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Attention: Section 8(e) Coordinator
(CAP Agreement)

SUBJECT: 8E CAP - 0024

Dear Section 8(e) Coordinator:

Enclosed are the original and two copies of a study CIBA-GEIGY Corporation is submitting pursuant to the TSCA Section 8(e) Compliance Audit Program and CAP Agreement number 8E CAP-0024. The information being submitted is not considered Confidential Business Information. We are submitting the following information, as required by the CAP Agreement:

| | |
|----------------|--|
| Company Name, | CIBA-GEIGY Corporation |
| Address and | Mr. Anthony Di Battista |
| Telephone No.: | Toxicology, Regulatory Auditing and Compliance Department 444 Saw Mill River Road Ardsley, New York 10502-2699 Tel. No. 914-479-2776 |

| | |
|------------------|--|
| Tested Chemical: | CGA-149071 Technical; 1-[4-(4-chlorophenoxy)-2-chloro-phenyl- (4-ethyl-1,3-dioxolan-2-yl)-methyl]-1H- 1,2,4-triazole (Currently a research and development pesticide) |
|------------------|--|

| | |
|-------------------|------------|
| CAS Registry No.: | 82097-14-1 |
|-------------------|------------|

| | |
|---------------|---|
| Report Title: | 3-Week Oral Dose-Range Toxicity Study in Dogs (Study Number 842247, October 22, 1987) |
|---------------|---|

Section 8(e) Coordinator
August 7, 1992
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Summary: Beagle dogs were dosed with 0, 100, 500, or 1000 mg CGA-149071 per kg body weight for 3 weeks via gelatin capsules. Treatment-related effects noted at necropsy included a shrunken appearance of the spleen, thymus, and prostate. Histopathologic findings included a depletion in thymocytes in the spleen and a reduction of cytoplasmic volume in hepatocytes.

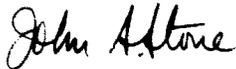
A TSCA Section 8(e) Notice has been previously submitted for this chemical, Document Control Number 8EHQ-0285-0545 C.

Category: Unit II.B.2.b

Prior Reporting: Not applicable

Please call the undersigned at telephone number 919-632-2179 if you have any questions about this submittal.

Very truly yours,



John A. Stone
Manager, Environmental Safety
& Compliance

L106CRM0713JG.1/RD17

Enclosures (Two additional copies of this letter
and three copies of the submitted study)

cc: Mr. A. Di Battista

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CGA 149071 TECHNICAL

3-WEEK ORAL DOSE-RANGE TOXICITY STUDY IN DOGS

(MIN 842247)

C.N. Tai, C. Breckenridge, and J.D. Green

October 22, 1987

RESEARCH DEPARTMENT, PHARMACEUTICALS DIVISION
CIBA-GEIGY CORPORATION
Summit, New Jersey

APPROVED:

SAG: 86-2, 1/29/86

J5/63 (MIN 842247)

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1. REPORT RELEASE SUMMARY

COMPOUND/PROJECT: CGA 149071 Technical (FL-841297)

REPORT I.D.:

Toxicology/Pathology Report 84253 (MIN 842247)

CGA 149071: 3-week oral dose-range toxicity study in dogs

C.N. Tai, C. Breckenridge, and J.D. Green

October 22, 1987

KEY WORDS:

CGA 149071 Technical, FL-841297, 3-week toxicity, oral, dog, dose-range

SUMMARY:

CGA 149071 Technical was administered orally by gelatin capsule to 2 male and 2 female dogs at daily doses of 0, 100, 500, or 1000 mg/kg for 3 weeks. All animals survived the experimental period and there were no treatment-related ophthalmoscopic findings. Body weight, body weight gain, and food consumption were significantly reduced at doses ≥ 100 mg/kg. Significant changes in clinical parameters and organ weight measurements, which were secondary to changes in body weight, were observed primarily at doses > 500 mg/kg and included: 1) increased hemoglobin, RBC count, and hematocrit and decreased WBC count; 2) reduced serum total protein, albumin and/or globulin, cholesterol, and glucose; 3) slight reductions in SAP, SGOT, total bilirubin, inorganic phosphorous, and calcium; 4) increased urinary specific gravity; and 5) a tendency toward decreased absolute organ weights or size and/or increased relative organ weights in the majority of the organs evaluated. Decreased cytoplasmic volume in hepatocytes at doses > 500 mg/kg was correlated with pallor of the liver. Based on these results, it is concluded that CGA 149071 Technical is not well tolerated by dogs at doses ≥ 500 mg/kg and the no-effect level is < 100 mg/kg.

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CGA 149071 TECHNICAL: 3-WEEK ORAL DOSE-RANGE TOXICITY STUDY IN DOGS (MIN 842247)

SUMMARY: CGA 149071 Technical was administered orally in gelatin capsules to 2 male and 2 female dogs at daily doses of 100, 500, or 1000 mg/kg for 3 weeks. An additional group of dogs received empty gelatin capsules and served as controls. Standard clinical observations, food consumption, body weight, ocular, hematology, biochemistry, urinalysis, organ weight, gross and microscopic evaluations were performed. All animals survived the experimental period and there were no treatment-related ophthalmoscopic findings. Compound-related effects, however, occurred at all dose levels. These changes were most severe at doses \geq 500 mg/kg, and included: 1) A dose-related body weight loss and a decrease in food consumption in all groups, with body weight and food consumption gradually recovering to baseline levels in the 100 mg/kg group by week 3; 2) Increased hemoglobin, RBC count, and hematocrit and decreased WBC count; 3) Reduced serum total protein, albumin and/or globulin, cholesterol and glucose; 4) Slight reductions in serum alkaline phosphatase, SGOT, total bilirubin, inorganic phosphorus, and calcium; 5) Increased urinary specific gravity; 6) Decreased absolute organ weights accompanied by increased relative weights; however, the absolute adrenal weights were increased in the mid- and high-dose group; and 7) Decreased apparent size of thymus gland, prostate and spleen, and pallid livers. These findings correlated microscopically with a decrease in the number of thymocytes, underdevelopment of the prostate, and a reduction in cytoplasmic volume in hepatocytes. The histomorphology of the spleen was within normal limits. The nature of these

CGA 149071 TECHNICAL: 3-WEEK ORAL DOSE-RANGE TOXICITY STUDY IN DOGS (MIN 842247)

treatment-related changes are considered secondary to the pronounced effects on body weight and food intake. Based on these results, it is concluded that CGA 149071 Technical is not well tolerated by dogs at oral doses of ≥ 500 mg/kg and the no-effect level is < 100 mg/kg.

* * * * *

CGA 149071 TECHNICAL: 3-WEEK ORAL DOSE-RANGE TOXICITY STUDY IN DOGS (MIN 842247)

ADMINISTRATIVE INFORMATION

MASTER INDEX NO.: 842247

SPONSOR REFERENCE NO.: SEF 139

PURPOSE: The objective of this study was to establish the maximum tolerated dose of CGA 149071 Technical in the dog for use in a subsequent chronic toxicity study.

RATIONALE: The use of the dog conforms with the regulatory requirements for subacute oral toxicity evaluation in a nonrodent species.^{1,2} The test substance was administered orally because this is the potential route of human exposure.

SPONSOR: CIBA-GEIGY Corporation, Agricultural Division, P. O. Box 18300, Greensboro, North Carolina 27419.

SPONSOR MONITOR/S:

Principal Monitors: G. Rolofson, Ph.D., L. Wetzel, Ph.D.

Alternate Monitor: J. Stevens, Ph.D.

TESTING FACILITY: Safety Evaluation Facility (SEF), Summit, NJ 07901.

INVESTIGATIVE GROUP: Subdivision of Toxicology, Toxicology/Pathology Division of CIBA-GEIGY Pharmaceuticals Research, Summit, New Jersey 07901.

PRINCIPAL INVESTIGATORS:

| | |
|--|--|
| <u>Study Director:</u> | C. Breckenridge, Ph.D., Manager |
| <u>Group Leader:</u> | C. N. Tai, M.S., Senior Scientist |
| <u>Section Leader:</u> | S. Johnson, M.S., Scientist |
| <u>Unit Leader:</u> | E. Guempel, B.A., Associate Scientist |
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| <u>Data Coordinator:</u> | N. Borman, Ph.D., Scientist II |
| <u>Statistician:</u> | C. Meng, Ph.D., Manager, Statistics |
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| <u>Toxicology/Pathology Administration and Technical Operations:</u> | R. Katz, Ph.D., Director |
| <u>Clinical Laboratory:</u> | V. Coester, E.S., Supervisor |
| <u>Consultant:</u> | D. Schiavo, Ph.D., Staff Ophthalmologist |

DATES: Initiation 9/10/84

Termination 10/2/84

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CGA 149071 TECHNICAL: 3-WEEK ORAL DOSE-RANGE TOXICITY STUDY IN DOGS (MIN 842247)

MATERIALS AND METHODS

TEST SUBSTANCE:

Identification: CGA 149071 Technical

Batch No.: 841297

Purity: 97.8%

Description: Yellowish liquid

Source: CIBA-GEIGY Corporation, Agricultural Division, P.O. Box 18300, Greensboro, N.C., 27419.

Chemical Analyses: The AgChem Division accepted all responsibilities related to the purity of the test substance.

Stability: The AgChem Division accepted responsibility for the stability of the test substance.

CONTROL SUBSTANCE:

Identification: Gelatin capsules (½ oz.)

Lot No.: 72537

Source: Chempharm

ANIMALS AND HUSBANDRY:

Species/Strain: Dogs/Beagles

Source: Marshall Research Animals, North Rose, New York, 14516

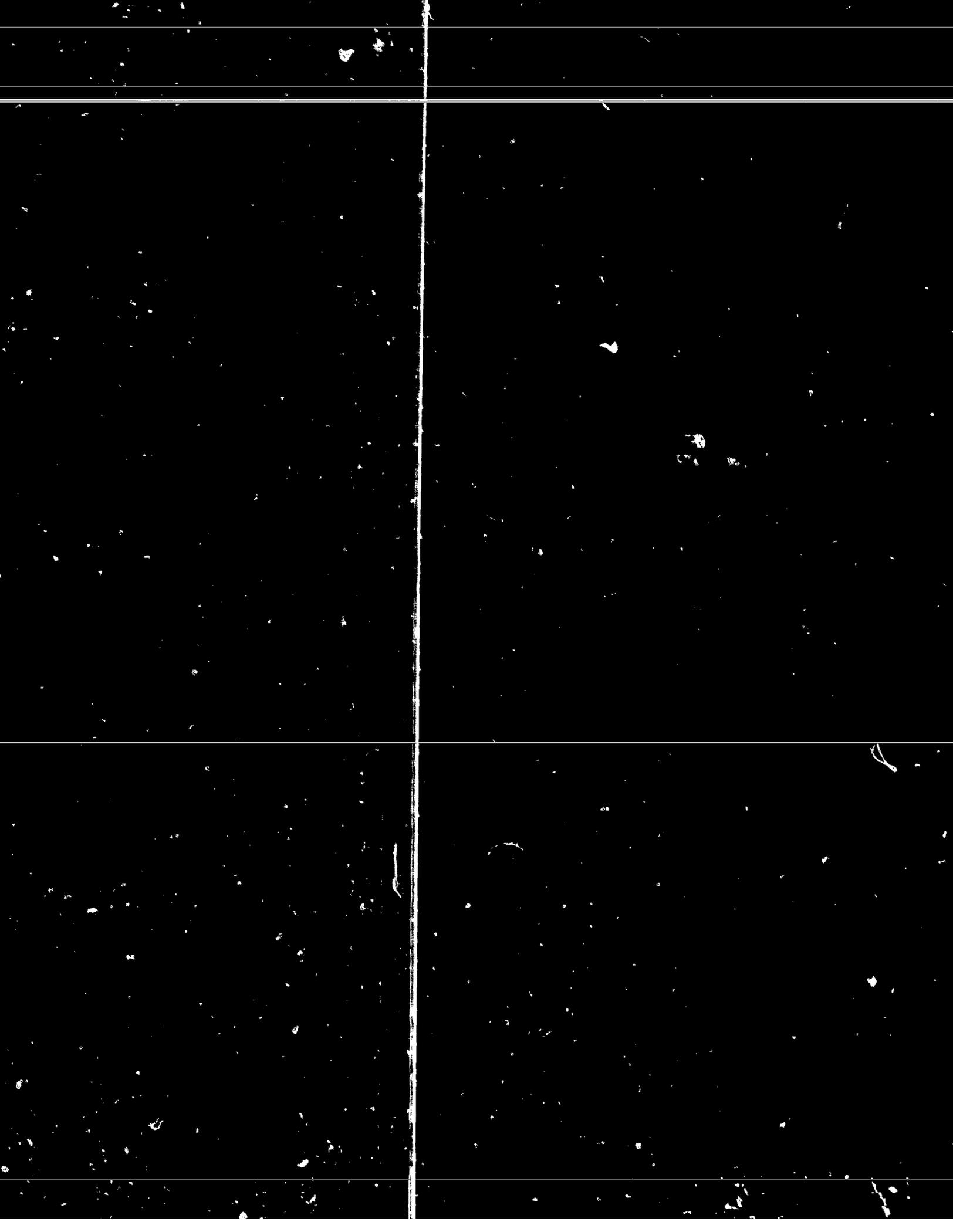
Age at Study Initiation: 6-7 months

Total Number in Study: 16 (8/sex)

Identification Method: Ear tattoo

Pretreatment: The dogs were treated by the supplier for intestinal parasites, vaccinated, and received from the supplier on July 12, 1984. The animals were assigned to a 4-week oral toxicity study on CGA 149071 (4) that ended on September 7 and were reassigned to the present study on September 10, 1984.

Housing: The animals were housed individually in 36" X 36" X 34" (high) stainless steel cages kept in sanitized rooms maintained at a mean daily temperature of 72 ± 4°F, a relative humidity of 50 ± 20%, and having an artificial light cycle of 12 hours.



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Diet: Approximately 400 g of pelleted Purina Canine Diet (#5006) was routinely offered to dogs in our laboratories each day with animals consistently demonstrating normal growth and development. Periodic testing of this diet for organophosphate pesticides, chlorinated insecticides, aflatoxin, and heavy metal levels has revealed no levels greater than those specified as maximum limits in the Federal Register.³ The drinking water was monitored periodically for contaminants according to the Standard Operating Procedures of the SEF.

EXPERIMENTAL DESIGN

Animal Selection and Distribution: Animals judged healthy based on general observations, body weight, physical examinations, clinical laboratory studies, and ophthalmological examinations were distributed into the following groups:

| Group No. | Sex | Dog ID No. | Accession No. | Dose (mg/kg) | Treatment Duration (days) |
|-----------|-----|-------------------|---------------|----------------|---------------------------|
| 1 | M | 7526 ^b | 40941 | 0 ^a | 21 |
| 1 | M | 9006 ^d | 40942 | 0 | 21 |
| 2 | M | 8735 ^c | 40943 | 100 | 21 |
| 2 | M | 8816 ^c | 40944 | 100 | 21 |
| 3 | M | 8743 ^b | 40945 | 500 | 21 |
| 3 | M | 6961 ^d | 40946 | 500 | 21 |
| 4 | M | 7623 ^b | 40947 | 1000 | 21 |
| 4 | M | 7542 ^d | 40948 | 1000 | 21 |
| 1 | F | 8930 ^b | 40949 | 0 ^a | 22 |
| 1 | F | 6112 ^d | 40950 | 0 | 22 |
| 2 | F | 6562 ^c | 40951 | 100 | 22 |
| 2 | F | 7330 ^c | 40952 | 100 | 22 |
| 3 | F | 6023 ^b | 40953 | 500 | 22 |
| 3 | F | 7968 ^d | 40954 | 500 | 22 |
| 4 | F | 9341 ^b | 40955 | 1000 | 22 |
| 4 | F | 9049 ^c | 40956 | 1000 | 22 |

^aReceived empty gelatin capsules in numbers equivalent to that given the high-dose group.

^bAnimal previously assigned to the control group of a 4-week dietary study on CGA 149071.⁴

^cAnimal previously assigned to the 20,000 ppm dose group for 6 days in a dietary study on CGA 149071.⁴

^dAnimal previously assigned to the 50,000 ppm dose group for 6 days in a dietary study on CGA 149071.⁴

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Dose Calculation: Doses of 0, 100, 500 and 1000 mg/kg were utilized for the control, low-, mid-, and high-dose groups, respectively. The amount of test substance administered daily to each dog was calculated on the basis of the dog's most recent body weight.

Test Substance Preparation: The test substance was weighed into gelatin capsules to the nearest 0.1 g. The capsules were prepared weekly by TPATO and used within 10 days of preparation.

Test and Control Substance Administration: Gelatin capsules alone or capsules containing CGA 149071 were administered daily between approximately 10.00 a.m. and 11.00 a.m. The number of capsules administered daily to the control, low-, mid-, and high-dose groups was 2, 1, 1, and 2, respectively.

Duration of Treatment: The test or control substances were administered daily for 21 or 22 consecutive days in males and females, respectively.

OBSERVATIONS AND RECORDS:

Physical Examinations: Physical examinations were conducted on all dogs during the predose period to select normal, healthy animals and weekly thereafter.

Ocular Examinations: Indirect ophthalmoscopic examinations were conducted during the predose period and again preterminally.

Clinical Signs: Each animal was monitored twice daily (a.m. mortality check, p.m. clinical signs) for appearance, mortality, toxicologic, and/or pharmacologic over effects. On weekends and holidays observations were made only once daily.

Food Consumption and Body Weights: These parameters were recorded weekly. Body weights were also recorded at study initiation.

Clinical Laboratory Tests: Fasted blood samples were obtained from the jugular vein of each dog. Serum was obtained for biochemical tests. Blood collected with an anticoagulant (EDTA) was used for hematology. The following clinical laboratory tests were conducted on each dog predose and after 3 weeks of treatment:

| <u>Hematology:</u> | <u>Biochemistry:</u> | |
|------------------------|----------------------|----------------------------|
| RBC Count | Total Protein | Cl ⁻ |
| Hematocrit | Albumin | CA ⁺⁺ |
| Hemoglobin | Globulin | NA ⁺ |
| Reticulocytes | A/G ratio | K ⁺ |
| Methemoglobin | Glucose | SGPT (alanine |
| Red Cell Morphology | Urea Nitrogen | aminotransferase) |
| WBC Count/Differential | Total Bilirubin | SGOT (aspartic |
| Platelet Count | Creatinine | aminotransferase) |
| Prothrombin Time | Total Cholesterol | Serum Alkaline Phosphatase |
| Heinz Bodies | Inorganic Phos. | |

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Urinalysis:

Urine was collected by catheterization whenever possible. If required, urine samples were collected using metabolic cages or by free catch. At necropsy, urine samples were harvested in syringes by needle puncture of the urinary bladder. The following parameters were evaluated:

| | |
|------------------|------------------------------------|
| Appearance | Glucose |
| Specific Gravity | Bilirubin |
| pH | Ketones |
| Blood | Sediment (microscopic examination) |
| Protein | |

Postmortem Examinations: Each animal was necropsied after a minimum of 21 days of treatment. The following tissues were harvested from each animal and placed in 10% neutral buffered formalin:

| | | |
|-------------------|----------|--------|
| Heart | Kidneys | Spleen |
| Liver | Adrenals | Lungs |
| Any abnormalities | | |

Organ Weights: The following organs were weighed at necropsy (paired organs were weighed as pairs):

| | | |
|-----------------------------|---------|-------------------------|
| Adrenals | Ovaries | Spleen |
| Brain (including brainstem) | Kidneys | Thyroid (w/parathyroid) |
| Testes with epididymides | Liver | Pituitary |
| Heart | | |

Histopathology: Histopathological examinations were conducted on the above listed tissue harvested from each dog.

Statistical Analyses: Tests for equality were conducted on baseline data and Fisher's Exact tests were performed, when possible, on pathology data.

Records: The following minimum records and specimens were maintained in the Archives of the SEF located in Summit, NJ.

- Amendments
- Animal Purchase Records and Accountability
- Body Weights
- Chemical Analyses (water, food, test substance)
- Circumstances or Events Which May Compromise the Integrity of Data
- Clinical Laboratory Test Results
- Clinical Signs
- Correspondence
- Environmental Records (temperature/humidity)
- Examinations (physical/ocular)
- Food Consumption
- Mortality Diary
- Necropsy Records (Pathology Records)
- Organ Weights
- Records of Animal Transfer to Pathology
- Protocol
- Test and Control Article Accountability

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RESULTS: Unless otherwise stated, results of general observations, including body weight and food consumption, hematology, biochemistry, urinalysis, organ weights, ophthalmologic examinations, and gross and histologic evaluations were within control or accepted limits.

Mortality/Clinical Signs: All animals survived the 3-week study period (Appendix III-1). A higher daily incidence of emesis, salivation, diarrhea, mucoid or bloody feces and hypoactivity was noted in males and females at doses \geq 500 mg/kg (Table 2, Appendix III-2). The number of animals displaying diarrhea, soft, bloody or mucoid feces, however, was comparable between treated and control groups (Table 1).

Ocular Findings: There were no ocular findings in treated or control animals prior to study termination (Appendix III-3).

Food Consumption: A dose-related reduction in food consumption was observed in males and females at doses \geq 100 mg/kg during the first week of the study (Table 3, Appendices II-1, II-4). An additional decrease in food consumption was noted during week 2 at doses \geq 500 mg/kg with food consumption remaining well below maintenance levels during week 3. Food consumption of females in the 100 mg/kg group gradually improved during the 3-week treatment period and was comparable to controls by week 3; whereas, food consumption of the 100 mg/kg males remained slightly below control levels at week 3.

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Body Weight: A dose-related reduction in body weight was noted in males and females at doses ≥ 100 mg/kg. All treated animals lost weight during the first week of the study (Table 4, Figures 3 and 4, Appendices II-1 and III-4). Progressive weight loss was observed during weeks 2 and 3 in animals at doses ≥ 500 mg/kg, while 2 out of 4 dogs (8735 σ , 6562 ϕ) treated with 100 mg/kg recovered to baseline body weights by week 2.

Hematology: Hemoglobin levels, RBC count, and hematocrit were increased in males and females at doses ≥ 100 mg/kg, while the WBC count was decreased at doses ≥ 500 mg/kg (Appendices II-2 and III-5). All other parameters were within the control or acceptable range.

Biochemistry: In males, a dose-related reduction in total protein, albumin and/or globulin, and cholesterol was noted at doses ≥ 100 mg/kg and in glucose levels at a dose of 1000 mg/kg (Appendices II-3 and III-6). Marginal reductions in alkaline phosphatase, inorganic phosphorus, and calcium levels were primarily noted at doses ≥ 500 mg/kg, however, inorganic phosphorus was also reduced from baseline levels in the 100 mg/kg group and total bilirubin was decreased in the 1000 mg/kg group. BUN levels were slightly increased at doses ≥ 500 mg/kg and SGPT levels were increased in the 1000 mg/kg males with one animal (7542 σ) being more severely affected than the second animal in this group (7623 σ).

Females displayed a similar profile with reductions in total protein, albumin and globulin being noted at doses ≥ 500 mg/kg. A notable reduction in cholesterol level and slight reductions in SGOT

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and alkaline phosphatase levels were noted at 1000 mg/kg. Slight elevations in BUN were noted in the 500 and 1000 mg/kg groups, and SGPT and SGOT levels were markedly increased in one female (60239) in the 500 mg/kg dose group. In addition, slight elevations in serum potassium and reductions in serum calcium were noted at doses \geq 500 mg/kg. All other clinical parameters were within the control or acceptable range.

Urinalysis: A trend toward increased specific gravity was noted in males and females at doses \geq 500 mg/kg. All other parameters evaluated were within the control or acceptable range.

Organ Weight: Reductions in absolute organ weights and increases in relative organ weights occurred in males and females of all dose groups, but these changes were most pronounced in the 500 and 1000 mg/kg groups. Absolute weights of liver, heart, brain, spleen, and ovary were reduced in males or females at doses \geq 100 mg/kg. Kidney weights in males and females and testicular weights were also reduced, but only at doses \geq 500 mg/kg. In addition, absolute adrenal weights were increased in both sexes in the 500 and 1000 mg/kg groups. In most cases, the changes in absolute weight were accompanied by increases in relative organ weights. Specifically, the relative weights of kidney, liver, heart, and brain were increased in males of all dose groups. The relative adrenal and testicular weights were also increased in males at doses \geq 500 mg/kg and at 1000 mg/kg, respectively. In females, comparable increases were noted in relative weights of adrenals, liver, and brain at doses \geq 500 mg/kg, while relative kidney, ovary, and heart weight were also notably increased in the high-dose group.

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Gross and Microscopic Pathology: At necropsy, treated males and/or females exhibited shrunken spleens, thymi and/or prostates primarily at doses \geq 500 mg/kg; although one male (no. 8735) in the 100 mg/kg dose group also had a small prostate. In addition, two high-dose males (7542 σ , 7623 σ) and one high-dose female (90499) had pale livers (Table 5, Appendix IV). Incidental gross findings noted at necropsy included: focal reddening of the duodenum, jejunum, and ileocecal valve (high-dose male no. 7542); parasites in the jejunum (low-dose male no. 8816); presence of a pituitary cyst (high-dose female no. 9341), or a white lesion on the pituitary (mid-dose female no. 6023); and a tissue mass on the spleen of one high-dose female (no. 9049).

Microscopic evaluations of the small prostates and spleens failed to reveal any morphological anomalies. Depletion of thymocytes provided the histological basis for the small size of the thymus noted in treated males and/or females at doses \geq 500 mg/kg. Pallor of the liver noted in two high-dose males (7542 σ , 7623 σ) and one high-dose female (90499) was accompanied by a reduction in cytoplasmic volume of hepatocytes (atrophy). Two additional males (nos. 6961 and 8743) in the mid-dose group and one additional female in each of the mid- (79689), and high-dose (93419) groups also had hepatocellular atrophy that did not correlate with any gross findings. The tissue mass observed in the spleen was diagnosed microscopically as an infarct and the pituitary glands of all animals were histologically normal. All other gross and microscopic changes noted were

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considered to be either induced by parasites or were spontaneous, degenerative changes. These findings are presented in the pathology report in Appendix IV.

DISCUSSION AND CONCLUSION:

CGA 149071 Technical was administered orally by gelatin capsule to male and female dogs at doses of 100, 500, or 1000 mg/kg. An additional group of dogs received empty gelatin capsules and served as controls. There were no deaths or treatment-related ophthalmoscopic findings noted during this study. An increased daily incidence of salivation and hypoactivity as well as gastrointestinal side-effects, which included emesis, diarrhea, and mucoid or bloody feces, was noted in males and/or females at doses \geq 500 mg/kg. It should be noted, however, that isolated occurrences of similar gastrointestinal effects were also observed in control animals.

A dose-related reduction in body weight and food consumption and dose-related weight loss was noted in males and females at doses \geq 100 mg/kg. The weight loss and degree of inappetence was most pronounced in mid- and high-dose groups. Gradual recovery of body weight and food consumption occurred in males and females at a dose of 100 mg/kg so that by week 3, several animals in this group had recovered to baseline levels.

Clinical laboratory evaluations and organ weight determinations demonstrated dose-related changes in a number of parameters. These changes are not considered to be indicative of target organ effects,

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rather the majority may be considered as secondary changes caused by the rather severe reduction in food intake and subsequent body weight loss that occurred primarily at doses \geq 500 mg/kg. These secondary changes included: 1) Increased hemoglobin, RBC count, and hematocrit and decreased WBC count; 2) Reduced total protein, albumin and/or globulin, cholesterol and glucose; 3) Slight reductions in alkaline phosphatase, SGOT, total bilirubin, inorganic phosphorus and calcium; 4) Increased specific gravity of the urine; and 5) Decreased absolute kidney, liver, testes, ovary, heart, brain, and spleen weights and increased adrenal weights. It should be noted that the absolute weights of several organs were also reduced in the 100 mg/kg group; however, these effects were typically less pronounced. In most cases, the reduced organ weight was accompanied by an increase in relative weight, which is expected in view of the pronounced effects on body weight.

Necropsy of animals at the termination of the study revealed a decrease in the apparent size of the thymus, spleen, and prostate. These changes were most common at doses \geq 500 mg/kg; however, one low-dose animal also exhibited a small prostate. Microscopically, a depletion of the number of thymocytes accounted for the small size of the thymus, while the spleen was unremarkable and the prostate appeared to be underdeveloped. The depletion of thymocytes was considered to be secondary to nonspecific stress. Atrophy (decreased cytoplasmic volume) was also noted in the livers of males and females at doses \geq 500 mg/kg and correlated with pallor of the liver and decreased absolute liver weights (Table 6). The reduction in cytoplasmic volume was considered secondary to reduced metabolic demand caused by decreased nutrient intake. There

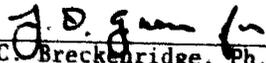


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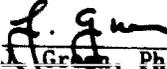
was no clear relationship between gross and microscopic pathologic changes and clinical indices of liver pathology (SGPT, SGOT), although the 2 high-dose males (nos. 7623 and 7542) and a mid-dose female (no. 6023), which had markedly increased SGPT and/or SGOT levels, also had the largest relative liver weights. All other gross and microscopic findings were considered incidental and unrelated to treatment.

Based on these results, it is concluded that CGA 149071 Technical is not well tolerated in dogs at oral doses of ≥ 500 mg/kg and the no-effect level is less than 100 mg/kg.


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SLJ/mv
October 22, 1987

J5/63 (MIN 842247)

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CGA 149071 TECHNICAL: 3-WEEK ORAL DOSE-RANGE TOXICITY STUDY IN DOGS (MIN 842247)

References

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CGA 149071 TECHNICAL: 3-WEEK ORAL DOSE-RANGE TOXICITY STUDY IN DOGS (MIN 842247)

TABLE 1
Incidence of Clinical Signs^a

| Sex: | Males | | | | Females | | | | |
|---------------|------------|-----|-----|------|---------|-----|-----|------|---|
| | Group No.: | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Dose (mg/kg): | 0 | 100 | 500 | 1000 | 0 | 100 | 500 | 1000 | |
| No. Dogs: | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Observations | | | | | | | | | |
| Emesis | 0 | 1 | 2 | 2 | 0 | 2 | 2 | 2 | 2 |
| Feces | | | | | | | | | |
| Bloody | 0 | 0 | 0 | 1 | 1 | 0 | 2 | 2 | 2 |
| Diarrhea | 1 | 1 | 2 | 2 | 1 | 0 | 2 | 2 | 2 |
| Mucous | 1 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 2 |
| Soft | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Hypoactivity | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 |
| Salivation | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |

^aThe incidence reported is based on the number of animals displaying the clinical sign on at least one occasion during the study.

CGA 149071 TECHNICAL: 3-WEEK ORAL DOSE-RANGE TOXICITY STUDY IN DOGS (MIN 842247)

TABLE 2

Incidence of Clinical Signs - Total Incidence Days^a

| Sex: | Males | | | | Females | | | |
|-----------------------|-------|-------|-------|-------|---------|-------|-------|-------|
| | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Group No.: | 0 | 100 | 500 | 1000 | 0 | 100 | 500 | 1000 |
| Dose (mg/kg): | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| No. Dogs: | 22 | 22 | 22 | 22 | 23 | 23 | 23 | 23 |
| No. Observation Days: | 44 | 44 | 44 | 44 | 46 | 46 | 46 | 46 |
| No. Incidence Days: | | | | | | | | |
| Observations | | | | | | | | |
| Emesis | 0/44 | 1/44 | 9/44 | 14/44 | 0/46 | 3/46 | 8/46 | 10/46 |
| Feces | | | | | | | | |
| Bloody | 0/44 | 0/44 | 0/44 | 2/44 | 1/46 | 0/46 | 2/46 | 5/46 |
| Diarrhea | 1/44 | 3/44 | 12/44 | 16/44 | 1/46 | 0/46 | 12/46 | 17/46 |
| Mucous | 1/44 | 4/44 | 13/44 | 14/44 | 1/46 | 4/46 | 16/46 | 16/46 |
| Soft | 11/44 | 13/44 | 10/44 | 13/44 | 6/46 | 10/46 | 9/46 | 8/46 |
| Hyposensitivity | 0/44 | 0/44 | 0/44 | 0/44 | 0/46 | 0/46 | 2/46 | 3/46 |
| Salivation | 0/44 | 0/44 | 2/44 | 0/44 | 0/46 | 0/46 | 0/46 | 2/46 |

^aTotal Incidence Days = Sum of All Daily Observations for Each Animal During the Observation Period
No. of Dogs X No. of Days in Observation Period

CGA 149071 TECHNICAL: 3-WEEK ORAL DOSE-RANGE TOXICITY STUDY IN DOGS (MIN 842247)

TABLE 3

Summary of Mean Daily Food Consumption (g/dog/day)

| Group | Sex | Dose (mg/kg) | Week | | | Mean Daily Food Consumption During the 3-Week Period | % Difference ^a |
|-------|-----|-----------------|------|-----|-----|---|------------------------------|
| | | | 1 | 2 | 3 | | |
| 1 | M | 0 | 342 | 345 | 399 | 362 | -- |
| 2 | M | 100 | 232 | 219 | 324 | 258 | -28.7 |
| 3 | M | 500 | 97 | 66 | 72 | 78 | -78.5 |
| 4 | M | 1000 | 116 | 16 | 12 | 48 | -86.7 |
| 1 | F | 0 | 271 | 289 | 306 | 289 | -- |
| 2 | F | 100 | 206 | 261 | 299 | 255 | -11.9 |
| 3 | F | 00 | 74 | 14 | 29 | 39 | -86.5 |
| 4 | F | 1000 | 55 | 2 | 11 | 23 | -92.0 |

^aPercent difference in food consumption was calculated relative to the control group mean.