1/3/97

DATA EVALUATION REPORT

AZOXYSTROBIN

STUDY TYPE: CHRONIC ORAL TOXICITY [CAPSULE] - DOG (83-1(b))

Prepared for

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

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Toxicology Branch I (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Chronic Oral Toxicity [capsule] - Dog
OPPTS 870.4100 [§83-1(b)]

DP BARCODE: D218319 SUBMISSION CODE: S489692
P.C. CODE: 128810 TOX. CHEM. NO.: none

TEST MATERIAL (PURITY): ICIA5504 (AZOXYSTROBIN)(96.2% w/w)
SYNONYMS: methyl (E)-2-(2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl)-3-methoxyacrylate

CITATION: Allen, S. (1995) ICIA5504: 1 Year oral toxicity study in dogs. Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, U.K. Report number CTL/P/4440, November 21, 1994. MRID 43678140. Unpublished.

SPONSOR: Zeneca Inc. Agricultural Products, Wilmington, DE 19897.

EXECUTIVE SUMMARY: In a chronic toxicity study (MRID 43678140) ICIA5504 (96.2% w/w) was administered to 4 beagle dogs/sex/dose by capsule at doses of 0, 3, 25, or 200 mg/kg/day for 52 weeks.

No animals died prior to the scheduled termination date. The most notable treatment-related clinical observation was an increase in the incidence of fluid feces in both sexes at 200 mg/kg/day: there were 414 occurrences in 4/4 males and 115 in 4/4 females compared to 3 occurrences in 2/4 males and 6 in 2/4 females in controls (statistical analysis was not performed). High-dose females had minor increases in salivation compared to control females, although their combined frequency was similar to that of concurrent control males. Treatment-related clinical chemistry changes at 200 mg/kg/day ($p \le 0.05$ or 0.01) during one or more weeks included increased levels of plasma cholesterol (14-48%, both sexes), triglycerides (65-124%, both sexes), alkaline phosphatase (17-156%, both sexes), gamma-glutamyl transferase (74%-112%, females) and lowered plasma albumin (9.4-13%, males). Mid-dose males had increased cholesterol (23-27%) and triglycerides (65%). These results suggest an effect on liver and possibly biliary function. Minor and/or transient alterations ($p \le 0.05$ or 0.01) in the total plasma protein, bilirubin, calcium, phosphorus, urea, potassium, and sodium were observed in one or both sexes. There was a small decrease in absolute brain weight in high-dose males (6.5%, $p \le 0.05$) that is of uncertain biological significance, and a dose-related increase in liver weight in high-dose males (15%, $p \le 0.01$)

and in mid- and high-dose females (12%, $p \leq 0.05$ and 19%, $p \leq 0.01$, respectively). The increased liver weight and clinical chemistry changes observed in both sexes lacked histopathological correlates. There were no treatment-related effects on body weight, food consumption, ophthalmology, urinalysis, and gross or microscopic pathology in either sex of dogs.

The LOEL is 200 mg/kg/day, based on clinical observations, clinical chemistry changes, and liver weight increase occurring in both sexes at this dose. The NOEL is 25 mg/kg/day based on lack of significant treatment-related effects.

This chronic toxicity study is acceptable and satisfies the guideline requirement for a chronic oral study (83-1(b)) in dogs.

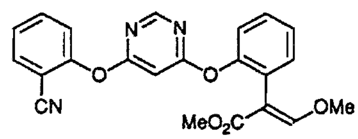
<u>COMPLIANCE</u>: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. <u>MATERIALS</u>

1. <u>Test material</u>: ICIA5504

   Description: light brown solid
   Lot/Batch #: Y06654/014/P49
   Purity: 96.2% (w/w) a.i.
   Stability of compound: stable at room temperature in dark, vented area
   CAS #: not available
   Structure:



2. <u>Vehicle and/or positive control</u>

   none; negative controls received empty capsules

3. <u>Test animals</u>

   Species: dog
   Strain: beagle
   Age and weight at study initiation: 21-24 weeks; individual weights ranged from 10.1-12.0 kg for males and 8.5-10.8 kg for females on day 1 of study.
   Source: Alderley Park, Macclesfield, Cheshire, U.K.
   Housing: 365 x 115 cm indoor pens with heated sleeping area. Dogs were housed in pairs or threes (same

256

sex) for at least 7 days, and individually thereafter.

Diet: Male dogs were fed 400 g and females 350 g of an expanded dry diet (Laboratory Diet A from Special Diets Services Ltd, Stepfield, Witham, Essex, U.K.).

Water: Potable water was supplied *ad libitum*.

Environmental conditions:

Temperature: 17-24°C (extremes of 12-28°C on occasion)
Humidity: not specified
Air changes: 10/hour
Photoperiod: 12 hours light per 24 hours

Acclimation period: at least 4 weeks

B. STUDY DESIGN

1. In life dates

Start: March 30 or April 6, 1993; end: April 1994

2. Animal assignment

Animals were assigned randomly to the test groups in Table 1, such that there was an even distribution according to litter and body weight among the groups.

TABLE 1: Study design

Test Group	Dose to Animal (mg/kg/day)	Number of Animals	
		Male	Female
Control	0	4	4
Low	3	4	4
Mid	25	4	4
High	200	4	4

Data taken from p. 14, MRID 43678140.

3. Dose selection rationale

The dose levels were selected based on results from previous dog studies performed in the performing laboratory--no further details were given.

4. Diet preparation and analysis

Animals were fed an expanded dry diet (see above) not containing any test material. The ICIA5504 was administered in gelatin capsules immediately prior to feeding each day; the amount of compound loaded into the capsules (by hand) was determined by the most recent body weight measurement and based on purity of 96.2%. Controls received empty gelatin capsules.

Results -
Homogeneity Analysis: not applicable; compound given by capsule

Stability Analysis: stability of compound in capsules was confirmed for the study duration, but actual final concentration was not given

Concentration Analysis: not applicable; compound given by capsule

5. Statistics

Statistical analysis was done by analysis of either variance or covariance using the GLM procedure in SAS (SAS Institute Inc. SAS/STAT User's Guide, Version 6, Fourth Edition, Volume 2, Cary, NC: SAS Institute Inc, 1989). The differences from the controls of the treated groups were represented by the differences in their least-squares means, and were tested statistically using a two-sided Student's t-test. Body weight changes were considered by analysis of covariance from day 1 weights, separately for males and females. Hematology, blood clinical chemistry, and urine clinical chemistry values were compared to pre-experimental values by analysis of covariance, except for monocyte and basophil counts, which were considered by analysis of variance. Male and female data was analyzed together to look for differences between control and treated groups that were consistent between the sexes. A covariate adjustment was made on the hematology and clinical chemistry parameters based on separate sex pre-experimental group means. Organ weight differences from controls were examined separately for males and females by analysis of variance and analysis of covariance on final

296

bodyweight. The presence of differential effects in left and right paired organs was investigated.

C. METHODS

1. Observations

Animals were inspected at least twice daily for signs of toxicity and mortality. They were given a thorough examination weekly, and a full clinical examination including cardiac and pulmonary auscultation at weeks 13, 26, 39, and prior to termination.

2. Body weight

Animals were weighed weekly (before feeding) throughout the pre-treatment period, on treatment day 1, and at weekly intervals thereafter.

3. Food consumption and compound intake

Food consumption for each animal was determined daily by measuring the food residues (which were thrown away) before each morning feeding. The compound was administered by gelatin capsules (mg/kg/day) based on animal body weight, and was independent of food consumption. Food efficiency was not calculated by the study author or by the reviewer, as there were no effects on body weight in either males or females.

4. Ophthalmoscopic examination

Eyes were examined by indirect ophthalmoscopy at weeks 13, 26, 39, and prior to termination.

5. Blood was collected from the jugular vein of all surviving animals before the morning feeding (i.e. after overnight fast) at weeks -1, 4, 13, 26, and 52 for hematology and clinical analysis. The CHECKED (X) parameters were examined.

306

a. <u>Hematology</u>

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

* Required for chronic studies based on Subdivision F Guidelines

b. <u>Clinical chemistry</u>

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

* Required for chronic studies based on Subdivision F Guidelines

316

6. Urinalysis

Urine was collected by catheterization from animals pre-experimentally and during weeks 26 and 52 (not specified whether fasted). The CHECKED (X) parameters were examined.

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

* Required for chronic studies

7. Sacrifice and pathology

All animals were sacrificed by sodium pentobarbitone anesthesia and exsanguination at study termination, and were subjected to gross pathological examination. The CHECKED (X) tissues were collected and examined histologically. The [XX] organs, in addition, were weighed.

36

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

1. Toxicity

There were some apparently treatment-related differences from controls in 200 mg/kg/day animals, although the clinical signs were not analyzed statistically. Comparing untreated controls to high-dose animals over a year's time, there was an increase in incidences of fluid feces in males (2/4 (3 occurrences) vs. 4/4 (414 occurrences)) and females (2/4 (6 occurrences) vs. 4/4 (115 occurrences)). High-dose females also had increased salivation (0/4 vs. 3/4 (21 occurrences)) and salivation at dosing (0/4 vs. 3/4 (80 occurrences)) compared to untreated control females, though their combined number of occurrences (101) was similar to that of concurrent control males (104).

356

2. Mortality

All animals survived to the scheduled termination date.

B. BODY WEIGHT

There were no effects on body weight or body weight gain in either sex at any dose of ICIA5504. The only statistically significant change seen was a 1.8% decrease in body weight at week 5 in high-dose females.

C. FOOD CONSUMPTION AND COMPOUND INTAKE

1. Food consumption

No treatment-related effects were seen in either sex. The dogs ate all their allocated food except for one mid-dose male at week 27 (8% residue) and one high-dose male at week 30 (12% residue).

2. Compound consumption

The compound was administered in gelatin capsules every morning before feeding, the amount given determined by the most recent body weight measurement (see Table 1).

D. OPHTHALMOSCOPIC EXAMINATION

No treatment-related effects were seen in either sex.

E. BLOOD WORK

1. Hematology

A number of parameters were significantly different from controls ($p \leq 0.05$ or 0.01). These were judged not to be toxicologically significant for a number of reasons, including: (1) small magnitude of difference (<5%: MCV in high-dose males, MCH at the low and/or high dose in both sexes, prothrombin time in low-, medium-, and high-dose females), and (2) lack of dose-response and/or transient nature (platelets in high-dose males, eosinophils in low-dose males, WBC in low-dose females, neutrophils in low- and mid-dose females, lymphocytes in mid-dose females, and kaolin-cephalin time in low-, mid- and high-dose females). The significance of the greatly lowered level of monocytes ($p \leq 0.05$) only at week 52 in mid- and high-dose males (55% and 75% lower, respectively) and in high-dose females (92% lower) is unclear. The monocyte counts were generally in the range of control values and had no histopathological correlates.

346

2. Clinical chemistry

Statistically significant alterations compared to concurrent controls ($p \leq 0.05$ or 0.01) were seen during one or more weeks in numerous parameters. In high-dose dogs of both sexes, there were increases in the levels of plasma cholesterol (14-48%; all weeks), triglycerides (65-124%; males weeks 26, 52; females, all weeks), and alkaline phosphatase (17-156%; males weeks 13-52; females all weeks). High-dose females had elevated gamma-glutamyl transferase (74-112%; weeks 4, 52), high-dose males had decreased plasma albumin (9.4-13%; weeks 13, 26, 52), and mid-dose males had increased cholesterol (23-27%; weeks 13, 26) and triglycerides (65%, week 52). These results are presented in Table 2, and are suggestive of impaired liver and possibly biliary function though there were no histopathological correlates. Other parameters altered at one or more weeks ($p \leq 0.05$ or 0.01) were transient and/or of uncertain biological significance. These include, in both sexes: minor changes in total protein (<7% increase/decrease, low and/or high dose) and small increases in plasma calcium (2.7-4.5%, low and/or mid-dose) and phosphorus (9.7-21%, high dose); in males: increased plasma urea (16%, low-dose) and potassium (6.5-11%, low and/or high-dose); and, in females: decreased plasma total bilirubin (30-32%, mid- and/or high-dose), elevated plasma sodium (1.9%, low dose) and plasma albumin changes (≤ 13% increase/ decrease, low and/or high dose).

356

TABLE 2: Clinical chemistry changes in dogs given ICIA5504[1]					
Parameter	Week	Dose (mg/kg/day)			
		0	3	25	200
Males					
Albumin (g/100 Ml)	-1	3.00	2.95	3.15	2.98
	4	3.01	3.10	3.13	2.94
	13	3.18	3.28	3.19	2.88**
	26	3.30	3.28	3.22	3.00*
	52	3.26	3.17	3.10	2.84**
Cholesterol (mg/100 mL)	-1	156	167	161	141
	4	147	155	160	183**
	13	137	146	174**	184**
	26	122	135	150**	181**
	52	125	133	147	172**
Triglycerides (mg/100 mL)	-1	36.0	33.3	30.5	34.0
	4	35.3	37.8	48.0	48.1
	13	24.1	27.4	29.4	31.6
	26	14.6	18.8	24.1	26.5*
	52	15.3	18.8	25.2*	30.0**
Alkaline phosphatase (IU/L)	-1	230	235	254	227
	4	224	222	225	220
	13	153	165	172	195*
	26	95	114	129	163*
	52	69	83	116	177**
Females					
Cholesterol (mg/100 mL)	-1	142	126	135	160
	4	148	152	147	169*
	13	143	146	150	175**
	26	147	135	154	205**
	52	149	146	151	189**
Triglycerides (mg/100 mL)	-1	25.5	26.0	30.3	30.0
	4	34.5	41.7	31.1	63.9**
	13	24.7	30.3	24.6	42.3**
	26	21.0	20.9	19.0	34.6*
	52	18.7	24.6	20.3	41.9**
Alkaline phosphatase (IU/L)	-1	255	264	236	244
	4	235	247	221	276*
	13	189	186	168	246**
	26	165	138	145	253**
	52	137	116	124	236**
Gamma glutamyl transferase (IU/L)	-1	1.5	1.3	1.0	2.3
	4	2.5	1.6	1.5	5.3*
	13	3.5	3.0	2.2	3.8
	26	3.5	2.7	3.4	2.6
	52	3.5	3.6	2.3	6.1*

Data taken from pages 89-124, MRID 43678140.
[1]The values presented for treatment weeks 4, 13, 26, and 52 are "adjusted means" that were obtained by making a covariate adjustment based on the separate sex pre-experimental group means.
Significantly different from control: *p ≤ 0.05; **p ≤ 0.01.

36b

F. URINALYSIS

The urine specific gravity was slightly increased ($\leq 1\%$, $p \leq 0.05$ or 0.01) in high-dose males and in low and mid-dose females at week 26. The urine pH in high-dose males at week 26 was lower than that of concurrent controls ($p \leq 0.05$), and in mid and low-dose males at week 52 was higher than concurrent controls ($p \leq 0.05$); the pH values measured were not dose-related and were similar to pre-experimental values. Neither of these quantitative changes were biologically or toxicologically significant. No treatment-related effects were seen in the qualitative urine tests or in urine cytology.

G. SACRIFICE AND PATHOLOGY

1. Organ weight

Only the absolute organ weights, with paired organ weights combined, were presented by the study author because there were no differential effects on the paired organs and there was no relationship of organ weight and final body weight. In males, there was a 6.5% decrease ($p \leq 0.05$) in absolute brain weight and a 15% increase ($p \leq 0.01$) in the liver weight at the high dose. In females, there was a 12% increase ($p \leq 0.05$) in liver weight at the mid-dose and a 19% increase ($p \leq 0.01$) at the high dose. The results are summarized below in Table 3. The small decrease in absolute brain weight in high-dose males was of unknown etiology and uncertain biological significance: it was not correlated with any histopathological findings, and the relative-to-body brain weight was not clearly affected (see Table 3).

The dose-related liver weight increase in both sexes, together with relevant clinical chemistry changes and lack of histopathological correlates, indicates that a treatment-related effect (adaptive response) was occurring in the liver which was biologically, but not toxicologically significant. The liver-to-body weights, as calculated by the reviewer, showed similar changes from control values as did the absolute weights (see Table 3).

TABLE 3: Organ weights (absolute and relative to body[1]) of dogs given ICIA5504				
Organ and Final Body Weight	Dose (mg/kg/day)			
	0	3	25	200
Males				
Body weight (kg)	15.90	16.38	15.50	15.35
Brain Absolute (g) Relative to body wt.[1]	 85.9 5.40	 84.8 5.18	 85.4 5.51	 80.3* (6.5) 5.23 (3.1)
Liver Absolute (g) Relative to body wt.[1]	 431 27.11	 431 26.31	 462 29.81	 496** (15) 32.31 (19)
Females				
Body weight (kg)	12.70	13.00	13.35	12.88
Brain Absolute (g) Relative to body wt.[1]	 78.0 6.14	 78.3 6.02	 77.8 5.83	 82.2 6.38
Liver Absolute (g) Relative to body wt.[1]	 338 26.61	 348 26.77	 379* (12) 28.39 (6.7)	 403** (19) 31.29 (18)

Data taken from pages 133 and 134, MRID 43678140.
Significantly different from control: *p ≤ 0.05; **p ≤ 0.01.
Numbers in parenthesis are the percent change relative to untreated controls calculated by the reviewer.
[1]Relative to body organ weight was calculated by the reviewer as (absolute organ weight x 1000)/body weight, and was not analyzed statistically.

2. Gross pathology

There were no treatment-related effects in either sex of dogs at any dose.

3. Microscopic pathology

a) Non-neoplastic - Lesions were seen in numerous organs, however, in all cases both the incidence and severity were comparable to controls. Lesions found were ones commonly seen in Alderley Park dogs of similar ages. Organs affected in one or both

386

sexes include the adrenals, cecum, duodenum, epididymis, eye, heart, jejunum, kidney, liver, lung, lymph nodes, parathyroid, pituitary, prostate, salivary gland, spinal cord, stomach, testis, thyroid, and trachea.

b) Neoplastic - No neoplastic lesions were found in any animals.

III. **DISCUSSION**

A. In a chronic toxicity study (MRID 43678140) ICIA5504 was administered to 4 beagle dogs/sex/dose by capsule at doses of 0, 3, 25, or 200 mg/kg/day for 52 weeks. Controls received empty gelatin capsules. Water was provided *ad libitum* and 350 g or 400 g food per female or male, respectively, was provided daily. The dogs were examined twice daily for clinical signs of toxicity and weighed weekly. Hematological and clinical chemistry parameters were measured at week -1 and during treatment weeks 4, 13, 26, and 52.

No animals died during this study. The major clinical observation was an increase in fluid feces in both sexes at only 200 mg/kg/day: there were 414 occurrences in 4/4 males and 115 in 4/4 females compared to 3 occurrences in 2/4 males and 6 in 2/4 females in controls (statistical analysis was not performed). High-dose females also had minor increases in salivation and salivation at dosing compared to female controls, although their combined frequency was similar to that seen in concurrent control males. It is unknown how these signs were caused by compound treatment; they are suggestive of a neurological effect or compound intolerance. The lack of histopathological correlates supports neither possibility and indicated the signs were not toxicologically important. Several hematology parameters were altered statistically significantly from controls ($p \leq 0.05$ or 0.01) including the MCV, platelets, and eosinophils in males; MCH and monocytes in both sexes; WBC, neutrophils, lymphocytes, kaolin-cephalin time and prothrombin time in females. These changes were not toxicologically significant because they were either transient, within 5% of controls, and/or lacked a clear dose-response. Additionally, there were no macroscopic or microscopic findings associated with the hematological changes.

A number of clinical chemistry parameters were significantly altered ($p \leq 0.05$ or 0.01) by compound treatment at one or more weeks compared to concurrent controls. In high-dose dogs of both sexes, there were increases in the levels of plasma cholesterol (14-48%; all weeks), triglycerides (65-124%; males weeks 26, 52; females, all weeks), and alkaline phosphatase (17-156%;

375

males weeks 13-52; females all weeks). Additionally, high-dose females had elevated gamma-glutamyl transferase (74, 112%; weeks 52, 4), high-dose males had decreased plasma albumin (9.4-13%; weeks 13, 26, 52), and mid-dose males had increased cholesterol (23-27%; weeks 13, 26) and triglycerides (65%, week 52). These changes are consistent with impaired liver function and possibly biliary function, and were accompanied by an increase in liver weight in high-dose males (15%, $p \leq 0.01$) and in mid- and high-dose females (12%, $p \leq 0.05$ and 19%, $p \leq 0.01$, respectively). The lack of histopathological correlates, however, suggests that the liver weight and clinical chemistry changes were an adaptive response to compound exposure. Small and/or transient alterations in other clinical chemistry parameters ($p \leq 0.05$ or 0.01) were not clearly related to treatment (both sexes: increased/decreased total plasma protein, increased plasma calcium and phosphorus; males: increased plasma urea, potassium; females: increased/decreased plasma total bilirubin, increased sodium).

There were no treatment-related effects on body weight, food consumption, ophthalmology, and gross or microscopic pathology in either sex of dogs. The minor alterations in pH and/or specific gravity ($p \leq 0.05$ or 0.01) of the urine in both sexes were spurious. The slight decrease in absolute brain weight in high-dose males (6.5%, $p \leq 0.05$) was of questionable biological significance. Based on the clinical observations, the clinical chemistry changes, and the small liver weight increase in both sexes, 200 mg/kg/day is the LOEL in both male and female dogs under the conditions of this study. The NOEL is 25 mg/kg/day due to a lack of significant treatment-related effects.

B. <u>STUDY DEFICIENCIES</u>

There were no major deficiencies that would compromise the interpretation or classification of this study. Minor deficiencies include failure to statistically analyze the clinical observations, to weigh the parathyroid glands, to provide historic controls for most of the parameters examined, and to give details of the dose selection rationale. It would have been helpful if the level of plasma glutamate dehydrogenase had been assayed as there were indications that the test compound was affecting the liver.

405