrophores
X	Creatine phosphokinase		
	Lactic acid dehydrogenase (LDH)		
X	Serum alanine amino-transferase (also SGPT)*		
X	Serum aspartate amino-transferase (also SGOT)*		
X	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

* Required for subchronic studies based on Subdivision F Guidelines

8. Urinalysis*

Urine was collected from dogs at pretest, day 49, and 91 for all groups. The CHECKED (X) parameters were examined. It was not stated that the animals were fasted. Method of urine collection not stated.

Table 4. Urine parameters examined.

X	Appearance (color)	X	Glucose
	Volume	X	Ketones
	Specific gravity	X	Bilirubin
X	pH	X	Blood
	Sediment (microscopic)		Nitrate
X	Protein	X	Urobilinogen

* Not required for subchronic studies

9. Sacrifice and Pathology

One male was moribund and was sacrificed on day 66 followed by gross pathological examination. All other animals survived for the duration of the study and were sacrificed on schedule (i.e., day 92-95). The CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed.

Table 5. Organs examined.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
	Tongue	X	Aorta*	XX	Brain*Periph.
	Salivary glands*	XX	Heart*		nerve*
	Esophagus*		Bone marrow*	X	Spinal cord (3 levels)[T]
X	Stomach*	X	Lymph nodes* (cervical,	X	Pituitary*
X	Duodenum*		mesenteric, popliteal)	X	Eyes (optic n.)[T]
X	Jejunum*	XX	Spleen*		
X	Ileum*	XX	Thymus*		GLANDULAR
X	Cecum*				
X	Colon*		UROGENITAL	XX	Adrenal gland*
X	Rectum*	XX	Kidneys*+	X	Lacrimal gland[T]
XX	Liver*+	X	Urinary bladder*	X	Mammary gland[T]
X	Gall bladder*	XX	Testes*+	XX	Parathyroids*++
X	Pancreas*	X	Epididymides	XX	Thyroids*++
		X	Prostate		
	RESPIRATORY		Seminal vesicle		OTHER
X	Trachea*	XX	Ovaries	X	Bone (sternum, rib)
X	Lung*	X	Uterus*	X	Skeletal muscle
	Nose			X	Skin
	Pharynx			X	All gross lesions and masses*
	Larynx				

* Required for subchronic studies based on Subdivision F Guidelines
+ Organ weight required in subchronic and chronic studies.
++ Organ weight required for non-rodent studies.
T = required only when toxicity or target organ

II. RESULTS

A. CLINICAL SIGNS:

1. Clinical signs- "Moderate" diarrhea and vomiting were observed in all dogs of the 150 and 500 mg/kg/day groups. As shown in the table, the majority of vomiting incidences in the 150 and 500 mg/kg/day occurred in the first week of dosing. Blood was observed in the feces of one dog in the 500 mg/kg/day group.

Table 6. Clinical signs observed. Number of incidences are reported.

	0 mg/kg/day	5 mg/kg/day	30 mg/kg/day	150 mg/kg/day	500 mg/kg/day
Male Moderate to Severe Diarrhea	1	2	3	161	209
Female Moderate to Severe Diarrhea	0	0	0	107	167
Male Vomiting	0	0	0	15 (14 in first 7 days of dosing)	28 (19 in first 7 days of dosing)
Female Vomiting	0	0	0	12 (11 in first 7 days of dosing)	22 (18 in first 7 days of dosing)

2. Mortality:
One moribund high dose male was sacrificed on day 66 due to significant decrease in locomotor activity. All other animals survived the duration of the study and were sacrificed on schedule.

B. BODY WEIGHT AND WEIGHT GAIN:

Body weight and weight gains are presented in Tables 7 and 8. Males in control, 5 and 30 mg/kg/day dose groups gained approximately 1.0 kg over the course of the study. Females in control, 5 and 30 mg/kg/day dose groups gained from 0.20 to 0.70 kg over the course of the study. Both males and females in the 150 mg/kg/day group lost weight (8% and 13% respectively) in the first month of the study but recovered slightly in months 2 and 3. Males and females in the 500 mg/kg/day dose groups lost weight throughout the study (45% and 26% total weight loss, respectively). Food consumption by dogs in the 500 mg/kg/day group was lower than other groups.

Table 7. Average body weight for males and females treated with trifloxystrobin in a subchronic oral toxicity study.

Dose Level	Initial body weight (kg)	Day 28	Day 56	Day 91
Males				
Control (0 mg/kg/day)	10.70	10.93	11.35	11.50
150 mg/kg/day	11.80	11.15	11.23	11.48
500 mg/kg/day	10.80	8.38*	7.80*	7.43*
Females				
Control (0 mg/kg/day)	10.50	10.53	10.73	10.70
150 mg/kg/day	10.73	9.90	10.00	10.35
500 mg/kg/day	10.58	9.33	8.65*	8.38*

*Statistical significance using the Wilcoxon test ($p < 0.05$)

Table 8. Average body weight gain (kg) and percent change for males and females treated with trifloxystrobin in a subchronic oral toxicity study.

Dose Level	Day 0-28	Day 0-56	Day 0- 91
Males			
Control (0 mg/kg/day)	0.23(2.1%)	0.65 (6.1%)	0.80 (7.5%)
150 mg/kg/day	-0.65 (-6.0%)	-0.57 (-5.9%)	-0.32 (2.8%)
500 mg/kg/day	-2.42* (-29%)	-3.00* (-38%)	-3.37* (-45%)
Females			
Control (0 mg/kg/day)	0.03 (0.3 %)	0.23 (2.2%)	0.20 (1.9%)
150 mg/kg/day	-0.83 (-8.4%)	-0.73 (-7.3%)	-0.38 (-3.7%)
500 mg/kg/day	-1.25* (-13%)	-1.93* (-22%)	-2.20* (-26%)

*Statistical significance using the Wilcoxon test ($p < 0.05$)

D. Ophthalmoscopic examination - Examination of the conjunctiva, sclera, cornea, lens and fundus did not show any adverse effects caused by the pesticide treatment. All animals showed conjunctivitis follicularis at pretest and at week 13. The intensity of the lesions did not worsen with pesticide treatment.

E. Blood work:

1. Hematology:

Female dogs in all dose groups only exhibited transient changes in hemtological parameters. Male dogs in 5, 30, and 150 mg/kg/day dose groups did not exhibit any changes attributable to pesticide treatment. In the 500 mg/kg/day, there was trend to microchromatic anemia as exhibited by reduced levels of RBC, hemoglobin, and hematocrit levels in. Males in the highest dose group exhibited greatly increased levels of WBC particularly monocytes. Based on increases in platelets, decreases in basophils, and increases in monocytes, it is likely that the males in the 500 mg/kg/day have acute infection possibly resulting from the overall poor health status of this group.

Table 9. Average hematological parameter at week 13and percent change for males treated with trifloxystrobin in a subchronic oral toxicity study.

	0 mg/kg/day[a]	5 mg/kg/day	30 mg/kg/day	150 mg/kg/day	500 mg/kg/day
Males					
RBC (T/l)	7.010	6.445 (92%)	6.730 (96%)	6.508 (93%)	5.557* (79%)
Hemoglobin (mmol/L)	9.850	9.225 (94%)	9.700 (98%)	9.288 (94%)	7.600* (77%)
Hematocrit (L)	0.471	0.434 (92%)	0.457 (97%)	0.438 (93%)	0.366* (78%)
Basophils (G/l)	0.043	0.048 (112%)	0.038 (88%)	0.028 (65%)	0.012* (28%)
Monocytes (G/l)	0.493	0.523 (106%)	0.415 (84%)	0.569 (115%)	0.987* (200%)
Platelets (G/l)	290.0	296.0 (102%)	271.0 (93%)	337.8 (116%)	493.3* (167%)

2. Clinical Chemistry:

As shown in Tables 10 and11, there are significant effects on many clinical chemistry parameters in the 500 mg/kg/day group. In the 150 mg/kg/day group the following changes were seen: decrease in creatine, increase in triglycerides, and decreased cholesterol in females. The following effects in the 30 mg/kg/day group were observed: an increase in triglycerides in males and a decrease in aspartate aminotransferase in females. The apparent increase relative to controls in triglycerides are incidental since the triglycerides levels did not change with time. At termination triglyceride levels were similar to pretest levels and therefore do not effect NOEL evaluation for males. Statistically significant decreases in aspartate aminotransferase are not toxicologically relevant and are incidental due to unusually high levels in control dogs.

Table 10. Clinical chemistry profile for males exposed to trifloxystrobin. Means and percent of control are reported.

	0 mg/kg/day[a]	5 mg/kg/day	30 mg/kg/day	150 mg/kg/day	500 mg/kg/day
Creatine (μmol/L) Week 7	76.15 (±3.73)	73.73 97%	69.73 92%	67.48* 89%	40.28* 53%
Creatine (μmol/L) Week 13	74.93 (±3.54)	72.55 97%	77.78 104%	78.3 104%	46.08* 61%
Total bilirubin (μmol/L) Week 13	2.38 (±0.20)	2.02 85%	1.73* 73%	1.96 82%	1.51* 63%
Albumin (g/L) Week 13	33.19 (±1.77)	33.11 100 %	33.30 100%	31.49 95%	27.18* 82%
Cholesterol (mol./L) Week 13	4.12 (±0.66)	3.40* 83%	3.72 90%	4.09 99%	2.84* 69%
Triglycerides (mol./L) Week 13	0.38 (±0.05)	0.35 92%	0.58* 153%	0.68* 179%	0.65* 171%

*Statistical significance using the Wilcoxon test ($p < 0.05$).

[a] Standard deviations are reported with control data.

Table 11. Clinical chemistry profile for females exposed to trifloxystrobin. Means and percent of control are reported.

	0 mg/kg/day [a]	5 mg/kg/day	30 mg/kg/day	150 mg/kg/day	500 mg/kg/day
Creatine (μmol/L) Week 13	81.13 (±7.43)	87.20 107%	80.88 100%	67.03* 83%	53.83* 665
Total bilirubin (μmol/L) Week 7	2.85 (±0.39)	2.73 96%	2.25 79%	2.14 75%	1.90* 67%
Protein (g/L) Week 13	55.84 (±2.83)	58.68 105%	59.71 107%	57.78 103%	48.64* 87%
Albumin (g/L) Week 13	33.16 (±0.89)	34.46 104%	34.86 105%	33.35 101%	28.02* 84%
Cholesterol (mol./L) Week 13	3.66 (±0.54)	4.08 111%	3.93 107%	2.83* 77%	2.49* 68%
Triglycerides (mol./L) Week 13	0.36 (±0.07)	0.46 128%	0.40 111%	0.64* 178%	0.59 164%
Aspartate amino-transferase (ASAT; U/L) Week 13	31.28 (±8.12)	23.50 75%	22.10* 71%	20.03* 64%	19.68 63%

*Statistical significance using the Wilcoxon test ($p < 0.05$).
[a] Standard deviations are reported with control data.

F. Urinalysis:

In females of the 500 mg/kg/day group, there was a slight decrease in the urine pH. Urinalysis profiles in other treatment groups were similar to the control group.

Week 1

G. Sacrifice and Pathology:

1. Organ weight - Organ weights and organ to body weight ratios are given in Table 12. There are significant effects on organ weight and organ to weight ratios in the 500 mg/kg/day group. In the 150 mg/kg/day group increases in liver weights and organ to weight ratios were observed. Significant weights observed in the thyroid gland do not demonstrate a dose-response relationship and are result from unusually low thyroid weights in control dogs.

Table 12. Organ weights and organ to body weight ratios for males. Means and percent of control are reported.

Organ		0 mg/kg/day	5 mg/kg/day	30 mg/kg/day	150 mg/kg/day	500 mg/kg/day
Male						
Brain	Organ Wt. Org/Wt Ratio	85.37 (±0.37) 7.93 (±0.64)	83.43 (98%) 7.97 (101%)	80.22 (94%) 7.00 (88%)	89.47 (105%) 8.38 (106%)	82.56 (97%) 12.19* (154%)
Heart	Organ Wt. Org/Wt Ratio	104.04 (±21.10) 9.58 (±1.54)	93.06 (89%) 8.85 (108%)	101.20 (97%) 8.77 (92%)	95.17 (91%) 8.84 (92%)	51.66* (50%) 7.43 (78%)
Liver	Organ Wt. Org/Wt Ratio	319.75 (±31.96) 29.55 (±1.62)	337.20 (82%) 32.39 (110%)	354.53 (111%) 30.81 (104%)	423.95* (133%) 39.48* (134%)	329.90 (103%) 47.54* (161%)
Adrenal gland	Organ Wt. Org/Wt Ratio	1.32 (±0.03) 0.13 (±0.01)	1.30 (95%) 0.12 (92%)	1.19 (90%) 0.10 (77%)	1.33 (101%) 0.12 (92%)	1.51 (114%) 0.23* (177%)
Thymus	Organ Wt. Org/Wt Ratio	7.80 (±1.42) 0.74 (±0.10)	7.76 (99%) 0.72 (97%)	11.58 (148%) 1.01 (136%)	8.77 (112%) 0.82 (111%)	2.14* (27%) 0.29* (39%)
Testis	Organ Wt. Org/Wt Ratio	21.07 (±1.43) 1.96 (±0.22)	19.86 (94%) 1.90 (97%)	17.92 (85%) 1.58 (81%)	19.48 (92%) 1.81 (92%)	6.94* (32%) 1.08* (55%)
Thyroid gland	Organ Wt. Org/Wt Ratio	0.76 (±0.03) 0.07 (±0.004)	0.91* (120%) 0.09* (129%)	0.94* (124%) 0.08* (114%)	1.04* (137%) 0.10* (143%)	0.62* (82%) 0.09* (129%)
Kidney	Organ Wt. Org/Wt Ratio	52.84 (±4.75) 4.89 (±0.44)	55.18 (104%) 5.24 (107%)	56.85 (108%) 4.90 (100%)	52.66 (100%) 4.91 (100%)	45.38 (86%) 6.64* (136%)
Female						
Heart	Organ Wt. Org/Wt Ratio	96.22 (±13.99) 9.58 (±1.00)	99.41 (103%) 9.67 (101%)	98.00 (102%) 9.37 (98%)	84.56 (88%) 8.87 (93%)	66.16* (69%) 8.69 (91%)
Liver	Organ Wt. Org/Wt Ratio	320.1 (±37.15) 31.83 (±0.88)	298.95 (93%) 29.14 (92%)	326.10 (102%) 31.22 (98%)	357.78 (112%) 37.66* (118%)	340.40 (106%) 44.66* (140%)
Kidney	Organ Wt. Org/Wt Ratio	47.44 (±5.98) 4.73 (±0.55)	43.99 (93%) 4.28 (90%)	49.50 (104%) 4.75 (100%)	47.75 (101%) 5.01 (106%)	43.60 (92%) 5.71* (121%)

*Statistical significance using the Wilcoxon test ($p < 0.05$).

2. Gross pathology -Emaciation of the body was observed in 3/4 males and 2/4 females of the 500 mg/kg/day group. Hair loss was noted in one female in the 500 mg/kg/day group. In the single male which was sacrificed early, the following observations were made: enlargement of the gall bladder and adrenal gland, mottled stomach, and dilatation of the large intestines. No other treatment related effects were observed in female dogs.

3. Microscopic pathology -

a) Non-neoplastic - As shown in tables 13 and 14, the results of the microscopic pathological examination reflect both trifloxystrobin exposure and effects of emaciation in the 500 mg/kg/day group. The following observations probably result from emaciation: myopathy of skeletal muscle observed and atrophy of the cervical, mesenteric, and popoliteal lymph nodes .

Table 13. Microscopic pathology of males exposed to trifloxystrobin.

Dose (mg/kg/day)	0	5	30	150	500
Liver hepatocyte-hypertrophy	0	0	0	3	3
Epithelium of gall bladder-hyperplasia	0	0	0	0	2
Small intestine peyer's patch-atrophy	0	0	0	0	2
Prostate-atrophy	0	0	0	0	4
Testis-tubular atrophy	0	0	0	0	4
Thymus-atrophy	0	1	1	1	3

Table 14. Microscopic pathology of females exposed to trifloxystrobin.

Dose (mg/kg/day)	0	5	30	150	500
Liver hepatocyte-hypertrophy	0	0	0	0	4
Thymus-atrophy	1	0	0	1	3

b) Neoplastic - There were no neoplastic lesions found that could be attributed to pesticide treatment.

III. DISCUSSION

A. Discussion: This is a 91 day sub-chronic study using beagle dogs. Dose groups included 5, 30, 150, and 500 mg/kg/day. Even though the NOEL and LOAEL for males and females are the same in this study, in general male beagle dogs were more sensitive to trifloxystrobin compared to females. This increased sensitivity of males is based on most of the categories analyzed. Additionally, the highest dose tested in this study, 500 mg/kg/day, exceeded the maximum tolerated dose for beagle dogs and resulted in one moribund male which had to be sacrificed early. Toxic effects and effects of emaciation and lack of nutrition were observed in females and males in the 500 mg/kg/day group. The 150 mg/kg/day dosage fulfills the guideline requirements for a high group with toxic effects and no fatalities. Toxic effects are observed in the 150 mg/kg/day group in clinical signs, hematology, organ weights, and microscopic hematology. In males the increase in liver weights corresponded to hypertrophy of liver hepatocytes. Because there were significant vomiting episodes in the both the 150 and 500 mg/kg/day groups, particularly during the first week of dosing, the amount of absorbed pesticide is likely to be less than the dose concentration. Effects are observed in the 30 mg/kg/day group in aspartate aminotransferase for females and triglycerides for males. Both of these do not effect NOEL determination. Statistically significant decreases in aspartate aminotransferase are not toxicologically relevant and are considered to be incidental due to unusually high levels in control dogs. In male dogs of the 30 mg/kg/day group, increases in triglycerides are considered incidental since levels at termination were the same as pretest levels for this group. No toxic effects are observed in the 5 mg/kg/day group.

The LOAEL for this study is 150 mg/kg/day based on clinical sign of vomiting and increased liver weights with parallel hepatocyte hypertrophy. The NOEL for this study is 30 mg/kg/day.

B. Study deficiencies: As shown in table 4, several parameters in the urinalysis were not analyzed. Additionally, the highest dose, 500 mg/kg/day does not fit the guideline requirement for a subchronic test where the highest dose does not cause fatalities. These deficiencies do not effect data acceptance.

C. CalEPA Review:
California EPA has also reviewed this chemical. The NOAEL and LOAEL for this DER differ from the conclusions of CalEPA which indicated that the NOAEL was 5 mg/kg/day and the LOAEL was 30 mg/kg/day based on triglyceride changes in males and aspartate aminotransferase in females. These conclusions are overly conservative since 1) no other effects were observed at 30 mg/kg/day and 2) based on the scientific reasoning from above both effects are considered incidental.