DATA EVALUATION REPORT

CGA-354743 (METOLACLOR ESA)
(METABOLITE OF METOLACHLOR)

STUDY TYPE: SUBCHRONIC ORAL TOXICITY FEEDING - DOG
[OPPTS: 870.3150 (§82-1b)]
MRID 44931709

4/25/01

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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DATA EVALUATION RECORD

STUDY TYPE: Subchronic Oral Toxicity- Dog [OPPTS: 870.3150 (§82-1b)]

DP BARCODE: D260393
P.C. CODE: 108801 (metolachlor)

SUBMISSION CODE: S570059
TOX. CHEM. NO.: 188DD

TEST MATERIAL (PURITY): CGA-354743 (99% a.i.)

SYNONYMS: none provided

CITATION: Altmann, B. (1999) 3-Month subchronic, comparative oral toxicity study in beagle dogs. Novartis Crop Protection AG, Toxicology, Stein, Switzerland. Laboratory Study Identification 971089, January 25, 1999. MRID 44931709. Unpublished.

SPONSOR: Novartis Crop Protection, Inc., 410 Swing Road, Post Office Box 18300, Greensboro, NC 27419.

EXECUTIVE SUMMARY: In a 90-day subchronic oral toxicity study (MRID 44931709), CGA-354743 technical (Batch Nos. KI-5408/4 and KI-5408/5, 99% a.i.) was administered to 4 purebred beagle dogs/sex/dose by capsule at dose levels of 0, 50, 200, 500, and 1000 mg/kg/day for 13 weeks. An additional group of 4 males and 4 females received parent compound (CGA-77102 technical, Batch No. P.501001, 98.5% a.i.) at 200 mg/kg/day for 13 weeks.

There were no significant treatment related effects on mortality, body weight, food consumption, food conversion ratios, ophthalmological findings, hematology and urinalysis parameters, or gross and histopathological findings. Vomiting did occur at a higher incidence in females treated with 1000 mg/kg/day of CGA-354743. Clinical signs in animals treated with CGA-77102 included vomiting, salivation and hematuria. Mean alkaline phosphatase activity was slightly increased in males receiving 1000 mg/kg/day CGA-354743 at weeks 7 and 13 to levels which were less than double the pretest mean for this group. This finding correlated with slightly increased absolute liver weights, but there were no corresponding histopathological findings, or toxicologically significant increases in other biochemistry parameters. In females, mean ALP activities remained within the reference range for untreated animals and mean GGT activity exceeded the reference range only at week 13 and only for the 500 mg/kg/day CGA-354743 group. Absolute liver weights and liver weights relative to body weights were increased in females receiving 500 and 1000 mg/kg/day. In the absence of corresponding histopathological findings or biologically significant increases in biochemistry parameters consistent with adverse hepatic effects, this finding is not considered toxicologically significant.

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Mean ALP and GGT activities were significantly increased in both sexes at weeks 7 and 13 given CGA-77102. In addition, ALT activity of males was increased at weeks 7 and 13. Absolute and relative liver weights were significantly increased in males and females. There were small increases in the incidences and severity of bile duct hyperplasia, perilobular fatty change in the livers of both sexes, and cystic hyperplasia of the gallbladder occurred only in the parent compound group.

The results appear to indicate that CGA-354743 may have effects (vomiting, slight increases in ALT and liver weight) similar to those of its parent compound, CGA-77102; however, at the limit dose, 1000 mg/kg/day, the effects observed were so slight and of questionable toxicological significance in CGA-35743-treated dogs that a definitive comparison of the two compounds cannot be made.

Based on the data presented in this study, the LOAEL was not determined, and the NOAEL was greater than or equal to 1000 mg/kg/day.

This subchronic oral toxicity study in dogs is classified as **Acceptable/Guideline** and satisfies the guideline requirements for a subchronic oral study [OPPTS: 870.3150 (§82-1b)] in dogs since the limit dose was tested.

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

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I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: CGA-354743 technical

   Description: solid
   Batch Nos.: KI-5408/4 and KI-5408/5
   Purity: 99% a.i. (Both batches)
   Stability of compound: not provided
   CAS #: not provided
   Structure: not provided

2. Parent compound: CGA-77102 technical

   Description: oil
   Batch No.: P.501001
   Purity: 98.5% a.i.
   Stability of compound: not provided
   CAS #: not provided
   Structure: not provided

3. Vehicle: none

4. Test animals

   Species: Dog
   Strain: Purebred beagle
   Age/weight at study initiation: males: 35 to 43 weeks, 11.20-13.70 kg; females: 34 to 49 weeks, 10.40-13.30 kg
   Source: Animal Production, Novartis Pharma AG, 4332 Stein / Switzerland
   Housing: 2/sex/dose in the same kennel. The dogs were chained for feeding.
   Diet: Certified pelleted standard diet (NAFAG 9405 Tox), 350 g/animal daily.
   Water: tap water, *ad libitum*
   Environmental conditions:
   Temperature: minimum room temperature of 15^0 C
   Humidity: not provided
   Air changes: not provided
   Photoperiod: 12 hour light/dark cycle
   Acclimation period: 16 weeks

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B. STUDY DESIGN

This study was designed to assess the subchronic oral toxicity potential of CGA-354743 technical when administered by capsule to dogs for 13 weeks and to compare its toxic effects with those of its parent compound, CGA-77102 technical.

1. In life dates - start: September 1, 1997; end: December 4, 1997

2. Animal assignment

Animals were assigned to the test groups in Table 1 by means of a randomized complete block design generated by SAS/STAT procedure PLAN (SAS Institute, Inc.), in order to avoid litter effects and provide homogenous mean body weights among groups.

TABLE 1: Study Design

Test Group	Test Article	Dose Level (mg/kg/day)	Male	Female
Negative Control	None	0	4	4
Low Dose	CGA-354743	50	4	4
Low-Mid Dose	CGA-354743	200	4	4
High-Mid Dose	CGA-354743	500	4	4
High Dose	CGA-354743	1000	4	4
Parent Compound	CGA-77102	200	4	4

Data taken from text table on p. 20, MRID 44931709.

3. Dose selection rationale

Dose selection for the test article and the parent compound was based on the results of a previously conducted rising dose-finding study in dogs (Laboratory Study ID 971088). CGA-354743 technical was administered to 2 male purebred beagle dogs by capsule at dose levels increasing from 350 to 1000 to 2000 mg/kg/day, with the high dose being given for 4 weeks. At 2000 mg/kg/day, the only observed effect was a slight increase in alkaline phosphatase activity.

CGA-77102 technical was administered to 2 male purebred beagle dogs by capsule at dose levels increasing from 50 to 100 to 200 mg/kg/day, with the high dose being given for 4 weeks. Dose levels of 350 or 500 mg CGA-77102 technical/kg/day were administered to either one or two female purebred beagle dogs; the phrasing in the report is unclear. The 350 and 500 mg/kg/day dose levels induced frequent vomiting and were therefore considered too high. The 200 mg/kg/day dose level was well tolerated for four weeks, and a slight increase in alkaline phosphatase activity was observed at this dose in one of the two males.

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The doses of CGA-354743 selected for this study were 50 mg/kg/day, which was expected to not induce any effects, 200 mg/kg/day to correspond to the dose selected for the parent compound, 500 mg/kg/day, which was expected not to induce any effects and to be a no-observable-effect level, and 1000 mg/kg/day, which represented a limit dose and was expected to cause minimal effects. The dose of CGA-77102 selected for this study was 200 mg/kg/day, which was expected to cause toxic effects in order to compare the toxicity of the two compounds.

4. Test article preparation and analysis

The test articles were administered in hard-gelatin capsules. Control animals received empty capsules. Capsules were prepared approximately weekly and the dosages were adjusted according to the body weight measurement from the preceding week. No analysis was performed because the test article and parent compound were used as supplied.

5. Statistics

For each time point and parameter a univariate statistical analysis was performed using nonparametric methods to allow for both normal and non-normal data distributions. Groups treated with CGA-354743 technical were compared to the negative control group using Wilcoxon's two-sample test and tested for trends by Jonckheere's test for ordered alternatives. The CGA-77102-treated group and the negative control group were compared using Wilcoxon's two-sample test. Two-sided asymptotic p-values were reported with significance levels of 4% and 1% for Wilcoxon's two-sample test and Jonckheere's test for ordered alternatives, respectively.

C. METHODS

1. Observations

Animals were observed twice daily for mortality, moribundity, and clinical signs.

2. Body weight

Animals were weighed once per week, starting a week before study initiation and throughout the study.

3. Food consumption

Food consumption was measured daily and reported as weekly means. Food consumption ratios (FCR) as "g food/kg body weight/day" were calculated weekly throughout the study.

4. Ophthalmoscopic examination

Ophthalmologic examinations were performed on all animals pre-dosing and towards the end of the treatment period. Mydriaticum™ (Ciba Vision) was used to induce mydriasis, and Novesin™ (0.4%) (Ciba Vision) was used for local anesthesia.

5. Blood was collected from all animals for hematology and clinical analysis pretest and during weeks 7 and 13 using jugular puncture after overnight fasting. The CHECKED (X) parameters were 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*	X	Reticulocyte count
	Blood clotting measurements*		
	(Thromboplastin time)		**OTHER**
	(Clotting time)	X	Red cell volume
X	(Prothrombin time)	X	distribution width
			Hemoglobin concentration distribution width

* Required for subchronic studies based on Subdivision F Guidelines

b. Clinical chemistry

	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*
		X	Total bilirubin
	ENZYMES	X	Total serum protein (TP)*
X	Alkaline phosphatase (ALK)	X	Triglycerides
	Cholinesterase (ChE)		Serum protein electrophoresis
X	Creatine phosphokinase		
	Lactic acid dehydrogenase (LDH)	X	A/G ratio
X	Serum alanine amino-transferase (also SGPT)*	X	Phospholipids
X	Serum aspartate amino-transferase (also SGOT)*		
X	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

* Required for subchronic studies based on Subdivision F Guidelines

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6. Urinalysis*

Urine was collected from fasted animals by catheterization pretest and during weeks 7 and 13. The CHECKED (X) parameters were examined.

X		X	
X	Appearance	X	Glucose
	Volume	X	Ketones
X	Specific gravity	X	Bilirubin
X	pH	X	Red blood cells
X	Sediment (microscopic)	X	White blood cells
X	Protein		Nitrate
		X	Urobilinogen

* Not required for subchronic studies.

7. Sacrifice and pathology

Animals were sacrificed at the end of week 13 via injection of T 61 (Hoechst) followed by exsanguination. Detailed necropsies were performed on all animals, and the CHECKED (X) tissues from each animal were preserved in 4% neutral buffered formalin, embedded in paraplast, sectioned, stained with hematoxylin and eosin, and subjected to microscopic examination. The (XX) organs, in addition, were weighed.

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

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II. RESULTS

A. MORTALITY AND CLINICAL SIGNS

No deaths or unscheduled sacrifices occurred during the study. The only treatment related clinical sign observed in animals receiving CGA-354743 technical was an increased number of occurrences of vomiting among females receiving 1000 mg/kg/day (8 occurrences vs. none for controls). These occurred mainly during the first two weeks of the study. Treatment related clinical signs observed from animals receiving CGA-77102 technical included increased numbers of occurrences of vomiting among both males (48 vs. none for controls) and females (111 vs. none for controls). Two females accounted for the majority of the occurrences. Gross hematuria was observed in the kennel of two males several times during weeks 7 and 12.

B. BODY WEIGHT AND WEIGHT GAIN

There were no statistically significant differences in absolute body weights between groups treated with the test material or parent compound and control groups during the study. However, the pretest mean absolute body weight of the male parent compound group was significantly greater than that of controls.

Body weight gain data are given in Table 2. For animals treated with the CGA-354743, there was a lot of variability between mean weight gains throughout the study, but statistical significance was seldom attained. In males receiving the test material, week 2 mean body weight gains were significantly decreased at 50, 200, and 500 mg/kg/day and week 3 mean body weight gains were decreased at 50 mg/kg/day. For females receiving the test material, week 2 mean body weight gains were significantly decreased at all dose levels with a negative trend evident up to the 500 mg/kg/day dose level. No consistent dose-related patterns were observed.

In animals receiving the CGA-77102, there were mean body weight losses in both sexes throughout the study, but statistically significant occurred only during weeks 1-5 and week 8 for males and during weeks 1-3 for females.

C. FOOD CONSUMPTION

1. Food consumption

There were no statistically significant differences in mean food consumption between treated and control groups during the study.

2. Food efficiency

Food efficiency was not determined by the study authors; however, food conversion ratios, which vary inversely as food efficiency, were calculated. There were no statistically significant differences in food conversion ratios between treated and

control groups during the study. Lower mean food consumption ratios were noted during weeks 2-4 for females treated with the parent compound due to the decreased food consumption by one female.

D. OPHTHALMIC EXAMINATION

There were no treatment related effects on ophthalmic examination findings in animals treated with the test material or parent compound.

E. CLINICAL PATHOLOGY

1. Hematology

Hematologic changes among animals treated with the CGA-354743 included increased absolute eosinophil counts among treated males at week 7 (0.158, 0.395, 0.550, 0.448, and 0.550 g/L) and week 13 (0.248, 0.480, 0.663, 0.675, and 0.670 g/L) for controls, 50, 200, 500, and 1000 mg/kg/day groups, respectively. The increase was statistically significant for the 1000 mg/kg/day group. The reference range for this parameter is 0.100-0.550 G/L (Appendix B, page 417).

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TABLE 2. Cumulative mean body weight gains (kg) of Beagle dogs administered CGA-354743 technical or CGA-77102 technical by capsule for 13 weeks.

Week	Control	CGA-354743 technical (mg/kg/day)				CGA-77102 tech. (mg/kg/day)
		50	200	500	1000	200
Males						
1	0.125	0.025 (-80)[a]	0.025 (-80)	0.000 (-100)	0.100 (-20)	-0.40*
2	0.175	0.050* (-71)	0.050* (-71)	0.000* (-100)	0.150 (-14)	-0.35*
3	0.200	0.000* (-100)	0.075 (-62)	0.125 (-37)	0.375 (+88)	-0.40*
4	0.250	0.050 (-80)	0.100 (-60)	0.125 (-50)	0.375 (+50)	-0.37*
5	0.250	0.125 (-50)	0.200 (-20)	0.100 (-60)	0.300 (+20)	-0.37*
6	0.175	0.075 (-57)	0.075 (-57)	0.025 (-86)	0.350 (+100)	-0.27
7	0.175	0.000 (-100)	-0.05 (-129)	0.000 (-100)	0.250 (+43)	-0.35
8	0.175	0.150 (-14)	0.125 (-29)	0.050 (-71)	0.250 (+43)	-0.35*
9	0.100	0.025 (-75)	-0.02 (-120)	0.000 (-100)	0.225 (+125)	-0.27
10	0.100	0.075 (-25)	0.050 (-50)	0.025 (-75)	0.250 (+150)	-0.35
11	0.200	0.125 (-38)	0.200	0.075 (+63)	0.500 (+150)	-0.27
12	0.125	0.100 (-20)	0.075 (-40)	0.025 (-80)	0.425 (+240)	-0.30
13	0.000	-0.02	-0.07	-0.02	0.300	-0.42
Females						
1	0.075	0.025 (-67)	0.050 (-33)	0.000 (-100)	0.050 (-33)	-0.30*
2	0.250	0.025* (-90)	0.000* (-100)	-0.05*# (-120)	0.100* (-60)	-0.32*
3	0.150	0.025 (-83)	0.100 (-33)	0.000 (-100)	0.075 (-50)	-0.37*
4	0.225	0.050 (-77)	0.125 (-44)	0.075 (-67)	0.175 (-22)	-0.45
5	0.300	0.050 (-83)	0.275 (-8)	0.000 (-100)	0.125 (-58)	-0.62
6	0.150	-0.02 (-113)	0.100 (-33)	0.100 (-33)	0.200 (+33)	-0.50
7	0.150	-0.02 (-113)	0.050 (-67)	0.075 (-50)	0.125 (-17)	-0.52
8	0.225	0.025 (-89)	0.075 (-67)	0.125 (-44)	0.150 (-33)	-0.37
9	0.100	0.000 (-100)	0.025 (-75)	0.025 (-75)	0.100	-0.42
10	0.100	0.000 (-100)	0.075 (-25)	-0.00 (-100)	0.150 (+50)	-0.32
11	0.200	0.100 (-50)	0.125 (-38)	0.000 (-100)	0.125 (-38)	-0.12
12	0.200	0.050 (-75)	0.075 (-63)	0.050 (-75)	0.225 (+13)	-0.20
13	0.100	-0.05 (-150)	0.000 (-100)	-0.02 (-120)	0.200 (+100)	-0.25

Data taken from Table 9.3, pp. 56-58, MRID 44931709.

* Significantly different than controls; $p<0.04$.

Significant negative trend from control up to the flagged dose level; $p<0.01$.

[a] Number in parenthesis equals percent greater than or less than control, calculated by reviewer.

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Other statistically significant inter-group differences were observed but were not considered to be treatment related because there was no dose-response pattern, the magnitudes of the changes were too small to be toxicologically significant, and/or the values were not appreciably different from pretest values.

2. Clinical chemistry

Selected clinical chemistry parameters are summarized in Tables 3 and 4. Alkaline phosphatase (ALP) activities were increased at week 7 in males receiving 1000 mg/kg/day and at week 13 in males receiving 500 and 1000 mg/kg/day CGA-354743. ALP activities of treated females remained within the reference range, although at 500 and 1000 mg/kg/day, ALP activities were slightly higher than controls. Gamma-glutamyl transpeptidase (GGT) activities were slightly increased in males at 1000 mg/kg/day CGA-354743 for week 7 and week 14, however, these values were within the reference range for untreated animals. In females, GGT activity was only increased above the reference range for the 500 mg/kg/day group and only at week 14.

For animals treated with CGA-77102, ALP and GGT activities were significantly increased in both sexes at week 7 and week 14. Albumin levels were decreased below the reference range in males at week 7 and week 13 while the mean globulin concentration was increased above the reference range for males at both time intervals. For males, mean ALT activity was increased at weeks 7 and 13 as compared with controls and referenced range values.

Other statistically significant inter-group differences were observed but were not considered to be treatment related and/or biologically significant because there was no dose-response pattern, the magnitudes of the changes were too small to be toxicologically significant, the values were not appreciably different from pretest values, or the values fell within the provided reference range for untreated animals.

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TABLE 3. Selected mean clinical chemistry parameters in male Beagle dogs administered CGA-354743 technical or CGA-77102 technical by capsule for 13 weeks.

Clinical Chemistry Parameter	Week	Treatment group						Reference Range
		Control	CGA-354743 tech. (mg/kg/day)				CGA-77102 tech. 200 mg/kg/day	
			50	200	500	1000		
ALP (U/L)	-1	85.95	91.30	91.60	77.95	82.75	82.33	56.60-137.7
	7	74.80	77.10	88.65	100.6	159.4#	265.4*	
	13	68.35	83.00	97.23	110.2*	141.4*#	308.7*	
GGT (U/L)	-1	2.800	3.100	2.950	3.025	3.275	2.225	0-5.4
	7	2.750	2.825	3.125	2.900	4.150*	6.350*	
	13	3.575	4.175	4.350	4.350	5.275*#	13.01*	
Albumin (g/L)	-1	31.31	32.34	32.28	32.13	32.41	32.95	30.53-36.14
	7	32.62	33.54	33.93	31.92	31.79	30.90	
	13	32.28	33.66	33.43	32.31	31.71	29.95*	
Globulin (g/L)	-1	24.20	24.68	24.53	25.47	25.78	24.26	21.45-28.22
	7	25.01	25.35	24.73	26.83	26.20	29.40*	
	13	26.73	27.48	26.17	28.39	27.41	29.52	
A/G ratio	-1	1.310	1.318	1.318	1.268	1.260	1.360	1.160-1.560
	7	1.303	1.335	1.375	1.195	1.223	1.058*	
	13	1.223	1.230	1.283	1.153	1.163	1.015	
ALT (U/L)	-1	56.65	67.83	56.30	55.48	46.20	51.78	36.30-61.60
	7	45.45	56.25	48.50	41.23	59.14	71.58	
	13	57.25	55.33	74.76	47.13	51.93	127.1	
Potassium (mmol/L)	-1	4.420	4.495	4.403	4.273	4.463	4.358	4.010-4.830
	7	4.205	4.400	4.385	4.345	4.383	3.895	
	13	4.281	4.245	4.149	4.075	4.173	3.858	

Data taken from Tables 9.10, 9.11, and 11.4 , pp. 132-139, 140-171, and 418-419, respectively, MRID 44931709.
* Significantly different than controls; $p<0.04$.
# Significant positive or negative trend from control up to the flagged dose level; $p<0.01$.

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TABLE 4. Selected mean clinical chemistry parameters in female Beagle dogs administered CGA-354743 technical or CGA-77102 technical by capsule for 13 weeks.

Clinical Chemistry Parameter	Week	Treatment Group						Reference Range
		Control	CGA-354743 tech. (mg/kg/day)				CGA-77102 tech. 200 mg/kg/day	
			50	200	500	1000		
ALP (U/L)	-1	78.88	91.38	73.98	82.23	66.38	72.70	48.7-123.6
	7	63.75	77.33	82.63	107.6*	116.0	211.9*	
	13	62.08	79.53	79.15	112.7*#	120.0	256.1*	
GGT (U/L)	-1	2.825	3.025	2.975	3.025	2.050	2.725	0- 5.1
	7	2.825	2.900	2.975	3.525	2.050	5.250*	
	13	1.800	3.950	3.750	5.450*#	4.650	8.525*	
Albumin (g/L)	-1	34.82	34.30	35.13	33.30	34.45	33.27	31.71-36.89
	7	35.45	35.14	35.09	32.92*	31.80*#	31.80*	
	13	36.10	35.48	35.93	33.20*	33.07*#	32.07*	
Globulin (g/L)	-1	25.00	23.22	24.60	25.41	23.88	24.44	20.30-26.95
	7	24.23	21.09	22.90	25.63	24.77	25.53	
	13	26.76	22.62*	24.59	28.38	26.20	29.10	
A/G ratio	-1	1.418	1.488	1.435	1.315	1.453	1.360	1.270-1.720
	7	1.478	1.678	1.538	1.288	1.295	1.253	
	13	1.363	1.573	1.468	1.168	1.273	1.118	

Data taken from Tables 9.10, 9.11, and 11.4 , pp. 132-139, 140-171, and 418-419, respectively, MRID 44931709.

* Significantly different than controls; $p<0.04$.
# Significant positive or negative trend from control up to the flagged dose level; $p<0.01$.

F. URINALYSIS

There were no treatment related effects on urinalysis parameters in animals treated with the test material or parent compound.

G. SACRIFICE AND PATHOLOGY

1. Organ weight

Selected organ weight data are given in Table 5. In animals treated with CGA-354743, absolute liver weights were increased in males at 1000 and females at 500 and 1000 mg/kg/day with a positive trend ($p<0.01$) evident in males at 1000 mg/kg/day. Relative liver weights were increased in females at 500 and 1000 mg/kg/day with a positive trend ($p<0.01$) evident at 1000 mg/kg/day. In animals treated with CGA-77102, absolute and relative liver weights were significantly increased in males and females. There were no other treatment related effects on organ weights.

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TABLE 5. Selected mean organ weight data of Beagle dogs administered CGA-354743 technical or CGA-77102 technical by capsule for 13 weeks.

Parameter	Control	CGA-354743 technical (mg/kg/day)				CGA-77102 tech. (mg/kg/day)
		50	200	500	1000	200
Males						
Liver weight (g)	344.2	314.8	344.8	373.4	375.1# (109)	470.2* (137)
Relative liver weight (%)	30.81	26.42	29.13	31.82	31.78	40.10 (130)
Females						
Liver weight (g)	288.1.	310.0	302.8	338.0 (117)	330.9 (115)	429.5* (149)
Relative liver weight (%)	26.03	27.44	27.95	29.55 (114)	30.12# (116)	40.02* (154)

Data taken from Tables 9.14-9.15, pp. 194-197, respectively, MRID 44931709.
* Significantly different than controls; $p<0.05$.
# Significant positive or negative trend from control up to the flagged dose level; $p<0.01$.
Number in parenthesis equals percent of control calculated by reviewer.

2. Gross pathology

There were no treatment related gross necropsy findings in the animals treated with the test material or the parent compound. Mottled lungs were observed in 7/24 males and 3/24 females with a random distribution among groups.

3. Microscopic pathology

Selected histopathology data are given in Table 6. There were no histopathology findings in the animals treated with CGA-354743. In the CGA-77102 group, there were small increases in the incidences and severity of bile duct hyperplasia and perilobular fatty change in the livers of both sexes as compared to controls and animals treated with the CGA-354743. Cystic hyperplasia of the gallbladder occurred only in the CGA-77102 group. Although, the incidence and severity of these findings were considered to be within the normal ranges for dogs of this age group, these findings were considered to be treatment related because they correlated with increased liver weights and changes in the biochemical profile. An unusual pattern of multifocal spermatic granulomata was observed in the testes of one male dog treated with the CGA-77102; it could not be determined whether this finding was treatment related. Acute bronchopneumonia (Grades 1-3) or chronic bronchopneumonia (Grades 1-2) were observed in male and females dogs representing all groups except the parent compound group. This finding was clearly not treatment related.

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TABLE 6. Incidences of selected histopathology findings in Beagle dogs administered CGA-354743 technical or CGA-77102 technical by capsule for 13 weeks.

Histopathology finding	Control	CGA-354743 technical (mg/kg/day)				CGA-77102 tech. (mg/kg/day)
		50	200	500	1000	200
Males						
Liver-						
Perilobular fatty change	0/4	0/4	0/4	0/4	0/4	4/4
Bile duct hyperplasia	1/4	0/4	0/4	1/4	1/4	4/4
Gallbladder-						
Cystic hyperplasia	0/4	0/4	0/4	0/4	0/4	2/4
Lungs-bronchopneumonia						
Acute	0/4	1/4	0/4	2/4	1/4	0/4
Chronic	0/4	1/4	1/4	0/4	0/4	0/4
Females						
Liver-						
Perilobular fatty change	0/4	1/4	0/4	0/4	0/4	2/4
Bile duct hyperplasia	0/4	1/4	1/4	2/4	0/4	4/4
Gallbladder-						
Cystic hyperplasia	0/4	0/4	0/4	0/4	0/4	3/4
Lungs-bronchopneumonia						
Acute	1/4	0/4	0/4	0/4	0/4	0/4
Chronic	0/4	1/4	0/4	0/4	2/4	0/4

Data taken from Pathology Report Summary Tables, pp. 467-469, MRID 44931709.

III. DISCUSSION

A. DISCUSSION

CGA-354743 technical: There were no significant treatment related effects on mortality, body weight, food consumption, food conversion ratios, ophthalmological findings, urinalysis parameters, or gross and histopathological findings. Eight occurrences of vomiting were observed among females at 1000 mg/kg/day. Vomiting is common among research dogs; however, because it occurred in the high dose animals, a treatment-related effect cannot be ruled out. Slight eosinophilia was observed in males at week 13 at 200, 500, and 1000 mg/kg/day with statistical significance being achieved for the 1000 mg/kg/day group. This finding was probably treatment related, as no findings consistent with other causes of eosinophilia (such as ecto- or endoparasites, food allergies, or allergic dermatitis) were identified among clinical signs, or gross and microscopic pathology findings. However, this finding is of questionable toxicological

significant. Males at 1000 mg/kg/day had increased mean ALP activities at weeks 7 and 13 which were both less than double the pretest mean for this group. This finding correlated with slightly increased absolute liver weights (9% greater than controls), but there were no corresponding histopathological findings, or increases in other biochemistry parameters (ALT, AST, GGT, bilirubin) which might indicate a significant adverse hepatic effect. Although GGT activity was significantly increased in males at 1000 mg/kg/day at week 7 and week 13, these values were within the reference range for untreated animals, and this finding is therefore not considered to be biologically significant. In females, mean ALP activities remained within the reference range for untreated animals, and mean GGT activity exceeded the reference range only at week 13 and only for the 500 mg/kg/day group. The study author also mentions decreased mean albumin concentrations and increased mean globulin concentrations in females at 500 and 1000 mg/kg/day. The only values outside the reference ranges were week 13 mean globulin concentration and A/G ratio for the 500 mg/kg/day group, not the high dose group. Absolute liver weights were increased in females at 500 and 1000 mg/kg/day and relative liver weights were increased in females at 500 and 1000 mg/kg/day with a positive trend evident at 1000 mg/kg/day. In the absence of corresponding histopathological findings or biologically significant increases in biochemistry parameters consistent with adverse hepatic effects, this finding is of questionable toxicological significance.

CGA-77102 technical (200 mg/kg/day): There were no significant treatment related effects on mortality, ophthalmological findings, urinalysis parameters, or gross necropsy findings. Clinical signs included vomiting, salivation, and hematuria. Food consumption was transiently decreased in one female. Both groups exhibited mean weight loss throughout the study, although there was no effect on mean absolute body weights. Mean ALP and GGT activities were significantly increased in both sexes at weeks 7 and 13 . Albumin levels were decreased below the reference range while globulin concentrations were increased in males at weeks 7 and 13. Globulin concentrations were increased above the reference range for females at week 13 only. For males, mean ALT activity was increased at weeks 7 and 13 as compared with controls and the reference range for untreated animals. Absolute and relative liver weights were significantly increased in males and females. There were small increases in the incidences of bile duct hyperplasia and perilobular fatty change in the livers of both sexes as compared to controls and animals treated with CGA-354743, and cystic hyperplasia of the gallbladder occurred only in the parent compound group. These findings were considered treatment related because they correlate with increased liver weights and changes in the biochemical profile.

A comparison of the effects of the two compounds indicates that CGA-354743 may have effects similar to those of its parent compound, CGA-77102; however, the data indicate that CGA-354743 needs substantially higher dose levels than that of the parent compound to obtain similar adverse effects. A definitive comparison of the two compounds cannot be made based on the results of this study.

Based on the data presented in this study, the LOAEL for CGA-354743 technical was not determined and the NOAEL was greater than or equal to the limit dose of 1000 mg/kg/day.

This subchronic oral toxicity study in dogs is classified as **Acceptable/Guideline** and satisfies the guideline requirements for a subchronic oral study since the limit dose was tested [OPPTS: 870.3150 (§82-1b)] in dogs.

B. STUDY DEFICIENCIES

There were no major deficiencies in the conduct of this study; however, the following minor deficiencies were noted. Animals were assigned to test groups by means of a randomized complete block design intended to avoid litter effects and provide homogenous mean body weight among groups. This was done immediately after the animals arrived at the lab, and when the study began 16 weeks later, the mean body weight of the male CGA-77102 group was significantly greater than that of controls. At initiation of dosing, males were up to 43 weeks old and females were up to 49 weeks old; however, the guideline specifies that dosing should commence "not later than 9 months of age." Housing the animals in groups of two made it impossible to accurately determine which and how many animals were exhibiting the clinical signs of vomiting, diarrhea, and hematuria. A brief description of the histopathology grading criteria should have been included for findings which were assigned a grade. Also, although the high incidence bronchopneumonia was not treatment related, it should have been mentioned and addressed by the study author.

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