Shaughnessy File
CASWELL FILE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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APR 17 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: 6(a)(2) 26-Week Oral Feeding Study of CGA 169374 in Dogs §82-1

Project No.: 2-0696 Shaughnessy No. 128847

FROM: K.E. Whitby, Ph.D. 4/16/92
Review Section II, Tox Branch II (H7509C)

TO: James Stone PM 22
RD (H7505C)

THRU: K.C. Swentzel, Section Head K. Clark Swentzel 4/17/92
Review Section II, Tox Branch II (H7509C)

and

Marcia van Gemert, Ph.D., Chief Marcia van Gemert 4/17/92
Tox Branch II, HED (H7509C)

Please find attached the Data Evaluation Record (DER) for the subject study. This study was flagged as 6(a)(2). CGA 169374 technical was administered in the diet to beagle dogs at 0, 100, 1000, 3000, or 6000 ppm for a minimum of 28 weeks. The LOEL and the NOEL respectively were, 3000 ppm and 1000 ppm. The most outstanding effect was bilateral lenticular cataracts, which was observed in 3 out of 3 animals/sex in the 6000 ppm group by ophthalmoscopic examination. The incidence in this group by microscopic exam was 3/3 females with bilateral cataracts and 2/3 males with unilateral cacaracts and 1/3 males with bilateral cataracts (3/3 males were observed to have cataracts). One female fed 3000 ppm was observed to have bilateral cataracts by ophthalmoscopic examination. Microscopic examination found the incidence in males to be 1/3 with bilateral cataracts and the incidence in females to be 2/3 with unilateral cataracts and 1/3 with bilateral cataracts. Ocular effects were not observed at dietary levels ≤ 1000 ppm. Additional findings included iridic changes secondary to induced uveitis. reductions in mean body weight and food consumption, and alterations in hematology and clinical chemistry.

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These observations as reported appear to be real treatment related effects. However, due to the fact that the cataracts only occur at high doses in the current study ($\geq$ 3000 ppm), and were not observed in the chronic dog study up to 1500 ppm (HDT), TBII is not of the opinion that these findings would present a risk at the proposed levels of human exposure (the proposed tolerance is 0.1 ppm each for wheat, barley, and rye grains).

The remaining studies under this action will be submitted collectively upon completion of their review since they were not flagged as 6(a)(2).

Reviewed by: Dan W. Hanke, Ph. D. Dan W Hanke 01 April 1992
Section III, Tox. Branch II (H7509C)
Secondary Reviewer: James N. Rowe, Ph. D. James N. Rowe 4/1/92
Section III, Tox. Branch II (H7509C)

DATA EVALUATION RECORD

STUDY TYPE: 26-Week Oral Feeding Study (§82-1)

TOX. CHEM. NO. (CASWELL NO.): new chemical

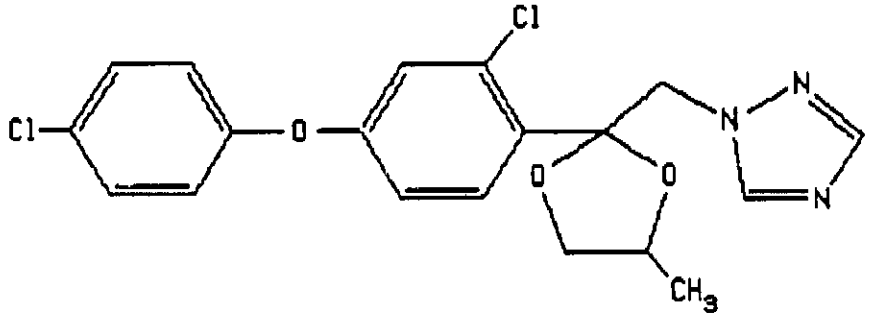
CAS REG. NO.: 119 446-68-3

EPA PESTICIDE CHEMICAL CODE/ACTIVE INGREDIENT CODE (SHANGHNESSY NO.): 128847

HED PROJECT NO.: 2-0696

MRID NO. (ACCESSION NO.): 420900-12

TEST MATERIAL: CGA-169374 Technical; 1-[2-(2-chloro-4-(4-chlorophenoxy)phenyl)-4-methyl-1,3-dioxolan-2-yl)-methyl]-1H-1,2,4-triazole



SYNONYMS: Difenoconazole; Dividend; triazole fungicide

STUDY NUMBER: 852197

SPONSOR: Agricultural Division
Ciba-Geigy Corporation
P. O. Box 18300
Greensboro, NC 27419

TESTING FACILITY: Research Department
Pharmaceuticals Division
Ciba-Geigy Corporation
556 Morris Avenue
Summit, NJ 07901

TITLE OF REPORT: 26-Week Oral Toxicity Study in Dogs

AUTHOR(S): Dennis J. O'Connor, Ph. D.

REPORT ISSUED: October 30, 1987

SUMMARY AND CONCLUSIONS:
CGA 169374 was offered in feed admixtures to five groups of beagle dogs composed of three animals/group/sex in dietary concentrations of 0 ppm, 100 ppm, 1000 ppm, 3000 ppm, or 6000 ppm for a minimum of 28 weeks. None of the dogs DOS. Compound-related effects developed essentially at the 3000 ppm and 6000 ppm dose levels. The singularly most striking compound effect was bilateral lenticular cataracts ophthalmoscopically-observed in all dogs at 6000 ppm and in one female beagle at 3000 ppm. Additionally, iridic changes (irregular pupillary margins, miosis), secondary to lens induced uveitis, were also present in the affected animals. There were also reductions in mean body weight in females and males at 6000 ppm test compound throughout the study; weight loss was observed during the first three weeks on study. Body weight loss was precipitated by moderate to severe reductions in mean food consumption in females and males at 6000 ppm during the study with slight reductions observed in males at 3000 ppm and 1000 ppm and in one female at 3000 ppm. Furthermore, there were slight reductions in values for red blood cell count, hemoglobin, and hematocrit in females and males at 6000 ppm. There were also decrements in some serum clinical chemistry measurements including calcium and total protein in females at 6000 ppm and moderate increases in serum alkaline phosphatase in one or both sexes at $\geq$ 3000 ppm. There were modest alterations in several absolute and/or relative organ weight measurements to include the heart, prostate gland, salivary gland, uterus, kidney, liver, and brain at the highest dose tested (HDT). Nevertheless, liver weight measurements were also increased in Group 4 females. There were no other test article-related changes in any other parameter examined. On the strength of the available data as they relate to the dose levels tested and the parameters observed, the LOEL and the NOEL for the test article in female and male beagle dogs were 3000 ppm and 1000 ppm, respectively, based primarily on microscopic examination of CGA 169374-related lenticular cataracts.

A signed quality assurance statement was present.
Flagging Statement Present: (40 CFR 158.34) 6(a)(2). Cataracts

Core Classification: Minimum
This study satisfies the guideline requirements (§82-1) for a Subchronic feeding study in dogs. Although reported as 6(a)(2) data, this study is not considered to represent findings of unusual risk concern at this time; the cataracts were observed at relatively high dose levels. Examination, however, of other long-term toxicity data for parallel findings is recommended.

MATERIALS:

1. Test compound. CGA-169374 Technical; difenoconazole; 1-[2-(2-chloro-4-(4-chlorophenoxy)phenyl)-4-methyl-1,3-dioxolan-2-yl)-methyl]-1H-1,2,4-triazole. Description: dark brown solid. Batch #: FL-851406. Purity: 94.5 % run on batch # ACL-5668 (from the rat subchronic/metabolism study); the solvent was dehydrated ethanol. Stability: difenoconazole was stable for at least 24 hrs at room temperature (unspecified) and for 22 days at 6 °C over a concentration range of 0.5 % to 50.0 %. The stability determinations were made on representative samples via gas chromatography equipped with a nitrogen-phosphorus detector. The test article was not detected in the control samples.

2. Test animals.
Species: Dog. Strain: pure bred beagle, 15 males and 15 females. Age: At the initiation of treatment dogs were approximately five to six months old. Weight: the range was 7.9 kg to 9.5 kg for males and 7.1 kg to 8.5 kg for females. Source: Marshall Farms, North Rose, New York.

METHODS:

1. Animal dosing/assignment
Dosing Schedule: Roughly 400 gram portions of the test article feed mixture or control diet were presented to the dogs daily for approximately 3-4 hrs for at least 28 consecutive weeks according to the schedule in table 1 below extracted from p 4 of the study report. Water was available ad libitum during the predosing and dosing periods. Dogs were assigned to treatment groups or to the control group by use of a computer-generated randomization table.

Table 1. Dosing Schedule[a]

Group	Number of dogs		Dietary level of test article (ppm)	Least number of dose weeks
	Male	Female		
1 (Control)	3	3	0[b]	28
2	3	3	100	28
3	3	3	1,000	28
4	3	3	3,000	28
5	3	3	6,000	28

[a]Data were extracted from p 4 of the study report.
[b]Dogs were fed untreated Purina Canine Diet #5007.

2. Diet preparation and dosage form.
The test substance was prepared as an admixture of CGA 169374 Technical in powdered Purina Lab Canine Diet # 5007 by Toxicology/Pathology Administration and Technical Operations (TPATO). CGA 153935 Technical was dissolved in acetone and premixed with an appropriate amount of feed. The acetone was evaporated overnight and the resulting premix was used in preparing the test substance/feed admixtures. The control/feed admixtures were prepared in a similar manner. The control feed was used prior to the expiration date. The frequency of test substance preparation was based on established stability data. The admixtures have been shown to be stable for 15 days at room temperature. The stability range covered the actual conditions of use of the admixtures at 100 ppm, 1000 ppm, 3000 ppm, and 6,000 ppm. TPATO determined the homogeneity and concentration of the feed admixtures. The test article concentration and homogeneity were measured in each feed admixture utilized during weeks 1, 5, 9, 13, 19, 24, and 28. The results of the analyses are summarized in appendix 1 of this DER, taken from pp 399-400 of the study report, and reflect acceptable stability, concentrations, and homogeneity of the test article in the feed admixtures.

3. Statistics.
The following procedures were utilized in analyzing the data. Analyses were performed separately for each sex. At pre-dose time points, F-tests were performed for the equality of all treatment means. If an F-test at the last pre-dose time point (baseline) was nonsignificant, then two-sided Dunnett's multiple comparisons with experiment-wise Type I error rate 0.05 were employed at all time points after the start of dosing. These tests detected possible differences between each of the treatment means against the control mean. If a significant difference was found via Dunnett's test, then the test procedure was employed again with experiment-wise Type I error rate 0.01. If an F-test at the baseline was significant, then analyses of covariance were performed at all times after dosing started. These analyses used the baseline measurements as a covariate. Nonparametric versions of the above test procedures based on ranks were performed on those parameters that were known not to be normally distributed (e.g., highly skewed distributions). Mean, Minimum, and Maximum were used as the summary statistics instead of Mean and Standard Error. Both the test statistics values (F-tests for parametric analyses and Kruskal-Wallis Chi-square tests for nonparametric analyses) and the p values were reported.

A more complete review of the statistical methods with references is in appendix 2 of this DER taken from pp 28-32 of the study report.

RESULTS AND DISCUSSION:

Clinical Signs.
The battery of clinical observations was performed according to the schedule shown in appendix 3 of this DER taken from pp 5-7 of the study report. They are summarized and discussed in turn below.

Mortality.
All the dogs survived the treatment period, and all animals, except those in Group 5 (the HDT), were in good physical condition when sacrificed at the termination of the study.

Body weight, percent body weight gain, and food consumption.
Select mean data of statistical significance regarding the effect of CGA 169374 on body weight, percent body weight gain, and food consumption for each week on test are shown below in table 2 for female beagles and in table 3 for male beagle dogs excerpted from pp 45-85 of the study report. Mean body weight changes at the end of the dosing period are shown in table 4 taken from p 40 of the study report. Treatment-related reductions in mean body weight, percent body weight gain, and in food consumption were recorded in the HDT group 5 female and male beagles throughout the test period. The HDT group dogs lost weight during the first three weeks of the treatment. However, stabilization and body weight gain were subsequently observed. There were no statistically significant differences in body weight noted between Groups 2, 3, or 4 when paired with the control group. At the end of the study the mean percent body weight gain for the HDT females and males was approximately -15 % and -12 % respectively. There was a positive correlation between decrements in body weight and decrements in food consumption. At the end of the study mean food consumption of the HDT group ranged from 65 % to 73 % of the control group with less dramatic, although statistically significant, decreases seen in the two mid-dose tested (MDT) group 3 & 4 males (1000 ppm and 3000 ppm respectively).

Table 2. Statistically significant effects of CGA 169374 on body weight, percent body weight gain, and food consumption in female beagle dogs during the dosing period as compared to the group one control data included below for comparison

	Days on study for female beagle dogs																										
Grp. #/Var	7	14	21	28	35	42	49	56	63	70	77	84	91	98	105	112	119	126	133	140	147	154	161	168	175	182	189	196
1/bw	7	7	7	8	8	8	8	8	8	8	8	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
1/bwg	7	6	4	0	2	2	4	8	9	11	11	11	12	11	15	13	13	13	13	12	14	15	16	18	18	20	21	21
1/fc	1	2	2	2	2	2	2	2	2	3	2	2	2	2	2	2	2	2	2	2	2	2	2	3	2	3	3	2
5/bw		6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
5/bwg	18	22	23	21	21	20	20	18	18	18	18	18	18	17	17	17	17	19	21	20	20	20	20	17	17	16	15	15
5/fc	.3	.6	.8	1		1	1	2	1	2	1		1	1	2				1	2	2	2	2	2	2	2	2	

Legend
Data were extracted from pp 45-85 of the study report and then rounded off.
Grp. # = group number: 1 = control; 5 = 6000 ppm
Var = variable or parameter
bw = body weight in kg
bwg = % body weight gain
fc = food consumption in kg
bolded entries represent decrements in the variable
blank entries are place holders for data of nonstatistical significance.

Table 3. Statistically significant effects of CGA 169374 on body weight, percent body weight gain, and food consumption in male beagle dogs during the dosing period as compared to the group one control data included below for comparison

	Days on study for male beagle dogs																										
Grp. #/Var	7	14	21	28	35	42	49	56	63	70	77	84	91	98	105	112	119	126	133	140	147	154	161	168	175	182	189	196
1/bw	8	8	8	9	9	10	10	10	10	10	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
1/bwg	4	2	.4	5	8	11	13	17	18	22	23	25	25	26	28	27	26	28	27	26	27	27	26	28	30	29	28	28
1/fc	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	2	3	3	2	3	2	3	3	3	3	2
3/bw	----------																											
3/bwg	----------																											
3/fc	-	2	2	2	2	2	-----		2	--	2	----------													2	----------		
4/bw	----------																											
4/bwg																												
4/fc	1	2	2	2	----------																							
5/bw	----------				7	----------			8	8	8	8	8	8	8	8	8	8	7	7	8	8	8	8	8	8	8	
5/bwg	15	20	20	18	17	15	14	13	12	11	11	11	10	10	8	9	9	11	13	15	15	14	14	13	13	12	10	12
5/fc	.3	.5	.7	2	1	2	1	2	2	2	1	1	1	2	2	1	1	1	1	2	1	2	2	2	2	2	---	1

Legend
Data were extracted from pp 45-85 of the study report and then rounded off.
Grp. # = group number: 1 = control; 2 = 100 ppm; 3 = 1000 ppm; 4 = 3000 ppm; 5 = 6000 ppm
Var = variable or parameter
bw = body weight in kg
bwg = % body weight gain
fc = food consumption in kg
bolded entries represent decrements in the variable
----- dashed entries denote data of nonstatistical significance

Table 4. Mean body weight change at the end of the dosing period[a]

Group	Dose Conc. (ppm)	Females			Males		
		Body Weight (kg)		Per Cent[b]	Body Weight (kg)		Per Cent[b]
		Baseline	Week 29	Change	Baseline	Week 29	Change
1	0	7.73	9.33	+20.7	8.57	11.03	+28.4
2	100	7.50	9.37	+24.6	8.67	11.03	+27.1
3	1000	7.80	9.43	+21.2	8.20	10.27	+25.4
4	3000	8.10	8.47	+4.2	8.97	10.13	+12.6
5	6000	7.47	6.33[c]	-15.1	8.67	7.67[c]	-11.7[d]

[a]Body weight data were taken from p 40 of the study report.
[b]Relative to baseline body weight
[c]Statistically different from control p = 0.05
[d]Statistically different from control p = 0.01

The average daily dose of test article over the course of the study is shown below in Table 5 taken from p 11 of the study report. In groups 2-4 test material intake was similar for both female and male dogs. The increased intake of compound in females over males in group 5 at the highest dose tested (HDT) was not statistically significant. The data for mean daily doses for each week of treatment can be found on pp 41-44 of the study report.

Table 5. Mean daily doses and range for CGA 169374 Technical

Group	Sex	Feed Concentration (ppm)	Mean Daily Dose (mg/kg)	Range (mg/kg/day)
2	F	100	3.4	2.9- 4.0
3	F	1000	34.8	25.3- 42.8
4	F	3000	110.6	56.1-126.9
5	F	6000	203.7	39.8-268.0
2	M	100	3.6	3.2- 4.2
3	M	1000	31.3	26.5- 35.8
4	M	3000	96.6	50.6-111.6
5	M	6000	157.8	27.9-192.0

Data were extracted from p 11 of the study report.

Ophthalmology.
Ophthalmoscopic examinations performed during the course of the study revealed ocular changes attributable to the administration of the test article CGA-169374 Technical. The week 11 examinations revealed bilateral subcapsular, equatorial, anterior cortical and posterior cortical lenticular aberrations (cataracts) affecting all dogs from group 5, and in one group 4 female dog. Microscopic examination revealed uni- or bilateral cataracts in all three female dogs and 1/3 of the males in group 4 at the 3000 ppm dose level. The lenticular changes were characterized as vacuoles, water clefts, spoke-like opacities, and splitting and separation of the lens suture lines with resultant "y"- shaped fissures, that is snowflake-like cataracts. At this point in the study there was no apparent visual deficit, and all other ocular structures appeared clinically unaffected in addition to no observed changes in the rest of the dogs on study. Subsequent examinations performed about every two weeks showed slight to marked progression of the lenticular aberrations in the affected animals. These changes included an increase in vacuoles, opacities and feathering of the lens suture, and the appearance of mature cataracts. Also, iridic changes were displayed as irregular pupillary margins, and miosis was considered to have occurred from lens-induced uveitis in concert with rapidly developing cataracts. There were no changes from normal seen in the eyes of the other dogs in group 4 or any animal in groups 2 and 3 on study. A summary of the incidence of ophthalmoscopic and microscopic ocular findings is in table 6 below taken from p 20 of the study report. A more detailed summary of ocular effects denoting the specific week on study when a given effect was observed is presented in appendix 4 of this DER, where the data were taken from pp 351-352 of the study report. Weekly group ocular findings can be found on pp 342-350 of the study report.

Table 6. Summary incidence of ophthalmoscopic and microscopic ocular findings

		Animal Group Number & Dose Level of CGA 169374			
		Group 4/3000 ppm		Group 5/6000 ppm	
		Male	Female	Male	Female
Ophthalmoscopic					
Lens:	Cataract				
	Unilateral	0/3	0/3	0/3	0/3
	Bilateral	0/3	1/3	3/3	3/3
	Total	0/3	1/3	3/3	3/3
Microscopic					
Lens:	Cataract				
	Unilateral	0/3	2/3	2/3	0/3
	Bilateral	1/3	1/3	1/3	3/3
	Total	1/3	3/3	3/3	3/3

These data were taken from p 20 of the study report.

Hematology.
There were statistically significant differences between paired groups. The mean platelet counts were elevated in group 5 males on days 116 and 191; mean percent monocytes were reduced on day 191 in males (groups 2 and 4); mean percent eosinophils were increased on day 191 in the males of group 3. These changes, however statistically significant, were considered incidental and of little toxicological significance. In fact the statistical significance of the elevated platelet count appeared to be partially related to low control values at the time points cited, and there was no clear dose-response relationship established. Additionally, no dose-response relationship was identified for the changes in monocytes and eosinophils as well, and in the absence of other supportive findings these changes were not considered toxicologically significant. Although not statistically significant there were slight reductions observed in red blood cell (rbc) count, hematocrit and hemoglobin in the HDT animals on day 191. These decrements appeared to be secondary to test article reductions in body weight and body weight gain. Paired data that were statistically significantly different are presented in appendix 5 of this DER taken from pp 96, 97, and 100 of the study report. All other determinations for groups 3, 4, and 5 were comparable to control values. The parameters examined are shown in Table 7.

Table 7. Hematology parameters[a] examined (x).

x	Hematocrit (HCT)*	x	Leukocyte differential count*
x	Hemoglobin (HGB)*		Mean corpuscular HGB (MCH)
x	Leukocyte count (WBC)*		Mean corpusc. HGB conc.(MCHC)
x	Erythrocyte count (RBC)*		Mean corpusc. volume (MCV)
x	Platelet count*	x	Reticulocyte count[b]
x	Blood clotting measurements	x	Heinz body
	(Thromboplastin time)		Erythrocyte morphology
	(Clotting time)		
x	(Prothrombin time)		

[a] Blood samples were obtained from the jugular vein of each dog. During the treatment period, these samples were taken prior to food presentation.
[b] Reticulocyte counts and Heinz body determinations were performed for all dogs during the pretreatment period and on control (Group 1) and high-dose (Group 5) dogs during the treatment period.
* Required for subchronic and chronic studies

Serum biochemistry.
There were some statistically significant differences between treatment groups and controls. Mean serum total protein was reduced in group 3 males on days 116 and 191; whereas mean SGOT was reduced in groups 3 and 5 males on day 116. The mean BUN was decreased in female dogs in group 3 and/or group 4 on days 116 and 191; as well as mean serum LDH levels were decreased in group 2 females on day 191. In each of the above-cited cases no toxicological or biological significance was attached to these findings. Furthermore, no evidence of a dose-response was noted, and most of the values were equivalent or in near approximation to control or the baseline values.

There were some modest, statistically significant reductions in mean serum total protein and calcium levels observed in group 5 females on day 191. However, it is feasible these reductions are secondary to the moderate to severe reductions in food intake that were noted primarily at the HDT. The mean serum alkaline phosphatase levels were moderately increased in group 5 males on day 116, and these levels remained elevated on day 191; this latter change, however, was not statistically significant. In the female dogs there were moderate increases in mean alkaline phosphatase in groups 4 and 5 on day 191. On day 116, however, these increments were statistically significant only for group 4 females despite evidence of an increased trend in group 5 females. The increased alkaline phosphatase levels correlated with increased liver weight measurements in the female dogs but not the males. There were no significant microscopic findings noted to support this latter biochemical change. Although the increase in mean alkaline phosphatase levels appeared to reflect CGA 169374 involvement, the study director did not consider this indicative of a pathologic, target organ change. All remaining clinical measurements were not statistically significantly different from the controls.

Appendix 6 of this DER contains statistically significant mean data for the serum chemistry parameters discussed above taken from pp 120, 121, 132, 138, 139, 142, 148, 153, 154, and 157 of the study report. The parameters examined are shown in Table 8.

Table 8. Clinical serum biochemistry parameters[a] examined (x)

	Electrolytes:		Other:
x	Calcium*	x	Albumin*
x	Chloride*	x	Blood creatinine*
	Magnesium#	x	Blood urea nitrogen*
x	Phosphorus*	x	Cholesterol*
x	Potassium*	x	Globulins
x	Sodium*	x	Glucose*
	Enzymes	x	Total bilirubin
x	Alkaline phosphatase (ALK)	x	Total serum Protein (TP)*
	Cholinesterase (ChE)#		Triglycerides
x	Creatinine phosphokinase*^		Serum protein electrophoresis
		x	A/G ratio
			Gamma G-T
		x	LDH[b]
	Lactic acid dehydrogenase (LAD)		
x	Serum alanine aminotransferase (serum glutamic pyruvic transaminase, SGPT)*		
x	Serum aspartate aminotransferase (serum glutamic oxaloacetic transaminase, SGOT)*		
	Gamma glutamyl transferase (or transpeptidase) (GGT)		
	Glutamate dehydrogenase		

[a]Blood samples were obtained from the jugular vein of each dog. During the treatment period, these samples were taken prior to food presentation.
[b]LDH determinations were not performed during predose.
*Required for subchronic and chronic studies
#Should be required for organophosphorus (OP) pesticides
^Not required for subchronic studies

Urinalysis.[a]
Although urinalysis is not required for a subchronic study, there were some statistically significant, but not treatment-related, changes in mean urine parameters. A statistically significant increase in mean urinary casts (granular) was noted in group 5 males on day 197, and a reduction in urinary protein was observed in group 4 and 5 females on day 119 (the interested reader is directed to pp 172 and 179 of the study report). These modest changes were essentially toxicologically insignificant. All other urinary measurements were comparable to the controls. The parameters examined are shown in Table 9.

Table 9. Urinalysis (x)

X		X	
	Appearance*	x	Glucose*
	Volume*[b]	x	Ketones*
x	Specific gravity*	x	Bilirubin*
x	pH		Blood*
x	Sediment (microscopic)*		Nitrate
x	Protein*	x	Urobilinogen
x	Occult blood		

[a]Urine was collected by catheterization or the plastic liner method predose and by stainless steel collection pans at termination. When crystals were present microscopically, an identification based upon morphology/pH was entered into the raw data.
[b]Urine volumes were determined at termination only.
*Not required for subchronic studies
*Required for chronic studies

Organ weight.
Statistically significant changes were noted in the HDT female and male dogs and the high intermediate dose females with regard to absolute and relative mean organ weights. The changes were considered to be secondary treatment-related effects. Paired mean absolute and relative to brain decrements were observed for heart weight in males in group 5. Absolute and relative to brain and body weight decrements were seen in prostate weight in males of group 5. Salivary gland weights were reduced relative to brain, and also mean absolute values were depressed in group 5 males. Paired mean absolute and relative to body weight increments were seen in liver weight determinations in females of groups 4 and/or 5. Increases in mean absolute brain weight were recorded for females in group 4; increases in mean brain weight relative to body weight were reported for males and females in group 5; and mean relative measurements for kidneys relative to body weight in females of group 5 were also increased. There were no other statistically significant differences recorded.

With the clear exception of the liver weight variations in the female dogs, the study report considers the statistically significant organ weight effects secondary to reduced body weight and, therefore, of diminished toxicological importance. It is important to note, however, that the absolute organ weight decreases in the HDT males correlate positively with decreased organ weight relative to brain weight. Therefore, since the absolute brain weights did not decrease, it can be argued that there was a primary compound-related effect on the heart, prostate, and salivary glands of those HDT males.

Although no microscopic evidence of hepatotoxicity was observed, the increases in liver weight did correlate positively with the increases in alkaline phosphatase levels in groups 4 and 5 females.

Statistically significant changes in absolute and/or relative organ weights are included in appendix 7 of this DER taken from pp 191, 193, 198, 200, 205, and 208 of the study report.

Pathology.
Gross pathology.
See the results and discussion of ophthalmoscopic examinations on p 11 of this DER for the principal gross findings and data citations dealing primarily with treatment-related ocular opacity/cataracts. There were no other treatment-related gross findings reported for any animals in groups 2-5. Any and all other gross lesions were considered to be spontaneous and/or incidental and of the type commonly encountered in laboratory beagle dogs.

Microscopic pathology.
The subject of this section is the definitive CGA-169374 treatment-related cataractous degeneration of the crystalline lens observed in the high-intermediate dose (3000 ppm) and the HDT (6000 ppm), groups 4 and 5 respectively. Groups 2 and 3 were not affected by treatment with test article. Histomorphology revealed cataractous degeneration of the crystalline lens in the left eye from one male dog (No 12) and all female beagles in group 4 and all male and female dogs in group 5. The varied degrees of lenticular aberrations were located principally in the posterior subcapsular aspect of the lens, and these were characterized by swelling, rounding, and degeneration of the cortical fibers and early bladder cell formation. The mature cataracts were observed in one male (No 13) and two female dogs (Nos. 28 and 30) from group 5, and in one female dog (No. 26) from group 4. All the lenses displayed diffuse distortion. Additionally, edema, liquefaction, and fragmentation of the lens fibers with Morgagnian globule formation were present. Rupture of the anterior lenticular capsule was seen on the left lens of one male dog (No. 13) from group 5. In this lens there was pyknosis of the epithelial cells with resultant neutrophilic infiltration . Also, the ciliary body adjacent to this lens was edematous, inflamed, and accompanied by multiple cyst formation.

Furthermore, cataractous degeneration of the lens fibers was also observed in the right eye of one male (No. 12) and one female (No. 26) dog of group 4, and in one male (No. 13) and all female dogs in group 5. There were no lesions detected in the right lens of two males (Nos. 14 and 15) from group 5 or in two females (Nos. 25 and 27) from group 4. Additionally, when the lesions were detectable, the degree of severity in the right lens of these animals (Nos. 12, 13, and 29) appeared less than the left lens of the same animals, even though the clinical ophthalmoscopic observations showed similar changes in both eyes.

Finally, the absence or presence of a lesser degree of lenticular lesions in the right lens was believed to be due to the preservation of the right eye in 10 % neutral buffered formalin instead of Russell's fixative. This latter treatment is considered to be a better fixative for the lens and retina of the eye and increases the accuracy of the histologic evaluations. See table 6 above in this DER on p 11 for a summary of the ophthalmoscopic and microscopic treatment-related changes. There were no other microscopic changes attributed to treatment with CGA-169374 reported. Any other lesions observed were considered to be spontaneous and/or incidental and of the type often encountered in laboratory beagle dogs.

The tissues that were collected at necropsy and preserved in 10 % neutral buffered formalin for histological examination (x), and organs that were weighed (xx) are shown in Table 10.

Table 10. Tissues selected for histology and organ weights

	Digestive system		Cardiovasc./Hemat.		Neurologic
x	Tongue	x	Aorta*	xx	Brain*+
xx	Salivary glands* submaxillary	xx	Heart*	x	Periph. nerve, sciatic*#
x	Esophagus*	x	Bone marrow*	x	Spinal cord, cervical lumbar, thoracic (3 levels)*#
x	Stomach*, glandular and nonglandular	x	Lymph nodes* axillary	xx	Pituitary*
x	Duodenum*	xx	Spleen	x	Eyes (optic n.)*#
x	Jejunum*	x	Thymic region*		
		xx	Lymph nodes, mesenteric & submaxillary		
					Glandular
x	Ileum*		Urogenital	xx	Adrenal gland*
x	Cecum*	xx	Kidneys*+	x	Lacrimal gland, exorbital#
x	Colon*	x	Urinary bladder*	x	Mammary gland, female*#
x	Rectum*	xx	Testes*+	x	Parathyroids*++
xx	Liver *+	xx	Epididymides	xx	Thyroids*++
				xx	Thymic region Harderian glands
				x	Pancreas
x	Gall bladder*	xx	Prostate		Other
x	Pancreas*		Seminal vesicle	x	Bone: femur with marrow and joint*#; sternum with marrow
	Respiratory	xx	Ovaries*+	x	Skeletal muscle, thigh*#
x	Trachea*	xx	Uterus*	x	Skin, abdominal mammary region*#
xx	Lung*	x	Vagina	x	All gross lesions and masses*
	Nose^				
	Pharynx^				
	Larynx^				

* Required for subchronic and chronic studies.
^ Required for chronic inhalation.
\# In subchronic studies, examined only if indicated by signs of toxicity or target organ involvement.
\+ Organ weight required in subchronic and chronic studies.
++ Organ weight required for non-rodent studies.
x selected for histological examination
xx selected for organ weight determination

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