DATA EVALUATION RECORD

BAS 510 F/128008

STUDY TYPE:CHRONIC TOXICITY - DOG [FEEDING] [OPPTS 870.4100B (§83-1B)]; OECD 452.

MRID 45404826.

7/23/2002

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
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Prepared by

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Task Order No. 02-06

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Template version 11/01

DATA EVALUATION RECORD
TXR#: 0050193

STUDY TYPE: Chronic toxicity - dog [feeding]; OPPTS 870.4100b [§83-1b]; OECD 452.

PC CODE: 128008

DP BARCODE: D278384
SUBMISSION NO.: S604279

TEST MATERIAL (PURITY): BAS 510 F (94.4% a.i.)

SYNONYMS: Reg. No. 300 355

CITATION: Wiemann, C., Deckardt, K., Kaufmann, W., et al. (2000) BAS 510 F - Chronic oral toxicity study in beagle dogs. Administration in the diet for 12 months. Experimental Toxicology and Ecology, BASF Aktiengeselischaft, 67056 Ludwigshafen/Rhein, FRG. Laboratory Project Identification No. 33D0179/97118, August 29, 2000. MRID 45404826. Unpublished.

SPONSOR: BASF Corporation, Agricultural Products, P.O. Box 13528, Research Triangle park, NC, 27709-3528

EXECUTIVE SUMMARY: In a chronic toxicity study (MRID 45404826), BAS 510 F (94.4% a.i., batch/lot N 37) was administered to 5 beagle dogs/sex/dose in the diet at dose levels of 0, 200, 800, 2000, or 20,000 ppm (equivalent to 0, 5.5, 21.8, 57.4, and 544.0 mg/kg bw/day for males, and 0, 5.8, 22.1, 58.3, and 592.9 mg/kg bw/day for females) for 12 months.

Biologically and statistically significant increases in alkaline phosphatase activities in the 2000-ppm males and in 20000 ppm males and females reflected hepatic enzyme induction, which would be consistent with the observed increases in triglyceride and cholesterol levels in high-dose animals. Increased absolute hepatic weights in high-dose males and females (130% and 142% of control, respectively) correlated with the clinical chemistry data, and were attributed to a toxicological effect of the compound. Although increased thyroid weights were observed at the high-dose in males and females (154% and 142% of control, respectively), the absence of additional clinical correlates precluded the identification of the thyroid as a target organ.

The LOAEL is 2000 ppm in beagle dogs (♂: 57.4 mg/kg/day; ♀: 58.3 mg/kg/day), based on elevated ALP activities in the 2000-ppm males, and elevated hepatic weights in the 2000-ppm males. The NOAEL is 800 ppm (♂: 21.8 mg/kg/day; ♀: 22.1 mg/kg/day).

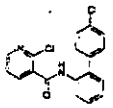
This chronic study (MRID 45404826) is **Acceptable/Guideline** and satisfies the guideline requirement for a subchronic toxicity oral study [OPPTS 870.4100, OECD 452] in the dog.

COMPLIANCE: Signed and dated Flagging Criteria, GLP, Quality Assurance, and Data Confidentiality statements were provided. The GLP statement notes that the study was conducted in accordance with the GLP provisions of the "Chemicals Act" (Chemikaliengesetz; Bundesgesetzblatt 1994, Teil 1, 29.07.94; FR Germany) and with the "OECD Principles of Good Laboratory Practice" (Paris, 1981).

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test material:** BAS 510 F

Description:	White solid
Lot/Batch #:	N 37
Purity:	94.4% a.i.
Compound Stability:	Study cited certificate of proof of stability dated Dec. 1, 1999.
CAS # of TGAI:	188425-85-6
Structure:	

2. **Vehicle and/or positive control:** Dog maintenance KLIBA laboratory diet ("Kliba Haltungsdiät Hund"), lot/batch # not provided; purity not provided

3. **Test animals:**

Species:	Dog	
Strain:	Beagle	
Age/weight at study initiation:	Males: 7-8 months of age, 10.0-14.5 kg; Females: 7-8 months of age, 8.8-12.7 kg	
Source:	BASF	
Housing:	Individually in kennels consisting of an inner (1.5 m^2) and outer kennel (4.5 m^2), up to study day 35; from days 35-373, the kennels consisted of an inner (2.7 m^2) and outer kennel (2.7 m^2).	
Diet:	Dog maintenance KLIBA laboratory diet: 350 g powdered food mixed with 350 ml drinking water, offered for a maximum of 2 hours.	
Water:	Demineralized water adjusted with drinking water to 2° German hardness, via automatic watering device, *ad libitum*	
Environmental conditions:	**Temperature:**	Not specified
	Humidity:	Not specified
	Air changes:	Number not specified
	Photoperiod:	"Natural day/night rhythm"
Acclimation period:	7 days	

B. STUDY DESIGN:

1. **In life dates:** Start: October 13, 1998 End: October 13-21, 1999.

2. **Animal assignment:** Animals were assigned by using a random number generator and body weight consideration, to the test groups noted in Table 1.

TABLE 1: Study design

Test group	Conc. in diet (ppm)	Dose to animal (mg/kg/day)		Main study 12 months	
		Male	Female	# Male	# Female
1	0	0	0	5	5
2	200	5.5	5.8	5	5
3	800	21.8	22.1	5	5
4	2000	57.4	58.3	5	5
5	20000	544	592.9	5	5

Data taken from pages 22 & 48, MRID 45404826.

3. **Dose selection rationale:** The dose levels were selected based on results from a subchronic oral toxicity study in which dietary administration of up to 25,000 ppm in beagle dogs (males: 728.9 mg/kg/day, females: 824.8 mg/kg/day) resulted in increased alkaline phosphatase (ALP) activities and liver weights at 2500 ppm in males and females, reduced body weight gains and food efficiencies in the 2500- and 25,000-ppm females, and increased thyroid weights in high-dose females.

4. **Diet preparation and analysis:** Diet was prepared at about 2-week intervals by mixing appropriate amounts of test substance with a small amount of KLIBA dog maintenance laboratory diet. Amounts of food appropriate to each dose were then added to this premix to achieve the nominal concentrations, and mixed in a laboratory mixer for about 10 minutes. The prepared test diet was then stored at room temperature. Immediately before administration, 350 g of the test diet was mixed with 350 mL of water for each dog. A certificate dated Dec. 1, 1999 was cited as verification that the stability of the test compound was proven at 94.4% after the in-life phase of the study. Stability of the test compound in the diet was carried out at 0, 13, and 32 days at a nominal concentration of 100 ppm. Homogeneity and concentration controls were analyzed at the study's beginning; concentration controls were analyzed at 3, 6, 9, and 12 months after the study's beginning. At about the study's midpoint, samples of the test diet wetted with water (1:1; w/w) were analyzed at 104 mg/kg, at 0, 1, 2, and 24 hours for stability and concentration.

Results:

Homogeneity analysis: Homogeneity ranges were (low to high-dose, respectively) 96.0-102.5%, 98.1%, 97.0%, and 98.5-102.7% of the nominal values. One sample each was taken from the 800- and 2000-ppm diets.

Stability analysis: Concentrations in dry feed ranged from 97.5-102.3% at day 0, 95.4-99.6% at day 13, and 94.5-99.6% of nominal at day 32. Stability in wetted test diet at 0, 1, 2, and 24 hours, respectively, were 101.9-106.1%, 109.5-113.0%, 110.0-114.5%, and 112.5-116.0% of nominal.

Concentration analysis: Concentration ranges (low to high-dose) at 3 months were 104.5-105%, 96.4-96.5%, 92.2-92.3%, and 94.6-94.9% of the nominal. The corresponding concentration ranges at 6 months were 115.0-115.5%, 101.8-101.9%, 100.6-100.9%, and 100.5-100.7% of nominal. Corresponding concentration ranges at 9 months were 104.5%, 101.5-101.6%, 101.5-101.7%, and 100.7-101.0% of nominal. Concentration ranges at the study's end (12 months) were 101.0-103.0%, 90.3-91.3%, 97.2-97.5%, and 92.8-93.5% of nominal.

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

5. **Statistics:** Means and standard deviations were calculated for food consumption, body weight, terminal body weight, body weight change, absolute and relative organ weights, food efficiency, test substance intake, hematological and clinical chemistry parameters. Body weight data were also analyzed using the two-sided ANOVA F-test. A comparison of each group to the control group was made using Dunnett's two-sided test if the resulting p-value was ≤ 0.05. Two-sided Kruskal-Wallis and Mann-Whitney U-tests were performed as needed on hematological (except the differential blood count) and clinical chemistry data. Fisher's exact test was used to analyze urinary parameters except volume, color, turbidity, sediment examination, and specific gravity. Absolute and relative organ weights and terminal body weights were analyzed using two-sided Kruskal-Wallis-H and, if needed, the Wilcoxon-Test, at $p \leq 0.05$ to 0.01. The Reviewer considers the analyses used appropriate.

C. METHODS:

1. **Observations:** Animals were inspected once or more daily for signs of toxicity and mortality.

2. **Body weight:** Animals were weighed on day -7, day 0 (beginning of test compound administration), and weekly thereafter. Relative organ weights were calculated by the investigators using the final (not terminal) body weight, and were calculated by the Reviewer using final body weights.

3. **Food consumption and compound intake:** Food consumption for each animal was determined and mean daily dietary consumption was calculated as g food/kg body weight/day. Food efficiency [body weight gain in g/food consumption in g per unit time ÷ 2*) × 100] and compound intake (mg/kg bw/day) values were calculated as time-weighted averages from the consumption and body weight gain data.

4. **Ophthalmoscopic examination:** Eyes were examined on study days -7 and 359 using a fundus camera.

5. **Hematology and clinical chemistry:** Blood was collected in the morning from fasted, unanesthetized animals (all dogs) for hematology and clinical chemistry analysis from all surviving animals. The CHECKED (X) parameters were examined. Differential blood smears and reticulocyte films were prepared but not examined.

a. Hematology:

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*	-	Reticulocyte count
	Blood clotting measurements*		
X	Thromboplastin time (PTT)		
-	Clotting time		
X	Prothrombin time (Quick's test, QT)		

* Recommended for chronic studies based on Guideline 870.4100. - Not examined

b. Clinical chemistry

	ELECTROLYTES		OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Creatinine*
X	Magnesium*	X	Urea nitrogen*
X	Phosphorus*	X	Total Cholesterol*
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
	ENZYMES (more than 2 hepatic enzymes)*	X	Total bilirubin
X	Alkaline phosphatase (ALK)*	X	Total protein (TP)*
-	Cholinesterase (ChE)	X	Triglycerides
-	Creatine phosphokinase	-	Serum protein electrophoresis
-	Lactic acid dehydrogenase (LDH)		
X	Alanine aminotransferase (ALT/SGPT)*		
X	Aspartate aminotransferase (AST/SGOT)*		
X	Gamma glutamyl transferase (GGT)*		
-	Glutamate dehydrogenase		

* Recommended for chronic studies based on Guideline 870.4100. - Not examined

6. **Urinalysis:** Urine was collected from overnight-fasted animals in metabolism cages. The CHECKED (X) parameters were examined.

X	Apprarance*	X	Glucose*
X	Volume*	X	Ketones
X	Specific gravity/osmolality*	X	Bilirubin
X	pH*	X	Blood*
X	Sediment (microscopic)	X	Nitrate/nitrite
X	Protein*	X	Urobilinogen

* Recommended for chronic studies based on Guideline 870.4100.

7. **Sacrifice and pathology:** Animals were sacrificed under anesthesia by exsanguination from the cervical and brachial vessels. All animals were subjected to gross pathological examination and the CHECKED (X) tissues were collected and examined histologically. The CHECKED (XX) organs, in addition, were weighed.

6

and the CHECKED (X) tissues were collected and examined histologically. The CHECKED (XX) organs, in addition, were weighed.

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

* Required for chronic studies based on Guideline 870.4100.
+Organ weight required in chronic studies.
++Organ weight required if inhalation route. - Not taken

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs of toxicity:** Soft, light-brown feces from all high-dose animals were observed from the beginning of the administration period until day 350; thereafter, this finding persisted in one high-dose male and female each and continued intermittently in four high-dose males and females each. One high-dose female experienced nearly daily vomiting from days 266-371.

2. **Mortality:** All animals survived to study termination.

3. **Neurological evaluations:** There were no behavioral or other data indicative of a neurological effect of the compound.

B. BODY WEIGHT AND WEIGHT GAIN: There were no biologically or statistically significant body weight differences between treated and control groups throughout the study. The final mean weights for high-dose males and females were 98% and 90% of the control groups, respectively (Table 2). Net weight gains (study days 0 - 364) for treated male groups approximated that of the control males, with the exception of the 2000-ppm males, whose net weight gain was 53% of the control gain. The 2000- and 20,000-ppm females also had reduced overall weight gains, each at 52% of the control gain. Individual body weight gains

7

for these groups ranged as follows: males - control = +2.6 to +4.0 kg, 2000 ppm = -0.8 to +2.5 kg, 20000 ppm = +0.3 to +2.7 kg; females - control = +1.3 to +3.6 kg, 2000 ppm = +0.9 to +1.6, 20000 ppm = +0.2 to +2.8 kg.

C. FOOD CONSUMPTION AND COMPOUND INTAKE:

1. **Food consumption:** Food consumption by each male group was essentially 100% of the diet offered. Total food consumption by treated females equalled or exceeded that of the control group, which had a slightly reduced overall intake (approx. 97% of the offered amount) (Table 2).

2. **Compound consumption:** Test compound intakes for males (low to high-dose) averaged 5.5, 21.8, 57.4, and 544.0 mg/kg/day, respectively; and 5.8, 22.1, 58.3, and 592.9 mg/kg/day for females.

3. **Food efficiency:** Food efficiencies for treated males were lower than that of the control group's, despite similar food intakes; however, there was no dose-response. Food efficiencies for treated females were also reduced, with the exception of the 800-ppm group. As with males, there was no dose-response, but the 2000- and 20,000-ppm females had the lowest efficiencies, at 51% and 52% of the control group's value, respectively.

TABLE 2. Mean body weight gains (and standard deviations), daily food consumptions, and food efficiencies in dogs fed BAS 510 F for 12 months[a,b]

Parameter	Study day	Exposure concentration (ppm) 0	200	800	2000	20000
		Males				
Body weight (kg)	0 =	12.1±1.7	11.8±1.3	11.9±1.1	11.7±1.1	11.9±1.4 (98)
	364 =	13.8±1.5	13.3±0.9	13.5±1.0	12.6±1.4	13.5±0.8 (98)
Net weight gain (kg)	0 to 364	1.7	1.5 (88)	1.6 (94)	0.9 (53)	1.6 (94)
Food intake/day (g)	0 to 364	350	350 (100)	349.3 (100)	350 (100)	349.9 (100)
Food efficiency (%)	0 to 364	1.33	1.17 (88)	1.26 (95)	0.71 (53)	1.25 (94)
		Females				
Body weight (kg)	0 =	11.0±1.1	10.5±1.1	10.8±1.0	10.7±0.7	10.8±0.8 (98)
	364 =	13.5±1.6	12.6±1.3	13.3±0.9	12.0±0.8	12.1±1.5 (90)
Net weight gain (kg)	0 to 364	2.5	2.1 (84)	2.5 (100)	1.3 (52)	1.3 (52)
Food intake/day (g)	0 to 364	337.7	342.1 (101)	337.7 (100)	343.2 (102)	340.6 (101)
Food efficiency (%)	0 to 364	2.03	1.68 (83)	2.03 (100)	1.04 (51)	1.05 (52)

Data taken from pages 67-162, MRID 45404826.
[a] Net weight gain, mean food consumption, and food efficiency values were calculated by the Reviewer. No additional statistical analyses were conducted on these data. Food intake amounts were divided by 2 to reflect the diet's composition of 50% water.
[b] Numbers in parentheses represent the percent of the control values, as calculated by the Reviewer.

D. OPHTHALMOSCOPIC EXAMINATION:

There were no ophthalmological findings that could be attributed to the treatment compound.

E. BLOOD ANALYSES:

1. **Hematology:** Slight, dose-related decreases in red blood cell (RBC), hemoglobin and hematocrit parameters were noted in treated males at study day 90 (high-dose males: 89.5-90.6% of control values). Thereafter, the values for high-dose males improved (94.0-95.5%); however, the high-dose males continued to have the lowest values for these parameters. Pre-dose percents for these parameters were 94.0-95.8. Similar effects were not observed in treated females. Prothrombin times (QT) were also slightly elevated in high-dose males. A dose-response was absent, but the high-dose males consistently had the highest QT values, at 104.1%, 104.2% and 107.5% of the control value for days 90, 185, and 360, respectively. The highest QT values for high-dose females were on days 188 and 360 (118.8% and 104.6% of the control, respectively), but a dose response was also absent.

2. **Clinical chemistry:** Dose-related elevations in alkaline phosphatase (ALP) activities were noted in all treated groups throughout the study, with the exception of the low-dose males (Table 3). Alanine aminotransferase (ALT) activities were reduced in treated males throughout the study, and in high-dose females. The decreases were most pronounced in the 2000- and 20,000-ppm males and high-dose females. Decreased aspartate aminotransferase (AST) activities were also noted, but the decreases were very mild, primarily affected in the high-dose groups, and were not dose-related. Triglycerides were elevated in a dose-responsive manner in males and females at study day 90, and in males at day 185. The greatest increases, as % of the control value, occurred at day 90, with high-dose males and females having statistically significant concentrations of 181% and 177% of the controls. The highest cholesterol levels were seen in high-dose males at each analysis, and in the high-dose females at day 91, but dose response patterns were not apparent. Total protein and serum globulin levels were statistically increased in high-dose females at day 91 (108% and 116% of control, respectively) but were of little biological or toxicological significance.

TABLE 3. Selected clinical chemistry results and standard deviations *in dogs fed BAS 510 F for 12 months*[a,b]

Parameter	Study day	Exposure concentration (ppm) 0	200	800	2000	20000
		Males				
ALP (µkat/L)	-4	4.67 ± 0.72	3.86 ± 0.44 (83)	4.06 ± 0.70 (87)	4.78 ± 0.80 (102)	4.42 ± 0.63 (95)
	90	3.63 ± 0.98	3.33 ± 0.74 (92)	4.74 ± 2.39 (131)	6.67** ±1.44 (184)	8.75** ± 2.76 (241)
	185	3.15 ± 0.68	2.70 ± 0.74 (86)	4.31 ± 2.74 (137)	6.27** ±1.67 (199)	8.43** ± 3.19 (268)
	360	2.95 ± 0.97	2.63 ± 0.91 (89)	3.53 ± 2.27 (120)	5.59 ± 1.93 (190)	7.02** ± 2.21 (238)
ALT (µkat/L)	-4	0.78 ± 0.25	0.69 ± 0.14 (88)	0.81 ± 0.25 (104)	0.53 ± 0.07 (68)	0.66 ± 0.07 (85)
	90	0.72 ± 0.16	0.59 ± 0.21 (82)	0.58 ± 0.21 (81)	0.39** ± 0.03 (54)	0.34** ± 0.10 (47)
	185	1.16 ± 0.82	0.75 ± 0.12 (65)	0.76 ± 0.23 (66)	0.49** ± 0.04 (42)	0.49** ± 0.09 (42)
	360	0.88 ± 0.20	0.74 ± 0.10 (84)	0.77 ± 0.22 (88)	0.50** ± 0.10 (57)	0.46** ± 0.09 (52)
AST (µkat/L)	-4	0.54 ± 0.16	0.50 ± 0.08 (93)	0.53 ± 0.15 (98)	0.52 ± 0.06 (96)	0.49 ± 0.04 (91)
	90	0.59 ± 0.17	0.47 ± 0.06 (80)	0.50 ± 0.10 (85)	0.47 ± 0.07 (80)	0.42 ± 0.06 (71)
	185	0.50 ± 0.13	0.45 ± 0.04 (90)	0.43 ± 0.03 (86)	0.43 ± 0.07 (86)	0.37 ± 0.06 (74)
	360	0.51 ± 0.08	0.49 ± 0.09 (96)	0.48 ± 0.08 (94)	0.49 ± 0.09 (96)	0.39 ± 0.04 (77)
Cholesterol (mmol/L)	-4	5.22 ± 0.96	4.93 ± 0.64 (94)	4.65 ± 0.78 (89)	4.62 ± 0.50 (89)	4.82 ± 0.95 (92)
	90	4.93 ± 0.96	5.03 ± 0.85 (102)	4.86 ± 0.65 (99)	5.16 ± 0.82 (105)	6.02 ± 1.54 (122)
	185	4.89 ± 0.66	4.63 ± 0.56 (95)	4.90 ± 1.13 (100)	5.04 ± 0.68 (103)	6.15 ± 1.39 (126)
	360	4.95 ± 0.80	4.76 ± 0.87 (96)	5.05 ± 0.84 (102)	5.22 ± 0.76 (106)	5.75 ± 1.16 (116)
Triglyceride (mmol/L)	-4	0.43 ± 0.11	0.48 ± 0.11 (112)	0.45 ± 0.09 (105)	0.46 ± 0.05 (107)	0.42 ± 0.07 (98)
	90	0.36 ± 0.06	0.39 ±0.04 (108)	0.45 ± 0.10 (125)	0.45 ± 0.07 (125)	0.65** ± 0.06 (181)
	185	0.40 ± 0.11	0.43 ±0.11 (108)	0.48 ± 0.13 (120)	0.60* ± 0.12 (150)	0.66** ± 0.06 (165)
	360	0.40 ± 0.10	0.37 ±0.05 (93)	0.47 ± 0.06 (118)	0.48 ± 0.08 (120)	0.60** ± 0.07 (150)
		Females				
ALP (µkat/L)	-1	4.56 ± 1.31	4.17 ± 0.44 (91)	4.35 ± 0.54 (95)	4.01 ± 0.61 (88)	4.22 ± 0.86 (93)
	91	3.78 ± 1.62	4.76± 1.98 (126)	4.89 ±1.85 (129)	5.92 ± 2.43 (157)	10.45** ± 3.80 (277)
	188	3.84 ± 1.75	4.71± 2.97 (123)	5.74 ±2.65 (150)	5.34 ± 2.37 (139)	11.36** ± 4.15 (296)
	360	3.49 ± 1.42	4.08 ±1.87 (117)	5.01 ±2.08 (144)	5.77 ± 3.11 (165)	11.70** ± 4.29 (335)
ALT (µkat/L)	-1	0.55 ± 0.16	0.63 ± 0.14 (115)	0.69 ± 0.12 (125)	0.56 ± 0.19 (102)	0.55 ± 0.11 (100)
	91	0.53± 0.012	0.49 ± 0.10 (93)	0.51 ±0.07 (96)	0.39 ± 0.13 (74)	0.26** ± 0.06 (49)
	188	0.47 ± 0.04	0.53 ±0.08 (113)	0.75* ±0.36 (160)	0.47 ± 0.12 (100)	0.37 ± 0.09 (79)
	360	0.51 ± 0.05	0.46 ± 0.04 (90)	0.51 ± 0.05(100)	0.45 ± 0.13 (88)	0.38 ± 0.17 (75)
AST (µkat/L)	-1	0.51 ± 0.08	0.55 ± 0.12 (108)	0.73 ± 0.29 (143)	0.49 ± 0.03 (96)	0.65 ± 0.15 (127)
	91	0.48 ± 0.12	0.47 ±0.05 (98)	0.51 ± 0.08(106)	0.44 ± 0.06 (92)	0.32** ± 0.04 (67)
	188	0.37 ± 0.12	0.40 ±0.12 (108)	0.42 ± 0.14(114)	0.38 ± 0.04 (103)	0.32 ± 0.03 (87)
	360	0.42 ± 0.02	0.40 ± 0.03 (95)	0.48 ± 0.08(114)	0.43 ± 0.05 (102)	0.37 ± 0.11 (88)
Cholesterol (mmol/L)	-1	3.96 ± 0.66	4.17 ± 0.36 (105)	4.82 ± 0.45 (122)	4.01 ± 0.33 (101)	4.81 ± 0.65 (121)
	91	4.12 ± 0.65	4.49 ±0.70 (109)	5.23** +0.38 (127)	4.84 ± 0.46 (118)	6.59** ± 1.17 (160)
	188	5.18 ± 1.67	5.37 ±1.53 (104)	6.99 ±2.10 (135)	5.29 ± 0.83 (102)	6.01 ± 0.53 (116)
	360	5.67 ± 2.13	4.98 ±0.71 (88)	7.19 ±1.99 (127)	5.29 ± 0.44 (93)	6.98 ± 1.51 (123)
Triglyceride (mmol/L)	-1	0.32 ± 0.05	0.37 ± 0.07 (116)	0.43** ± 0.04 (134)	0.30 ± 0.08 (94)	0.42* ± 0.08 (131)
	91	0.39 ± 0.09	0.48 ±0.13 (123)	0.52* ± 0.04 (133)	0.53 ± 0.19 (136)	0.69** ±0.23 (177)
	188	0.43 ± 0.09	0.48 ±0.14 (112)	0.52 ±0.19 (121)	0.40 ± 0.13 (93)	0.53 ± 0.05 (123)
	360	0.50 ± 0.23	0.46 ±0.12 (92)	0.71 ±0.16 (142)	0.48 ± 0.07 (96)	0.58 ± 0.06 (116)

[a] Data from pages 225-248, study report MRID 45404826.
[b] Number in parentheses represent percent of control value, as calculated by reviewer, and rounded to whole numbers.
ALP = alkaline phosphatase, ALT = alanine aminotransferase, and AST = aspartate aminotransferase
* Significantly different ($p \leq 0.05$) from the control.
** Significantly different ($p \leq 0.02$) from the control.

F. URINALYSIS: No treatment-related changes in urinary parameters were noted.

G. SACRIFICE AND PATHOLOGY:

1. **Organ weight:** Hepatic and thyroid weights were increased in the 2000- and 20,000-ppm males, and in high-dose females (Table 4). The increased thyroid weights in mid- and high-dose males were statistically significant.

TABLE 4. Terminal weights, selected mean absolute (g) and relative (to body) organ weights, and standard deviations in dogs fed BAS 510 F for 12 months[a,b]

Organ	Exposure concentration (ppm)				
	0	200	800	2000	20000
Males					
Terminal BW (kg)	13.86 ± 1.75	13.36 ± 0.92 (96)	13.56 ± 1.04 (98)	12.72 ±1.40 (92)	13.56 ± 0.76 (98)
Liver Absolute Relative (%)	406.2 ± 31.0 2.9	381.8 ± 42.4 (94) 2.9	420.3±68.4 (104) 3.1	481.1 ±87.2 (118) 3.8	527.5 ± 90.0 (130) 3.9
Thyroid Absolute Relative (%)	0.954 ± 0.07 0.07	1.226±0.28 (129) 0.09	0.898 ± 0.15 (94) 0.07	1.322*±0.26 (139) 0.07	1.468*±0.30 (154) 0.11
Females					
Terminal BW (kg)	13.50 ± 1.4	12.58 ± 1.3 (93)	13.26 ± 0.9 (98)	12.06 ±1.0 (89)	12.26 ± 1.5 (91)
Liver Absolute Relative (%)	384.7 ± 67.0 2.8	366.6 ±72.8 (95) 2.9	409.8±62.7 (107) 3.1	421.0 ±24.1 (109) 3.5	544.6*± 97.9 (142) 4.4
Thyroid Absolute Relative (%)	1.16 ± 0.29 0.09	1.14 ± 0.35 (98) 0.09	1.03 ± 0.15 (89) 0.08	1.16 ± 0.20 (100) 0.10	1.65 ± 0.59 (142) 0.13

Data taken from pages 265-268, study report MRID 45404826.
[a] Values in parentheses represent percent of control, as calculated by reviewer, and rounded to the nearest whole number. Relative organ weights (%) calculated by reviewer.
[b] Standard deviations rounded to the first or second decimal place by reviewer.
* Significantly different ($p \leq 0.05$) from the control.

2. **Gross pathology:** Several gross lessions were identified in treated animals but could not be attributed to the treatment compound. An enlarged thyroid was noted in one high-dose female.

3. **Microscopic pathology:** Hemosiderosis of the Kupffer cells was observed in one female control, two females each from the 200- and 800-ppm groups, and four 2000-ppm females (none at 20000 ppm). Bile duct proliferation was noted in one low-dose and one high-dose female. Follicular epithelial hypertrophy of the thyroid was noted in one 2000-ppm female. One high-dose male had a hemangioma cavernosum of the spleen.

III. DISCUSSION AND CONCLUSIONS:

A. **INVESTIGATORS' CONCLUSIONS:** The study authors concluded that dose-dependent effects occurred at 2000- and 20,000-ppm of BAS 510 F. The reduced body weight gains and food efficiencies in the 2000- and 20,000-ppm females were interpreted as growth impairment induced by the test compound. The increased ALP activities in the 2000-ppm

males and the high-dose males and females were identified as an indication of hepatic enzyme induction, which would be consistent with the increases in triglyceride and cholesterol levels in high-dose animals, and increased serum protein and globulin levels in high-dose females. Increased hepatic absolute and relative (to body) weights in high-dose males, and relative liver weights in the 2000-ppm females (and, presumably high-dose females) were also attributed to a toxicological effect of the compound. The authors concluded that because no additional findings were associated with the increased thyroid weights observed at the high-dose, the thyroid enlargement could not be definitively attributed to the test compound.

B. REVIEWER COMMENTS: The Reviewer does not agree that there is a toxicologically significant decrease in body weight gain or food efficiency in 2000 or 20000 ppm females. There is an increase in alkaline phosphatase activity at 2000 and 20000 ppm in both sexes. A LOAEL of 2000-ppm for BAS 510 F, and the findings upon which the NOAEL and LOAEL for beagle dogs were established, were consistent between the subchronic and chronic oral toxicity studies (MRIDs 45404823 and 45404826, respectively). In addition to the clinical chemistry correlates of increased ALP and triglycerides, and decreased AST and ALT with the increased absolute liver weights, the mild increases in QT values were consistent with a hepatic congestion at doses of 2000 ppm and above. Although these findings correlate with the altered hepatic clinical chemistry results and increased liver weights, dose responses were absent, and/or only one animal was affected; the histopathological findings do not necessarily reflect a toxicological response to the compound.

The LOAEL is 2000 ppm in beagle dogs (♂: 57.4 mg/kg/day; ♀: 58.3 mg/kg/day), based on elevated ALP activities and elevated hepatic weights in the 2000-ppm males. The NOAEL is 800 ppm (♂: 21.8 mg/kg/day; ♀: 22.1 mg/kg/day).

This chronic study (MRID 45404826) is **Acceptable/Guideline** and satisfies the guideline requirement for a subchronic toxicity oral study [OPPTS 870.4100 (§83-1b) in the dog]. There are a few deficiencies, which are detailed in the "Study Deficiencies" section of this DER.

C. STUDY DEFICIENCIES: The most significant deficiencies were the failure to note whether detailed, cageside clinical examinations were conducted; the failure to obtain weights for heart, spleen or uterus; and the failure to collect tissues from the nose, pharynx or larynx for histological examination. In addition, the environmental conditions under which the animals were housed should have been specified. A minor deficiency was that at least one of the stability studies was conducted using unspecified "dog feed". None of these deficiencies compromised the acceptability of the study.

DATA FOR ENTRY INTO ISIS

Chronic Study - dogs (870.4100b)

PC code	MRID	Study	Species	Duration	Route	Admin	Dose range: ppm, (mg/kg/day)	Doses: ppm, (mg/kg/day)	NOAEL: ppm, (mg/kg/day)	LOAEL: ppm, (mg/kg/day)	Target organ	Comments
128008	45404826	chronic	dogs	1 year	oral	diet	200-20,000 (5.5-592.9)	0; 200; 800; 2000; 20,000 (♂: 5.5, 21.8, 57.4, 544.0; ♀: 5.8, 22.1, 58.3, 592.9)	800 ppm (♂: 21.8; ♀: 22.1)	2000 ppm (♂: 57.4; ♀: 58.3)	Decreased body weight gain (females only); liver	