

DATA EVALUATION RECORD

BAS 510 F/128008

STUDY TYPE: SUBCHRONIC ORAL TOXICITY FEEDING-DOG
[OPPTS 870.3150 (§82-1b)]
(non-rodent); OECD 409

MRID. 45404823

7/23/02

Prepared for

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Office of Pesticide Programs
U.S. Environmental Protection Agency
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Prepared by

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This review may have been altered subsequent to the contractors' signatures above.

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DATA EVALUATION RECORD**TXR#: 0050193****STUDY TYPE:** Subchronic Oral Toxicity Feeding-Dog; OPPTS 870.3150 [§82-1b] (non-rodent); OECD 409.**PC CODE:** 128008**DP BARCODE:** D278384**SUBMISSION NO.:** S604279**TEST MATERIAL (PURITY):** BAS 510 F (94.4%)**SYNONYMS:** None**CITATION:** Schilling, K., Deckardt, K., Kaufmann, W., et al. (2000) BAS 510 F - Subchronic oral toxicity study in Beagle dogs. Administration in the diet for 3 months. Experimental Toxicology and Ecology, BASF Aktiengesellschaft, 67056 Ludwigshafen/Rhein, FRG. Laboratory Project Identification No. 31D0179/97101, May 11, 2000. MRID 45404823. Unpublished**SPONSOR:** BASF Corporation, Agricultural Products, P.O. Box 13528, Research Triangle Park, NC 27709-3528.**EXECUTIVE SUMMARY:** In a 90-day oral toxicity study (MRID 45404823), BAS 510 F (94.4% purity, Batch No. N-37) was administered to groups of 5 Beagle dogs/sex/dose in the diet at dose levels of 0, 250, 2500, or 25,000 ppm (equivalent to 0, 7.6, 78.1, and 728.9 mg/kg/day for males; and 0, 8.1, 81.7, and 824.8 mg/kg/day for females).

Dose-related increases in alkaline phosphatase activities and triglyceride levels (often statistically significant at higher doses) were noted in both sexes at the mid- and end-study analyses. Decreases in alanine aminotransferase and aspartate aminotransferase activities generally paralleled dose in both sexes. Absolute hepatic weights were increased in a dose-related manner in males (low to high-dose: 112%, 118%, and 142% of control, respectively) and females (103%, 119%, and 149% of controls, respectively), and were statistically significant at the mid and high doses. Dose-related increases in relative liver:body weight were also noted in both sexes. Absolute thyroid weights were slightly increased in high-dose females (137% of control), but were without histopathological correlates. The LOAEL is 2500 ppm (♂: 78.1 mg/kg/day, ♀: 81.7 mg/kg/day), based on increased alkaline phosphatase activity and hepatic weights in the mid-dose dogs. The NOAEL is 250 ppm (♂: 7.6 mg/kg/day, and ♀: 8.1 mg/kg/day).

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This 90-day oral toxicity study in the dog is **Acceptable/Guideline** and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3150; OECD 409) in dog.

COMPLIANCE: Signed and dated GLP, Flagging Criteria, Quality Assurance, and Data Confidentiality statements were provided. The study differed from the requirements of 40 CFR Part 160 by complying with the GLP provisions of the "Chemicals Act" (Chemikaliengesetz/ Bundesgesetzblatt 1994, Teil 1, 29.07.94; FRG), and with the "OECD Principles of Good Laboratory Practice" (Paris, 1981).

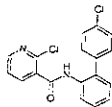
I. MATERIALS AND METHODS

A. MATERIALS:

1. Test material:

BAS 510 F

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



2. Vehicle and/or positive control: Dog Maintenance KLIBA laboratory diet

3. Test animals:

Species: Dog
 Strain: Beagle
 Age/weight at study initiation: Males: approx. 8 months, 8.9-14.1 kg; Females: approx. 8 months, 8.2-13.2 kg
 Source: BASF
 Housing: Individually in kennels consisting of an inner (1.5 m²) and outer (4.5 m²) kennel.
 Diet: Dog maintenance KLIBA 3353 Mehl laboratory diet. 350 g powdered food mixed with 350 mL drinking water, offered every morning for up to 2 hours.
 Water: Demineralized water from automatic watering device, *ad libitum*
 Environmental conditions: Temperature: Not specified
 Humidity: Not specified
 Air changes: Not specified
 Photoperiod: "Natural day/night rhythm"
 Acclimation period: 7 days

B. STUDY DESIGN:

1. **In life dates:** Start: January 20, 1998; End: April 22-28, 1998 (necropsy)

2. **Animal assignment:** Animals were assigned randomly to the test groups noted in Table 1.

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TABLE 1: Study design					
Test group	Conc. in diet (ppm)	Dose to animal (mg/kg/day)		# Male	# Female
		Male	Female		
Control	0	0	0	5	5
Low	250	7.6	8.1	5	5
Mid	2500	78.1	81.7	5	5
High	25000	728.9	824.8	5	5

Data taken from pages 20 & 45, study report MRID 45404823.

3. **Dose selection rationale:** No previous study was cited as the basis for dose selections.
4. **Diet preparation and analysis:** Diet was prepared at approximately two-week intervals by mixing appropriate amounts of test substance with powdered dog maintenance KLIBA 3353 Mehl laboratory diet and storing at room temperature. Immediately prior to administration, 350 g of food was mixed with 350 mL water for each dog. The study noted that stability of the test substance was shown by "reanalysis" after study termination, citing a certificate dated December 1, 1999 (not included). Homogeneity was tested at study day 10 (samples prepared study day -1 and frozen until analysis); concentration control samples were prepared on study day 69 and frozen until analysis 49 days later. Stability analysis of the test substance (91.7% purity, batch no. N 21) in dry feed (100 ppm) was conducted over unspecified dates in June-July, 1997, after 13 and 32 days at room temperature. Stability in wetted food was analyzed at 0, 1, 2, and 24 hours after preparation.

Results:

Homogeneity analysis: Concentration ranges for the low, mid, and high-dose diets were, respectively 90.0-94.8%, 91.1-91.2% (2 replicates from same sample) and 94.9-95.5% of the nominals.

Stability analysis: Concentrations in dry feed on days 0, 13, and 32 ranged from 94.5-102.3% of the nominal. Concentrations in wetted feed ranged from 101.9-116.0% of the nominal.

Concentration analysis: Concentration values for the low to high-dose diets were, respectively: 104.0-105.2%, 94.7% (both samples), and 95.1-95.2% of the nominals.

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 and organ weights, body weight change, test substance intake, and food efficiency. Two-sided ANOVA was used to analyze body weight and body weight changes; if $p \leq 0.05$, each group was compared to the control group by using Dunnett's two-sided test. Organ weights were subjected to nonparametric one-way analysis using the Kruskal-Wallis test; if $p \leq 0.05$, each group was compared to the control group by using the Wilcoxon test. Hematology (except differential white blood count) and clinical chemistry results were compared using Kruskal-Wallis test; if $p \leq 0.05$, dose groups were compared to the control group using the Mann-Whitney U-test for equal medians. Fisher's exact test was used to analyze urinary parameters

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except volume, color, turbidity, and specific gravity. The Reviewer considers the analyses used to be appropriate.

C. METHODS:

1. Observations:

1a. Cageside observations: There was no mention of detailed, cageside clinical examinations.

1b. Clinical examinations: Animals were inspected at least once each working day for signs of toxicity.

2. Body weight: Animals were weighed on study days -7 and 0, and at weekly intervals thereafter. Body weight change was calculated as the difference between the body weight on the day of weighing and the body weight on study day 0.

3. Food consumption and compound intake: Food consumption for each animal was determined and mean daily diet consumption was calculated for each group as g food/kg body weight/day. Weekly food efficiencies [(body weight gain in g/food consumption in g per week ÷ 2*) X 100] and compound intake (mg/kg bw/day) values were presented. Because the weekly food efficiency values were extremely variable and thus difficult to interpret, the Reviewer calculated total (days 0-91) average food efficiencies, using consumption and body weight gain data and the formula [(total body weight gain in kg/total food consumption in kg ÷ 2) X 100].

4. Ophthalmoscopic examination: The eyes of all study animals were examined (fundus camera) prior to the treatment period and on study day 91.

5. Hematology and clinical chemistry: After overnight fasting, blood was collected ("vena cephalica antibrachii") from all males on the mornings of study days -4, 43, and 87, and from all females on study days -1, 44, and 90 for hematology and clinical chemistry. The CHECKED (X) parameters were examined. Blood smear reticulocyte preparations were prepared but not evaluated.

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)		
-	(Clotting time)		
X	(Prothrombin time)		

* Recommended for 90-day oral non-rodent studies based on Guideline 870.1350
- Not measured

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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		X	Total bilirubin*
X	Alkaline phosphatase (ALK)*	X	Total protein (TP)*
-	Cholinesterase (ChE)	X	Triglycerides
-	Creatine phosphokinase		
-	Lactic acid dehydrogenase (LDH)		
X	Alanine aminotransferase (also SGPT)*		
X	Aspartate aminotransferase (also SGOT)*		
-	Sorbitol dehydrogenase*		
X	Gamma glutamyl transferase (GGT)*		
-	Glutamate dehydrogenase		

* Recommended for subchronic non-rodent studies based on Guideline 870.1350

- Not measured

6. **Urinalysis:** Urine was collected overnight from fasted animals in metabolism cages on study days -6, 37, and 85 (males) and days -5, 38, and 86 (females). The CHECKED (X) parameters were examined.

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

* Recommended for subchronic non-rodent studies based on Guideline 870.1350

7. **Sacrifice and pathology** All animals were subjected to gross pathological examination and the CHECKED (X) tissues were examined histologically. The (XX) organs, in addition, were weighed.

* Recommended for 90-day oral non-rodent studies based on Guideline 870.1350
+ Organ weight required for non-rodent studies. - Not taken

1. **Food consumption:** There was no significant effect on food consumption in treated animals. Dog # 36 was the only male which ate less than 700 g on any day (43/91 days, ate 531-690 g).

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2. **Compound consumption:** Test compound intakes for males (low to high-dose) were 7.6, 78.1, and 728.9 mg/kg/day, respectively; and 8.1, 81.7, and 824.8 mg/kg/day for females.
3. **Food efficiency:** Food efficiencies for treated males were unremarkable. Values for treated females were (low to high-dose) 59.4%, 59.4%, and 18.8% of the control value, respectively.

TABLE 2. Mean body weight gains (and standard deviations), daily food consumptions, and food efficiencies in dogs fed BAS 510 F for 90+ days ^{a,b}					
Parameter	Study day	Exposure concentration (ppm)			
		0	250	2500	25,000
Males					
Body weight (kg)	0	11.0±2.0	10.9±1.4 (99)	11.1±2.0 (101)	11.5±1.8 (105)
	91	11.7±0.8	12.1±1.3 (103)	11.6±1.5 (99)	12.3±1.9 (105)
Net weight gain (kg)	0 to 91	0.7	1.2 (171)	0.5 (71)	0.8 (114)
Food intake/day (g)	0 to 91	700	700	700	670.9 (96)
Food efficiency (%)	0 to 91	2.2	3.7 (168)	1.6 (73)	2.6 (118)
Females					
Body weight (kg)	0	10.1±1.6	10.3±1.2 (102)	10.4±1.4 (103)	10.4±1.9 (103)
	91	11.1±1.4	10.9±1.1 (98)	11.0±1.3 (99)	10.6±1.6 (96)
Net weight gain (kg)	0 to 91	1.0	0.6 (60)	0.6 (60)	0.2 (20)
Food intake/day (g)	0 to 91	688.7	691.3 (100)	695.6 (101)	674.8 (98)
Food efficiency (%)	0 to 91	3.2	1.9 (59)	1.9 (59)	0.6 (19)

Data taken from pp. 62-96, MRID 45404823.

^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.^b Numbers in parentheses represent the percent of the control values, as calculated by the Reviewer.

D. OPHTHALMOSCOPIC EXAMINATION: Ophthalmoscopic examination of the eyes of all study animals revealed no pathological findings.

E. BLOOD ANALYSES:

1. **Hematology:** The authors noted mild decreases in hemoglobin (Hgb) and red blood cell counts (RBC), relative to control values, in mid and high-dose males (93-98% of controls) and in the high-dose females (89-93% of controls) at the mid- and end-study analyses. Although the decreased Hgb and RBC values in the high-dose females were usually statistically significant, the decreases were not biologically significant for males or females, and dose responses were absent. Clotting analysis revealed slight, dose-related increases in prothrombin times (QT) in treated females at study days 44 (low to high-dose: 110%, 111%, and 118% of control value, respectively) and 90 (101%, 104%, and 111%, respectively). The increases were not statistically significant. High-dose males also experienced increased QT values at days 43 and 87 (108% and 112% of the control value, respectively), but a dose response was absent and the values were not statistically significant. The dose response in females, and the increases at the study's end in both males and females suggest a slight effect of the compound on clotting time.
2. **Clinical chemistry:** Increases in alkaline phosphatase activities and triglycerides were noted primarily at the 25000 ppm dose in both sexes. Treated values were lower than respective controls for alanine and aspartate transaminases in males and females at 25000 ppm.

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Cholesterol increases in treated groups were of a lesser magnitude, not dose-related, and not statistically significant.

TABLE 3. Selected clinical chemistry results and standard deviations in dogs fed BAS 510 F for 90+ days ^{a,b}						
Parameter	Study day	Exposure concentration (ppm)				
		0	250	2500	25,000	
Males						
ALP (μkat/L)	-4	4.82±0.90	4.93±1.36 (102)	4.22±1.04 (88)	4.83±0.53 (100)	
	43	4.57±0.91	5.56±1.83 (122)	5.50±1.75 (120)	12.95**±6.50c (283)	
	87	3.60±0.66	4.97±2.01 (138)	5.17±1.82 (144)	9.99**±1.29 (278)	
ALT (μkat/L)	-4	0.58±0.10	0.46±0.12 (79)	0.55±0.12 (95)	0.49±0.11 (85)	
	43	0.59±0.14	0.53±0.24 (90)	0.47±0.09 (80)	0.33±0.16 (56)	
	87	0.69±0.19	0.57±0.08 (83)	0.58±0.16 (84)	0.35**±0.08 (51)	
AST (μkat/L)	-4	0.51±0.15	0.40±0.08 (78)	0.45±0.09 (88)	0.49±0.06 (96)	
	43	0.49±0.06	0.46±0.07 (94)	0.48±0.07 (98)	0.39±0.08 (80)	
	87	0.52±0.08	0.48±0.11 (92)	0.44±0.06 (85)	0.38**±0.07 (73)	
Cholesterol (mmol/L)	-4	5.37±0.74	5.61±1.05 (105)	5.51±0.68 (103)	4.99±0.73 (93)	
	43	4.17±0.62	5.36±1.16 (129)	5.52±1.37 (132)	6.11±1.50 (147)	
	87	4.10±0.65	5.19±0.97 (127)	5.41±1.15 (132)	4.93±1.14 (120)	
Triglycerides (mmol/L)	-4	0.45±0.06	0.48±0.14 (107)	0.37±0.03 (82)	0.44±0.07 (98)	
	43	0.38±0.08	0.41±0.06 (108)	0.52±0.08 (137)	0.81**±0.22 (213)	
	87	0.30±0.07	0.40*±0.04 (133)	0.44*±0.09 (147)	0.60**±0.11 (200)	
Females						
ALP (μkat/L)	-1	4.59±0.61	4.63±1.25 (101)	4.89±0.99 (107)	4.21±1.78 (92)	
	44	3.85±1.14	4.39±1.38 (114)	6.44±2.10 (167)	8.13±4.47 (211)	
	90	3.05±0.51	4.24±1.83 (139)	5.70**±1.33 (187)	8.80**±4.21 (289)	
ALT (μkat/L)	-1	0.63±0.23	0.53±0.05 (84)	0.55±0.09 (87)	0.61±0.14 (97)	
	44	0.74±0.27	0.63±0.16 (85)	0.42**±0.08 (57)	0.40**±0.11 (54)	
	90	0.98±0.41	0.66±0.16 (67)	0.43**±0.07 (44)	0.47*±0.10 (48)	
AST (μkat/L)	-1	0.51±0.13	0.44±0.12 (86)	0.44±0.06 (86)	0.44±0.04 (86)	
	44	0.49±0.07	0.51±0.08 (104)	0.57±0.26 (116)	0.41±0.06 (84)	
	90	0.69±0.39	0.47±0.06 (68)	0.38**±0.01 (55)	0.37**±0.06 (54)	
Cholesterol (mmol/L)	-1	5.06±0.19	4.94±0.70 (98)	4.95±0.43 (98)	5.08±0.35 (100)	
	44	5.00±0.70	4.51±0.99 (90)	5.12±0.64 (102)	5.40±0.94 (108)	
	90	4.19±0.36	4.84±1.10 (116)	5.35±1.14 (128)	5.17±0.92 (123)	
Triglycerides (mmol/L)	-1	0.38±0.10	0.38±0.08 (100)	0.38±0.07 (100)	0.38±0.07 (100)	
	44	0.39±0.13	0.43±0.10 (110)	0.51±0.10 (131)	0.71**±0.09 (182)	
	90	0.33±0.03	0.44±0.16 (133)	0.49*±0.15 (149)	0.66**±0.11 (200)	

^a Data from pages 122-126 and 130-138, study report MRID 45404823.

^b Number in parentheses represent percent of control value, as calculated by reviewer.

^c The individual dog values for ALP were: 24.50, 11.21, 10.03, 9.83 and 9.20.

ALP = alkaline phosphatase, ALT = alanine aminotransferase, and AST = aspartate aminotransferase

* Significantly different (p < 0.05) from the control.

** Significantly different (p < 0.02) from the control.

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1. **Organ weight:** Biologically and statistically significant increases in absolute and relative (to body) liver weights occurred in a dose-related manner in treated males and females. Thyroid weights were slightly increased in treated males and females, with a dose-response present only in females.

TABLE 4. Terminal weights, selected mean absolute (g) and relative (to body) organ weights, and standard deviations in dogs fed BAS 510 F for 90+ days ^{a,b}				
Organ	Exposure concentration (ppm)			
	0	250	2500	25,000
Males				
Terminal BW	11040±808.1	12220±1331.2 (111)	11580±1520.5 (105)	12260±1835.2 (111)
Liver				
Absolute	357.234±16.6	401.44±36.6 (112)	420.836*±35.1 (118)	506.576**±61.6 (142)
Relative (%)	3.3±0.4	3.3±0.3 (100)	3.7±0.2 (112)	4.2*±0.3 (127)
Thyroid				
Absolute	0.830±0.26	0.964±0.16 (116)	0.924±0.18 (111)	0.954±0.14 (115)
Relative (%)	0.008±0.003	0.008±0.001 (100)	0.008±0.001 (100)	0.008±0.001 (100)
Females				
Terminal BW	11320±1147.6	11040±1101.4 (98)	11100±1268.9 (98)	10360±1422.3 (92)
Liver				
Absolute	321.882±24.1	332.17±51.5 (103)	381.932*±38.8 (119)	479.736**±63.0 (142)
Relative (%)	2.9±0.2	3.0±0.4 (103)	3.5*±0.3 (121)	4.7**±0.5 (162)
Thyroid				
Absolute	0.794±0.10	0.798±0.23 (101)	0.862±0.13 (109)	1.084±0.24 (137)
Relative (%)	0.007±0.001	0.007±0.002 (100)	0.008±0.001 (114)	0.010±0.001 (143)

Data taken from pages 151-154, study report MRID 45404823.

^a Values in parentheses represent percent of control, as calculated by reviewer.^b Standard deviations rounded to the first or second decimal place by reviewer.

* Significantly different (p < 0.05) from the control.

** Significantly different (p < 0.01) from the control.

2. **Gross pathology:** No gross lesions were noted in the liver of any animal. None of the macroscopic lesions reported for other organs were either dose-related or related to clinical or histopathologic findings.

3. **Microscopic pathology:** Microscopic evaluation of the livers from treated animals revealed no dose-related findings.

III. **DISCUSSION AND CONCLUSIONS**

- A. **INVESTIGATORS' CONCLUSIONS:** The investigators concluded that treatment-related effects occurred at the mid and high doses in both sexes. Reduced body weight gain and "slight impairment of" food efficiencies in both sexes at the high dose were noted by the authors. Treatment-related findings included the "marginal adverse effect" on RBCs in high-dose females, as evidenced by mild decreases in RBC and Hgb values; the elevated ALP activity in mid-dose females and in both high-dose groups, which was interpreted as a reflection of microsomal enzyme system induction; and the statistically increased triglyceride

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levels in the high-dose animals. Triglyceride elevations in the low and mid-dose groups were considered "incidental" by the investigators because (1) the control values were coincidentally low, (2) the magnitude of the increases, relative to the control values, was not notable, and (3) the levels in these groups were within the normal range of historical data for similar dogs. The increased liver weights in the mid and high-dose groups were considered treatment related, as were the increased thyroid gland weights in high-dose females. On the basis of their conclusions, the investigators established a NOAEL of 250 ppm for male and female dogs (7.6 and 8.1 mg/kg/day, respectively).

- B. **REVIEWER COMMENTS:** The elevated, dose-related triglyceride levels and increased ALP activities correlate with the increased hepatic weights in treated groups, suggesting toxicological relevance at the mid dose and above. Although possible sources of increased ALP activities are the bone and intestines, the absence of histopathological correlates in those organs indicates that the source is intrahepatic. Thus, the clinical chemistry and hepatic weight data point to intrahepatic congestion and extrahepatic cholestasis at the mid and high doses, which would also be supported by the slight elevations in triglycerides and prothrombin times. Because the histopathological report does not specify hepatic hypertrophy or hyperplasia, it is uncertain whether the increased hepatic weights reflect an adverse hyperplastic effect of the compound.

Although increased absolute thyroid weights were dose-related in females, only the high-dose had an elevated relative organ:body ratio (0.010% vs. 0.007% for the control). In the absence of associated findings (histopathological), the toxicological relevance of the increased thyroid weights in females is uncertain.

The LOAEL is 2500 ppm (σ^7 : 78.1 mg/kg/day, φ : 81.7 mg/kg/day), based on increased alkaline phosphatase activity and hepatic weights in the mid-dose dogs. The NOAEL is 250 ppm (σ^7 : 7.6 mg/kg/day, and φ : 8.1 mg/kg/day).

This subchronic study (MRID 45404823) is **Acceptable/Guideline** and satisfies the guideline requirement for a subchronic toxicity oral study [OPPTS 870.3150 (§82-1b) in the dog. There are several deficiencies, which are detailed in the "Study Deficiencies" section of this DER.

- C. **STUDY DEFICIENCIES:** The failure to note whether detailed cageside clinical examinations were conducted. Weights for the uterus, gallbladder, spleen, heart, and thymus were not obtained. The environmental conditions under which the animals were housed (temperature, humidity, etc.) should have been specified.

Minor deficiencies included the omission of peripheral blood sorbitol dehydrogenase analysis, and the failure to collect and examine tissues from the nose, pharynx, and larynx.

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 OPPTS 870.3150 [882-1b] (non-rodent); OECD 409

DATA FOR ENTRY INTO ISIS

Subchronic Oral Study - non-rodents (870.3150)

PC code	MRID #	Study type	Species	Duration	Route	Dosing method	Dose range: ppm, (mg/kg/day)	Doses tested: ppm, (mg/kg/day)	NOAEL: ppm; (mg/kg/day)	LOAEL: ppm; (mg/kg/day)	Target organ(s)	Comments
128008	454048 23	subchronic	dog	91-97 days	oral	dietary	250- 25,000 (7.6 - 824.8)	0, 250, 2500, 25,000 (♂: 0, 7.6, 78.1, 728.9; ♀: 0, 8.1, 81.7, 824.8)	250 ppm (♂: 7.6, ♀: 8.1)	2500 ppm (♂: 78.1, ♀: 81.7)	retarded body weight gain (females only), liver	