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OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 981

011742

JAN 17 1996

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: CHLOROTHALONIL - Review of 30-Day, 90-Day and One-Year Dog Studies (Oral Administration, Gelatin Capsules)

PC Code: 081901 Caswell No.: 215B
DP Barcode: D221842 Submission: S488162
MRID Nos.: 43653601 (30-Day); 43653602 (90-Day);
43653603 (One-Year)

FROM: Alan C. Levy, Ph.D., Toxicologist *Alan C. Levy* JAN. 3, 1996
Review Section I, Toxicology Branch II
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TO: Walter Waldrop/Andrew W. Ertman, PM 71
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THRU: Yiannakis M. Ioannou, Ph.D., Section Head
Review Section I, Toxicology Branch II
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and

Stephanie Irene, Ph.D., Acting Branch Chief
Toxicology Branch II
Health Effects Division (7509C) *Stephanie Irene* 1/4/96

REQUEST: Review the 30-day, 90-day and one-year dog studies with
CHLOROTHALONIL

Registrant: ISK Biotech Corporation, Mentor, OH

SUMMARY:

30-Day Study: Doses of 0, 50, 150 and 500 mg/kg/day; NOEL =
150 mg/kg/day; LOEL = 500 mg/kg/day based on emesis, body
weight loss (males) and increase in liver weights (females)

90-Day Study: Doses of 0, 15, 150 and 500 mg/kg/day; NOEL =
15 mg/kg/day; LOEL = 150 mg/kg/day based on decreased body
weight gain in males

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One-Year Study: Doses of 0, 15, 150 and 500 mg/kg/day; NOEL = 150 mg/kg/day; LOEL = 500 mg/kg/day based on decreased body weight gains in both sexes

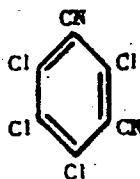
CHEMICAL:

PC Code: 081901

Name: CHLOROTHALONIL; T-117-12; 2,4,5,6-tetrachloroisophthalonitrile

Purity: 97.9-98.9%

Formula:

**EXECUTIVE SUMMARIES:**

30-Day Study: MRID No. 43653601

In a subchronic toxicity study (MRID No. 43653601), CHLOROTHALONIL (98.9% purity) was administered orally by gelatin capsule to Marshall beagle dogs (2/sex/group) at doses of 0 (empty capsules), 50, 150 and 500 mg/kg/day for 30 days.

The following parameters were not affected: mortality, hematology, urinalysis, macroscopic pathology and microscopic pathology. The incidence of emesis was increased primarily in males at 500 mg/kg/day. There was body weight loss for the 500 mg/kg/day male dogs with a gain for the controls and lower dose animals. Food consumption was less in both 500 mg/kg/day males and one female. Alanine aminotransferase was lower in all treated dogs than in controls. Only females at 500 mg/kg/day had higher absolute and relative liver weights than did controls.

The Systemic Toxicity NOEL = 150 mg/kg/day

The Systemic Toxicity LOEL = 500 mg/kg/day based on emesis, body weight loss (males) and an increase in liver weights (females)

This study is classified as Supplementary and does not satisfy the data requirement (§82-1) for a subchronic toxicity study (non-guideline study). 2

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90-Day Study: MRID No. 43653602

In a subchronic toxicity study (MRID No. 43653602) CHLOROTHALONIL (97.9-98.2% purity) was administered orally by gelatin capsules to Marshall beagle dogs (4/sex/group) at doses of 0 (empty capsules), 15, 150 and 500 (reduced from 750 on study day 5) mg/kg/day for 95-98 days.

The following parameters were not affected: mortality, hematology, urinalysis, macroscopic pathology and microscopic pathology. There were increased incidences of emesis at 500 mg/kg/day (both sexes). Body weight gains were decreased at 150 and 500 mg/kg/day in males and possibly at 500 mg/kg/day in females. Alanine aminotransferase values were reduced approximately 90% in all dosed animals compared with controls as well as with pre-treatment levels.

The Systemic Toxicity NOEL = 15 mg/kg/day

The Systemic Toxicity LOEL = 150 mg/kg/day based on decreased body weight gain in males

This study is Acceptable and satisfies the data requirement (§82-1) for a subchronic toxicity study in dogs.

One-Year Study: MRID No. 43653603

In a chronic toxicity study (MRID No. 43653603), CHLOROTHALONIL (98.3% purity) was administered orally by gelatin capsules to Marshall beagle dogs (5/sex/group) at doses of 0 (empty capsules), 15, 150 and 500 mg/kg/day for 52 weeks.

There were decreases in body weight gains in males and females at 500 mg/kg/day. Alanine aminotransferase levels were reduced about 90% in all dosed animals compared with controls as well as with pretreatment levels. There were no effects on the following parameters: mortality, clinical signs, food consumption, ophthalmology, hematology, urinalysis, macroscopic pathology, organ weights and microscopic pathology.

The Systemic Toxicity NOEL = 150 mg/kg/day

The Systemic Toxicity LOEL = 500 mg/kg/day based on decreased body weight gains in both sexes

This study is Acceptable and satisfies the data requirement (§83-1) for a chronic toxicity study in dogs.

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Chlorothalonil

30-Day Dog Study \$82-1

Reviewed by: Alan C. Levy, Ph.D. *Alan C. Levy*
Section I, Tox. Branch II (7509C) JAN. 3, 1996

Secondary reviewer: Yiannakis M. Ioannou, Ph.D. *Y. M. Ioannou* 1/3/96
Section I, Tox. Branch II (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Subchronic (30-day) Toxicity Study - Dog (\$82-1)

TEST MATERIAL: Chlorothalonil; T-117-12

MRID No.: 43653601 **PC Code:** 081901

STUDY NUMBERS: Bio/dynamics = 91-3762

Ricerca = 91-0354

Experimental Pathology Laboratory = 156-057

SPONSOR: ISK Biotech Corporation, Mentor, OH

TESTING FACILITY: Bio/dynamics, Inc., East Millstone, NJ

TITLE OF REPORT: A 30-Day Oral Toxicity Study in Dogs with T-117-12

AUTHORS: George E. Fillmore and James Laveglia

REPORT ISSUED: June 26, 1992

EXECUTIVE SUMMARY:

In a subchronic toxicity study (MRID No. 43653601), CHLOROTHALONIL (98.9% purity) was administered orally by gelatin capsule to Marshall beagle dogs (2/sex/group) at doses of 0 (empty capsules), 50, 150 and 500 mg/kg/day for 30 days.

The following parameters were not affected: mortality, hematology, urinalysis, macroscopic pathology and microscopic pathology. The incidence of emesis was increased primarily in males at 500 mg/kg/day. There was body weight loss for the 500 mg/kg/day male dogs with a gain for the controls and lower dose animals. Food consumption was less in both 500 mg/kg/day males and one female. Alanine aminotransferase was lower in all treated dogs than in controls. Only females at 500 mg/kg/day had higher absolute and relative liver weights than did controls.

The Systemic Toxicity NOEL = 150 mg/kg/day

The Systemic Toxicity LOEL = 500 mg/kg/day based on emesis, body weight loss (males) and an increase in liver weights (females)

This study is classified as **Supplementary** and does not satisfy the data requirement (\$82-1) for a subchronic toxicity study (non-guideline study). *y*

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I. MATERIALS, METHODS AND RESULTS**A. Statistical Analyses (Report page 33)**

As there were only 2 dogs/sex/group, statistical analyses were not performed.

B. Regulatory Compliance

A signed and dated Good Laboratory Practice compliance statement, Quality Assurance statement and a list of Quality Assurance inspections were included in the Report.

A signed statement of no confidentiality claim was provided.

C. Test Article

Name and Formula: Chlorothalonil; T-117-12; 2,4,5,6-Tetrachloroisophthalonitrile



Lot Number: 1002
Composition: 100% T-117-12
Purity: 98.9%
Description: gray powder

D. Dose Selection

The Report did not mention how the doses were selected for this 30-day dog study.

Doses chosen for this study were: 0 (control, empty gelatin capsules), 50, 150 and 500 mg/kg/day orally by gelatin capsule.

E. Test Article Purity and Stability

No analytical data for these parameters were included in the Report.

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a = total number of incidences; 2 dogs/sex/group
Data extracted from Report page 72.

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Of the 17 episodes in the 500 mg/kg/day males, 8 occurred during days 8-13. For the 500 mg/kg/day females, 4/9 episodes occurred during days 1-3.

I. Body Weights

Individual body weights were recorded prior to the start of the study and weekly thereafter. See Table 2.

Table 2

INDIVIDUAL ANIMAL WEIGHTS AND WEIGHT GAINS IN A 30-DAY DOG STUDY
WITH CHLOROTHALONIL ADMINISTERED ORALLY BY GELATIN CAPSULE

Weeks	Males (mg/kg/day)							
	0		50		150		500	
BODY WEIGHT-kg								
0	10.0	10.2	9.5	10.5	10.2	9.7	9.8	10.3
4	10.9	12.2	10.4	10.8	11.0	10.5	9.7	9.2
BODY WEIGHT CHANGE-kg								
0-4	+0.9	+2.0	+0.9	+0.3	+0.8	+0.8	-0.1	-1.1
Weeks	Females (mg/kg/day)							
	0		50		150		500	
BODY WEIGHT-kg								
0	7.9	7.3	7.9	6.9	7.5	7.5	6.8	7.9
4	8.6	8.0	8.2	7.2	7.6	7.6	7.2	8.0
BODY WEIGHT CHANGE-kg								
0-4	+0.7	+0.7	+0.3	+0.3	+0.1	+0.1	+0.4	+0.1

Data Extracted from Report Appendix D (D-4), page 99.

For males, all individual animals in the 0, 50 and 150 mg/kg/day groups gained weight; whereas, at 500 mg/kg/day, both dogs lost weight over the 4-week period. Females in all 4 groups gained weight. However, the controls gained more (0.7 kg each) than did any of the treated dogs (+0.1-+0.4 kg). From these limited data, there appears to have been a test article effect only on the males administered 500 mg/kg/day.

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J. Food Consumption (Report Appendix E, pages 102 and 103)

Four times/week, consumption was estimated for the 1st 200 g and then on the entire 400 g. The estimation was "quantified" by 0 = none consumed, 1 = up to 1/4 consumed, 2 = up to 1/2, 3 = up to 3/4 consumed, 4 = up to but NOT including total consumed and 5 = total consumed.

For males, at 50 mg/kg/day, one dog ate about the same amount during the 4 weeks and the other ate less during weeks 3 and 4 compared with week 0 (prior to test article administration). At 150 mg/kg/day, both males ate about the same during the 4 weeks as they did during week 0. At 500 mg/kg/day, one dog ate less primarily during week 4 and the other ate less during weeks 2, 3 and 4 (compared with week 0). One 500 mg/kg/day female ate less during week 4.

K. Clinical Pathology

Blood samples were taken from the jugular vein of unanesthetized animals (fasted overnight) prior to the start of the study and at termination. A 16-hour urine sample was collected in metabolism pans from water-deprived (2 hours) dogs (no food or water during the 16 hours).

1. HEMATOLOGY - The following parameters were examined:

Hemoglobin	Mean corpuscular volume
Hematocrit	Mean corpuscular hemoglobin
Erythrocyte count	Mean corpuscular hemoglobin concentration
Reticulocyte count	Total leukocyte count
Prothrombin time	Differential leukocyte count
Erythrocyte morphology	
Platelet count	

There were no parameters which appeared to be altered by test article administration.

2. CLINICAL CHEMISTRY - The following parameters were examined:

Alkaline phosphatase	Aspartate aminotransferase
Urea nitrogen	Alanine aminotransferase
Creatinine	Sodium
Glucose	Potassium
Cholesterol	Chloride
Total protein	Calcium
Total bilirubin	Phosphorus
Albumin	
Globulin	
A/G ratio	



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The only difference between treated and control dogs was a decrease in alanine aminotransferase in all treated animals when compared with controls. At termination, for males, the two controls had values of 26 and 28 IU/L; whereas, the 6 treated dogs had values of 3-5 IU/L. For females, the control values were 16 and 24 IU/L and the 6 treated dog values were 3 or 4 IU/L. The pretest values for all 16 dogs on study were 13-29 IU/L. Report page 74 stated, "It is possible the test substance interacted with the enzyme such that the enzyme could not be detected. However, a test substance effect on enzyme production or activity cannot be ruled out."

3. URINALYSIS - The following parameters were examined:

Appearance	Specific gravity	pH
Protein	Glucose	Ketones
Bilirubin	Occult blood	Urobilinogen
Sediment (microscopic)		Volume

There were no apparent test article effects on any of the parameters.

L. Sacrifice and Pathology

After at least 31 days of treatment, all dogs were anesthetized with sodium pentobarbital and exsanguinated. A complete gross necropsy was performed and the following organs were weighed with weights expressed as absolute, relative-to-body weight and relative-to-brain weight: adrenals, brain, heart, kidneys, liver, ovaries, testes with epididymides and thyroid/parathyroids.

The following tissues were preserved and examined (Experimental Pathology Laboratories, Inc., William M. Busey, D.V.M., Ph.D.):

DIGESTIVE

Salivary glands
Esophagus
Stomach
Duodenum
Jejunum
Ileum
Cecum
Colon
Rectum
Liver
Pancreas
Gallbladder
Tongue

RESPIRATORY

Trachea
Lungs

CARDIOVAS/HEMAT

Aorta
Heart
Lymph nodes
Spleen
Thymus
Bone marrow

UROGENITAL

Kidneys
Urinary bladder
Testes
Ovaries
Prostate
Uterus
Epididymides

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NEUROLOGIC

Brain
Peripheral nerve
Spinal cord (3 levels)
Eyes (optic n.)
Pituitary

GLANDULAR

Adrenals
Mammary gland
Parathyroids
Thyroids

OTHER

Bone
Skeletal muscle
Skin
Gross lesions and masses

1. MACROSCOPIC PATHOLOGY

There were no apparent effects of test article administration.

2. ORGAN WEIGHTS

Absolute and relative (to-body weight and to-brain weight) liver weights of the 500 mg/kg/day females were greater than the controls (Table 3).

Table 3

INDIVIDUAL LIVER WEIGHTS IN A 30-DAY DOG STUDY WITH CHLOROTHALONIL
ADMINISTERED ORALLY BY GELATIN CAPSULE

	mg/kg/day							
	0		50		150		500	
MALES								
Absolute - g ..	293	337	297	265	294	319	293	242
To-body weight	2.74	2.91	3.06	2.52	2.80	3.32	3.06	2.65
To-brain weight	4.12	3.96	3.80	3.16	4.18	3.70	3.87	3.11
FEMALES								
Absolute - g ..	213	208	234	184	220	220	241	230
To-body weight	2.56	2.74	2.82	2.62	3.06	2.93	3.49	2.99
To-brain weight	2.73	3.02	3.26	2.78	3.08	3.35	3.50	3.10

Data extracted from Report Appendix J, pages 124-164.

3. MICROSCOPIC PATHOLOGY

No histopathological differences between treated and control groups were reported.

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II. DISCUSSION

There were no analytical data for test article purity and stability.

No dogs died during the study. The only clinical sign observed which appeared to be associated with test article administration was an increased incidence of emesis in the 500 mg/kg/day males with the possible suggestion of this finding at the same dose in females.

Body weights were effected by 500 mg/kg/day only in males where dogs lost 0.1 and 1.1 kg during the 30 days compared with control weight gains of 0.9 and 2.0 kg. No females lost weight.

Food consumption was decreased in males, primarily at the 500 mg/kg/day dose. There was a decrease in one 500 mg/kg/day female.

There was a decrease (≤ 5 IU/L) in alanine aminotransferase in all treated dogs compared with both control values as well as pretest treated values (13-29 IU/L). The Report indicated that either the test article interacted with the enzyme so that it could not be detected or there was an effect on enzyme production. [In a 90-day dog study, the same results were observed at 15, 150 and 500 mg/kg/day]. There were no apparent effects on any hematology, other clinical chemistry or any urinalysis parameters.

Females administered 500 mg/kg/day of CHLOROTHALONIL had somewhat higher absolute and relative liver weights than did controls. All other organ weights seemed to be unaffected.

Neither macroscopic nor microscopic pathology revealed any test article effects.

III. CONCLUSIONS

In a subchronic toxicity study, CHLOROTHALONIL (98.9% purity) was administered orally by gelatin capsule to Marshall beagle dogs (2/sex/group) at doses of 0 (empty capsules), 50, 150 and 500 mg/kg/day for 30 days. The following parameters were examined: mortality, clinical signs, body weights, food consumption, hematology, clinical chemistry, urinalysis, macroscopic pathology, organ weights and microscopic pathology.

The following parameters were not affected: mortality, hematology, urinalysis, macroscopic pathology and microscopic pathology. The incidence of emesis was increased primarily in males at 500 mg/kg/day. There was body weight loss for the 500 mg/kg/day male dogs with a gain for the controls and lower dose animals. Food consumption was less in both 500 mg/kg/day males and one female. Alanine aminotransferase was lower in all treated dogs than in controls. Only females at 500 mg/kg/day had higher absolute and relative liver weights than did controls.

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The Systemic Toxicity NOEL = 150 mg/kg/day

The Systemic Toxicity LOEL = 500 mg/kg/day based on emesis, body weight loss (males) and an increase in liver weights (females)

This study is classified as Supplementary and does not satisfy the data requirement (§82-1) for a subchronic toxicity study (non-guideline study).

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Chlorothalonil

90-Day Dog Study \$82-1

Reviewed by: Alan C. Levy, Ph.D. *Alan C. Levy*
Section I, Tox. Branch II (7509C) JAN. 3, 1996

Secondary reviewer: Yiannakis M Ioannou, Ph.D. *Y.M. Ioannou* 1/3/96
Section I, Tox. Branch II (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Subchronic toxicity Study - Dog (\$82-1)

TEST MATERIAL: Chlorothalonil; T-117-12

MRID Nos.: 43653602

PC Code: 081901

STUDY NUMBERS: Bio/dynamics = 92-3820
Ricerca = 92-0103

SPONSOR: ISK Biotech Corporation, Mentor, OH

TESTING FACILITY: Bio/dynamics, Inc., East Millstone, NJ

TITLE OF REPORT: A 90-Day Oral Toxicity Study in Dogs with
Chlorothalonil

AUTHORS: George E. Fillmore and James Laveglia

REPORTS ISSUED: April 6, 1993

EXECUTIVE SUMMARY:

In a subchronic toxicity study (MRID No. 43653602) CHLOROTHALONIL (97.9-98.2% purity) was administered orally by gelatin capsules to Marshall beagle dogs (4/sex/group) at doses of 0 (empty capsules), 15, 150 and 500 (reduced from 750 on study day 5) mg/kg/day for 95-98 days.

The following parameters were not affected: mortality, hematology, urinalysis, macroscopic pathology and microscopic pathology. There were increased incidences of emesis at 500 mg/kg/day (both sexes). Body weight gains were decreased at 150 and 500 mg/kg/day in males and possibly at 500 mg/kg/day in females. Alanine aminotransferase values were reduced approximately 90% in all dosed animals compared with controls as well as with pretreatment levels.

The Systemic Toxicity NOEL = 15 mg/kg/day

The Systemic Toxicity LOEL = 150 mg/kg/day based on decreased body weight gain in males

This study is Acceptable and satisfies the data requirement (\$82-1) for a subchronic toxicity study in dogs.

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I. MATERIALS, METHODS AND RESULTS**A. Statistical Analyses** (Report pages 35 and 36; Appendix A, pages 86-88)

The following group mean parameters were submitted to statistical analyses: mean body weights, mean body weight changes, clinical laboratory values, terminal organ weights, organ-to-body weight ratios and organ-to-brain weight ratios.

EQUALITY OF MEANS - one-way analysis of variance followed by multiple comparison if needed - Bartlett's Test (1½ two sided) to determine if groups have equal variance - if variances equal, parametric procedures; if not equal, nonparametric

PARAMETRIC PROCEDURES - one-way ANOVA using the F distribution to assess significance - if significant differences among means are indicated, Dunnett's Test to determine which means are significantly different from control

NONPARAMETRIC PROCEDURES - if needed to test equality of means, Kruskal-Wallis Test used, and if differences are indicated, Dunn's summed rank test to be used to determine which treatments differ from control

STATISTICAL TEST FOR TREND - in parametric (equal variance), standard regression techniques with test for trend and lack of fit; nonparametric, Jonckheere's Test for monotonic trend

B. Regulatory Compliance

A signed and dated Good Laboratory Practice Compliance statement, Quality Assurance statement and a list of Quality Assurance inspections were included in the Report.

A Flagging Statement for potential adverse effects (40 CFR 158.34) was included in the Report and stated that the study neither met nor exceeded any of the acceptable criteria.

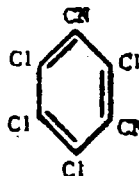
A signed statement of no confidentiality claim was provided.

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C. Test Article

Name and Formula: Chlorothalonil; T-117-12; 2,4,5,6-tetrachloroisophthalonitrile



Lot Number: 1002

Composition: 100% T-117-12

Purity: 97.9% (prior to study); 98.2% (after study completed)

Description: Gray powder

D. Dose Selection

Prior to this study, a 30-day oral (gelatin capsule) dog study was performed (Study Nos. - Bio/dynamics = 91-3762; Ricerca = 91-0354; Experimental Pathology Laboratory = 156-057; MRID No. - 43653601). The doses were 0 (empty capsules), 50, 150 and 500 mg/kg/day. There was an increase in the incidence of emesis primarily in males at 500 mg/kg/day. There was body weight loss and a decrease in food consumption in 500 mg/kg/day males. Alanine aminotransferase was lower in all treated dogs compared with controls. Only females at 500 mg/kg/day had higher absolute and relative liver weights than did controls.

In the current 90-day study, the doses were 0 (empty gelatin capsules), 15, 150 and 750 mg/kg/day. On study day 5, the 750 mg/kg/day dose was lowered to 500 mg/kg/day because of one fatality and "a severe emetic response observed in all dogs in the high dose group."

E. Test Article Purity and Stability

No analytical data for these parameters were included in the Report.

F. Dosing

An appropriate amount of test article for each dog, based on it's most recent body weight, was placed in gelatin capsules. The capsules were prepared each week. Controls received empty capsules (the same number as was given to the high-dose animals). Capsules were administered about 30 minutes after feeding 1/2 of the dogs' daily ration of food (200 g). The remaining 200 g of food was given about 30 minutes post capsule administration. The animals were dosed 7 days/week for 95-98 days (depending upon sacrifice day).

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G. Animals

Species: beagle dog

Source: Marshall Farms, U.S.A., Inc., North Rose, NY

Group Size: 4/sex

Method of Assignment to Groups: ranked by body weight and randomly assigned

Acclimation: one month

Age at Study Start: about 6 months

Weight at Study Start: males = 9.0 kg (7.3-10.0)

females = 7.6 kg (6.6-9.0)

Housing: individual

Food: 400 g/day (200 g twice daily; total of 4.5 hours)

Water: ad libitum

Room Temperature, Humidity and Light Cycle (actual):
59-76°F; 40-74%; 12 hours light/dark

H. Mortality and Clinical Signs

Animals were examined A.M. and P.M. daily. In addition, there were post-dose observations particularly for emesis. Detailed physical examinations were performed prior to the start of the study and weekly thereafter.

One 750 mg/kg/day male was found dead on study day 3 (received two doses). On study day 2, this animal exhibited "excessive" emesis and no apparent food consumption. Microscopic tissue examination revealed pulmonary changes which indicated that death was caused by bronchitis and pneumonia which followed aspiration of foreign matter. [Because of this death, plus the incidence of emesis exhibited by all 750 mg/kg/day dogs, the high dose was lowered to 500 mg/kg/day starting with study day 5.]

An increased incidence of emesis was the only clinical sign attributed to test article administration. Table 1 presents a summary of dog incidences.

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Table 1

**GROUP MEAN INCIDENCE OF EMESIS IN A 90-DAY DOG STUDY WITH
CHLOROTHALONIL ADMINISTERED ORALLY BY GELATIN CAPSULE**

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	15	150	500a	0	15	150	500a
No. of dogs	4	4	4	3b	4	4	4	4
Total No. days with emesis	12	6	6	20	13	4	11	25
Total No. of episodes	18	8	8	25	18	5	12	42
Range: No. of episodes for all dogs	0-12	0-3	0-5	6-11	0-10	1-2	1-6	1-18
Group mean No. of episodes	4.5	2.0	2.0	8.3	4.5	1.3	3.0	10.5

a = 750 mg/kg/day for days 1-4; 500 mg/kg/day for days 5-7

b = dog found dead on day 3

NOTE: number of emesis episodes during 750 mg/kg/day dosing not included in this table

Data extracted or calculated from Report Appendix C, page 99.

I. Body Weights

Individual body weights were recorded prior to the start of the study, each week during treatment and at the end of the study (fasting weight).

Table 2

**GROUP MEAN BODY WEIGHTS AND WEIGHT GAINS IN A 90-DAY DOG STUDY WITH
CHLOROTHALONIL ADMINISTERED ORALLY BY GELATIN CAPSULE**

Week	Males (mg/kg/day)				Females (mg/kg/day)			
	0	15	150	500	0	15	150	500
BODY WEIGHT-kg								
0	9.0	9.0	9.0	9.0	7.6	7.6	7.6	7.6
1	9.4	9.4	9.0	8.9	8.1	8.1	7.6	7.9
4	9.7	9.4	9.3	8.9	8.3	8.6	7.8	7.9
8	10.8	10.1	9.7	9.3	8.8	9.4	8.6	8.2
13	11.5	11.0	10.1	9.8	9.2	10.1	9.1	8.4
BODY WEIGHT GAIN-kg								
0-4	0.8	0.5	0.3	0.1	0.7	1.0	0.2	0.3
4-8	1.1	0.7	0.4	0.4	0.5	0.5	0.8	0.3
8-13	0.7	0.9	0.4	0.5	0.4	0.8	0.5	0.2
0-13	2.5	2.1	1.1**	1.0**	1.6	2.4	1.5	0.9

Number of dogs = 4/sex/group except 3 males at 500 mg/kg/day from weeks 1-13 (one found dead study day 3).

Body weight gain = weeks 0-4 and 0-13, values from the Report; weeks 4-8 and 8-13 calculated by the Reviewer.

Statistical Significance: ** = p<0.01

Data extracted from Report Appendix E, pages 144-152.

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For males, there was a statistically significant decrease in body weight gains from weeks 0-13 for the 150 and 500 kg/kg/day groups. Though not statistically significant, the 500 mg/kg/day females had a group mean body weight gain for the study of 0.9 kg compared with 1.6, 2.4 and 1.5 kg for the 0, 15 and 150 mg/kg/day groups.

J. Food Consumption (Report Appendix F, pages 177-181)

This was "estimated" (then quantitated) four times each week from one week prior to the start of the study through week 13.

Although there was some interval-to-interval variation, there did not appear to be a clear test article effect on this parameter.

K. Ophthalmology (Report pages 89 and 90)

Indirect ophthalmoscopy was performed on each dog prior to the start of dosing and at study termination.

There were no findings that were considered to have been related to test article administration.

L. Clinical Pathology

Blood was taken from the jugular vein of unanesthetized (fasted overnight) dogs twice prior to the start of dosing as well as survivors at about 45 and 90 days. Urine was collected in metabolism pans pretest as well as at 45 and 90 days (approximately). Animals were water deprived for about 2 hours for the collection of freshly voided urine and were without food or water for the 16-hour urine volume collection.

1. HEMATOLOGY - The following parameters were examined:

Hemoglobin*	Mean corpuscular volume
Hematocrit*	Mean Corpuscular hemoglobin
Erythrocyte count*	Mean corpuscular hemoglobin concentration
Reticuloctye count	
Platelet count*	Prothrombin time*
Leukocyte count*	Erythrocyte morphology
Leukocyte differential*	Activated partial thromboplastin time*

* = EPA Guideline requirement

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The administration of CHLOROTHALONIL did not appear to have an effect on any of the above parameters.

2. CLINICAL CHEMISTRY - The following parameters were examined:

Creatinine*	Aspartate aminotransferase*
Glucose*	Alanine aminotransferase*
Cholesterol	Alkaline phosphatase
Total protein*	Sodium*
Albumin*	Potassium*
Globulin	Chloride*
A/G ratio	Calcium*
Urea nitrogen*	Phosphorus*
Total bilirubin*	

* = EPA Guideline requirement

Table 3 presents parameters which may have been effected.

Table 3

CLINICAL CHEMISTRY PARAMETERS WHICH APPEARED TO HAVE BEEN ALTERED
IN A 90-DAY DOG STUDY WITH CHLOROTHALONIL ADMINISTERED ORALLY
BY GELATIN CAPSULE

Parameter Interval	Males (mg/kg/day)				Females (mg/kg/day)			
	0	15	150	500	0	15	150	500
ALANINE AMINOTRANSFERASE								
Pretest I	19	19	20	19	19	21	20	19
Pretest II	16	17	18	16	18	24	17	19
1.5 Months	19	1*	1	0**	21	2**	2**	0**
3 Months	22	1**	1**	0**	23	2**	1**	0
CHOLESTEROL								
Pretest I	196	210	193	211	206	208	199	198
Pretest II	180	184	175	199	177	185	194	185
1.5 Months	167	192	199	273 ^a	141	178	194*	237**
3 Months	162	177	192	256*	137	178	209*	218*
ALBUMIN								
Pretest I	3.1	3.2	3.2	3.1	3.1	3.1	3.1	3.1
Pretest II	3.0	3.2	3.2	3.1	3.1	3.1	3.1	3.1
1.5 Months	3.2	3.2	3.0*	2.9*	3.4	3.2	3.0	3.1
3 Months	3.4	3.4	3.1*	2.9**	3.4	3.4	3.2	3.0*

Number of dogs: 4/sex/group except 3/group for males at 500 mg/kg/day at 1.5 and 3 months

a = Individual values of 349, 268 and 203 mg/dl; dog No. 4375 had the highest cholesterol (pretest I, pretest II, 1.5 month and 3 month) of any animal at any interval throughout the study

Alanine aminotransferase = IU/L; Cholesterol = mg/dl; Albumin = g/dl

Statistical Significance: * = p<0.05; ** = p<0.01

Data extracted from Report Appendix I, pages 232-248.

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Group mean alanine aminotransferase values for males and females of all doses were ≤ 2 IU/L compared with control means of 16-24 IU/L for the 1.5 and 3 month intervals.

Cholesterol group mean values for 500 mg/kg/day males at both treatment intervals were above control values. However, this appeared to be due to one dog (No. 4375) which had the highest levels throughout the study, including pretest I and pretest II. Group mean female cholesterol levels were significantly ($p < 0.05$ or 0.01) elevated compared with controls at 150 and 500 mg/kg/day.

Albumin group mean values for 150 and 500 mg/kg/day males at 1.5 and 3 months were lower ($p < 0.05$ or 0.01) than controls. For females, the only significantly ($p < 0.05$) lower value was for the 500 mg/kg/day group at the 3 month interval.

3. URINALYSIS (not required by EPA Guidelines)

Appearance	Refractive index	Specific gravity
pH	Protein	Glucose
Ketones	Bilirubin	Occult blood
Urobilinogen	Volume	Sediment (microscopic)

There were no apparent test article effects on any of the parameters.

M. Sacrifice and Pathology

After at least 95 days of treatment, all animals were anesthetized with sodium pentobarbital and exsanguinated. Complete necropsies were performed on all survivors as well as on the 750 mg/kg/day dog which was found dead on study day 3. The following organs were weighed (from terminal sacrifice dogs) with weights expressed as absolute, relative-to-body weight and relative-to-brain weight: brain, kidneys, liver, ovaries, testes with epididymides and thyroid/parathyroids. The following tissues were preserved and examined microscopically:

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DIGESTIVE

Salivary glands*
Esophagus*
Stomach*
Duodenum*
Jejunum*
Ileum*
Cecum*
Colon*
Rectum*
Liver*
Pancreas*
Gallbladder*
Tongue

RESPIRATORY

Trachea*
Lungs*

CARDIOVASC/HEMAT

Aorta*
Heart*
Lymph nodes*
Spleen*
Thymus*
Bone marrow*

UROGENITAL

Kidneys*
Urinary bladder*
Testes*
Ovaries
Prostate
Uterus*
Epididymides

NEUROLOGIC

Brain*
Peripheral nerve*
Spinal cord (3 levels)
Pituitary*
Eyes (optic n.)

GLANDULAR

Adrenals*
Mammary gland.
Parathyroids*
Thyroids*

OTHER

Bone
Skeletal muscle
Skin
Gross lesions and
masses*

* = EPA Guideline requirements

1. MACROSCOPIC PATHOLOGY

No findings appeared to have been related to test article administration.

2. ORGAN WEIGHTS

There were statistically significant ($p < 0.05$) increases in relative liver weights for 500 mg/kg/day males and females. These appeared to be the result of a decrease in body weight gain for these dogs.

3. MICROSCOPIC PATHOLOGY

There were no histopathological findings which were considered to have been the result of test article administration.

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II. DISCUSSION

No analytical data for test article purity or stability were included in the Report.

Male dog No. 4378 (750 mg/kg/day) was found dead on study day 3 after having received 2 doses. Histopathology indicated bronchitis and pneumonia which may have been caused by the aspiration of foreign matter. Because of this death and the amount of emesis observed in the 750 mg/kg/day dogs, the high dose was lowered to 500 mg/kg/day beginning with study day 5.

The only clinical sign attributed to test article administration was the increase in the incidences of emesis in 500 mg/kg/day dogs of both sexes.

There was a statistically significant ($p < 0.01$) decrease in body weight gains over the 13-week period in males given 150 or 500 mg/kg/day. Females at 500 mg/kg/day exhibited a non-statistically significant decrease in weight gain.

The following parameters did not appear to be altered by the administration of CHLOROTHALONIL: food consumption, ophthalmology, hematology, urinalysis, macroscopic pathology, organ weights or microscopic pathology.

The primary clinical chemistry parameter effected by the test article was alanine aminotransferase levels which were ≤ 2 IU/L (group mean) at all doses for both sexes at both the 1.5 and 3 month intervals compared with control and pretreatment levels of 16-24 IU/L. Decreased levels of this enzyme is not known to be the result of tissue damage and the cause of these observations is unclear. Similar results occurred in the 30-day preliminary dog study (doses of 50, 150 and 500 mg/kg/day). In addition, there were elevated levels of cholesterol in males and females primarily at 500 mg/kg/day when compared with respective control values, but not when compared with pretreatment levels. Slightly lower albumin group mean values were noted primarily in 500 mg/kg/day dogs of both sexes.

III. CONCLUSIONS

In a subchronic toxicity study (MRID No. 43653602), CHLOROTHALONIL (97.9-98.2% purity) was administered orally by gelatin capsules to Marshall beagle dogs (4/sex/group) at doses of 0 (empty capsules), 15, 150 and 500 (reduced from 750 on study day 5) mg/kg/day for 95-98 days. The following parameters were examined: mortality, clinical signs, body weights, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, macroscopic pathology, organ weights and microscopic pathology.



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The following parameters were not affected: mortality, hematology, urinalysis, macroscopic pathology and microscopic pathology. There were increased incidences of emesis at 500 mg/kg/day (both sexes). Body weight gains were decreased at 150 and 500 mg/kg/day in males and possibly at 500 mg/kg/day in females. Alanine aminotransferase values were reduced approximately 90% in all dosed animals compared with controls as well as with pretreatment levels.

The Systemic Toxicity NOEL = 15 mg/kg/day

The Systemic Toxicity LOEL = 150 mg/kg/day based on decreased body weight gain in males

This study is Acceptable and satisfies the data requirement (§82-1) for a subchronic toxicity study in dogs.

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Reviewed by: Alan C. Levy, Ph.D. *Alan C. Levy*
Section I, Tox. Branch II (7509C) *JAN. 3, 1996*

Secondary reviewer: Yiannakis M. Ioannou, Ph.D. *J.M. Ioannou 1/3/96*
Section I, Tox. Branch II (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Chronic Oral Toxicity - Dogs (S83-1)

TEST MATERIAL: Chlorothalonil

MRID No.: 43653603

PC Code: 081901

STUDY NUMBERS: Ricerca = 92-0457; Pharmaco LSR = 92-3125
Ricerca Document No. = 5211-92-0457-TX-003

SPONSOR: ISK Biosciences Corporation

TESTING FACILITY: Pharmaco LSR Inc., East Millstone, NJ

TITLE OF REPORT: A Chronic (12-month) Oral Toxicity Study in Dogs
with Technical Chlorothalonil

AUTHORS: Maija Mizens and James Laveglia

REPORT ISSUED: December 19, 1994

EXECUTIVE SUMMARY:

In a chronic toxicity study (MRID No. 43653603), CHLOROTHALONIL (98.3% purity) was administered orally by gelatin capsules to Marshall beagle dogs (5/sex/group) at doses of 0 (empty capsules), 15, 150 and 500 mg/kg/day for 52 weeks.

There were decreases in body weight gains in males and females at 500 mg/kg/day. Alanine aminotransferase levels were reduced about 90% in all dosed animals compared with controls as well as with pretreatment levels. There were no effects on the following parameters: mortality, clinical signs, food consumption, ophthalmology, hematology, urinalysis, macroscopic pathology, organ weights and microscopic pathology.

The Systemic Toxicity NOEL = 150 mg/kg/day

The Systemic Toxicity LOEL = 500 mg/kg/day, based on decreased body weight gains in both sexes

This study is Acceptable and satisfies the data requirement (S83-1) for a chronic toxicity study in dogs.

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I. METHODS AND MATERIALS**A. Statistical Analysis (Report Appendix A, pages 57-59)**

The following parameters were analyzed: body weight/changes, clinical laboratory values and terminal organ weights/to body weight/to brain weight.

"Statistical evaluation of equality of means was made by the appropriate one way analysis of variance technique, followed by a multiple comparison procedure if needed. First, Bartlett's test was performed to determine if groups had equal variance. If the variances were equal, parametric procedures were used; if not, nonparametric procedures were used. The parametric procedures were the standard one way ANOVA using the F distribution to assess significance. If significant differences among the means were indicated, Dunnett's test was used to determine which means were significantly different from the control. If a nonparametric procedure for testing equality of means was needed, the Kruskal-Wallis test was used, and if differences were indicated a summed rank test (Dunn) was used to determine which treatments differed from control."

"A statistical test for trend in the dose levels was also performed. In the parametric case (i.e., equal variance) standard regression techniques with a test for trend and lack of fit were used. In the nonparametric case Jonckheere's test for monotonic trend was used."

"The test for equal variance (Bartlett's) was conducted at the 1%, two-sided risk level. All other statistical tests were conducted at the 5% and 1%, two-sided risk level."

B. Regulatory Compliance

A Good Laboratory Practice Compliance statement, a Quality Assurance statement and a list of Quality Assurance inspections were included in the Report.

A signed statement of no confidentiality claim was provided.

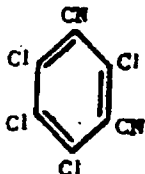
A Flagging statement for potential adverse effects (40 CFR 158.34) was included in the Report and stated that the study neither met nor exceeded any of the acceptable criteria.

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C. Test Article

Name and Formula: chlorothalonil; T-117-12; 2,4,5,6-tetrachloroisophthalonitrile



Ricerca Identification Number: T-117-12
Sponsor I.D. Number: SDS-2787-1002
Lot Number: 1002
Purity: 98.3%
Description: gray powder

D. Dose Selection

There was no indication in the Report as to the basis for choosing the doses used in this study.

In a 30-day study (Study No. 91-3762, MRID No. 43653601), dogs were dosed at 0, 50, 150 and 500 mg/kg/day with the following results: incidence of emesis increased primarily in males at 500 mg/kg/day; body weight loss for 500 mg/kg/day males; food consumption less in 2/2 males and 1/2 females at 500 mg/kg/day; alanine aminotransferase lower in all treated dogs than in controls; only females at 500 mg/kg/day had higher absolute and relative liver weights than did controls.

In a 90-day study (Study No. 92-3820, MRID No. 43653602), dogs were dosed at 0, 15, 150 and 500 mg/kg/day with the following results: increased incidences of emesis for both sexes at 500 mg/kg/day; decreased body weight gains at 150 and 500 mg/kg/day for males and possibly at 500 mg/kg/day for females; reduced alanine aminotransferase levels by 90% in all dosed dogs compared with controls and pretreatment levels.

The doses in this one-year study were: 0 (control), 15, 150 and 500 mg/kg/day body weight/day by gelatin capsule.

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Individual body weights were recorded prior to the start of the study, each week during treatment and at the end of the study (fasting weight).

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J. Food Consumption (Report Appendix F, pages 247-261)

Consumption was estimated daily from week -1 through week 2, and 4 times/week from week 3 through week 52. The estimated amount eaten was "quantitated" as follows: 0 = no observable food consumed, 1 = up to and including 1/4 consumed, 2 = up to and including 1/2 consumed, 3 = up to and including 3/4 consumed, 4 = up to but not including the entire amount consumed, and 5 = total amount consumed. Recordings of food consumed were made about 30 minutes after the first 200 g of food was given to the dogs (prior to capsule administration) and amount 4.5 hours after the initial 200 g were given (recording based on a total of 400 g of food).

K. Ophthalmology (Report pages 196 and 197)

Ophthalmoscopy was performed prior to treatment and at study termination.

L. Clinical Pathology

Blood was taken from the jugular vein of unanesthetized (fasted overnight) dogs at weeks -1, 0, 13, 26/27 and 52. Urine was collected in metabolism pans at the same intervals. Animals were water deprived for the collection of freshly voided urine and were without food or water for the 16-hour volume collection.

NOTE: Report page 34 (Methods and Materials) stated that clinical chemistry and urinalysis parameters were examined at the week 13 interval, but these data were not included in the Report.

1. HEMATOLOGY - The following parameters were examined:

Hemoglobin*	Mean corpuscular volume
Hematocrit*	Mean corpuscular hemoglobin
Erythrocyte count*	Mean corpuscular hemoglobin concentration
Reticulocyte count	Prothrombin time*
Platelet count*	Erythrocyte morphology
Leukocyte count*	Activated partial thromboplastin time*
Leukocyte differential*	

* = EPA Guideline requirement

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2. CLINICAL CHEMISTRY - The following parameters were examined:

Creatinine*	Aspartate aminotransferase*
Glucose*	Alanine aminotransferase*
Cholesterol*	Alkaline phosphatase
Total protein*	Sodium*
Albumin*	Potassium*
Globulin	Chloride*
A/G Ratio	Phosphorus*
Urea nitrogen*	Calcium*
Total bilirubin*	

* = EPA Guideline requirement

[Creatine phosphokinase* not examined]

3. URINALYSIS - The following parameters were examined:

Appearance*	Protein*	Specific gravity*
pH	Bilirubin*	Occult blood*
Ketones*	Volume*	Sediment (microscopic)*
Urobilinogen	Glucose*	

* = EPA Guideline requirement

M. Sacrifice and Pathology

Animals were fasted prior to pentobarbital anesthesia and exsanguination. Complete necropsies were performed. The following organs were weighed with weights expressed as absolute, relative-to-body weight and relative-to-brain weight: brain, kidneys, liver and testes with epididymides. The following tissues were preserved and examined microscopically:

DIGESTIVE

Salivary glands*
 Esophagus*
 Stomach*
 Duodenum*
 Jejunum*
 Ileum*
 Cecum*
 Colon*
 Rectum*
 Liver*
 Pancreas*
 Gallbladder*
 Tongue

RESPIRATORY

Trachea*
 Lungs*

CARDIOVASC/HEMAT

Aorta*
 Heart*
 Lymph nodes*
 Spleen*
 Thymus*
 Bone marrow*

UROGENITAL

Kidneys*
 Urinary bladder*
 Testes*
 Ovaries*
 Prostate*
 Uterus*
 Epididymides*

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NEUROLOGIC

Brain*
Peripheral nerve*
Spinal cord (3 levels)*
Pituitary*
Eyes (optic n.)*

GLANDULAR

Adrenals*
Mammary gland*
Parathyroids*
Thyroids*

OTHER

Bone*
Skeletal muscle*
Skin*
Gross lesions and masses*

* = EPA Guideline requirement

II. RESULTS**A. Mortality and Clinical Signs**

All dogs survived until the scheduled sacrifice after one year. Individual dog incidences of emesis are presented in Report Appendix C, pages 81-84. There was no distinct pattern regarding this parameter which differentiated treated from control animals.

B. Body WeightsTable 1

GROUP MEAN BODY WEIGHTS AND WEIGHT GAINS IN A 12-MONTH DOG STUDY
WITH CHLOROTHALONIL ADMINISTERED ORALLY BY GELATIN CAPSULE

Week	Males (mg/kg/day)				Females (mg/kg/day)			
	0	15	150	500	0	15	150	500
Body Weight-kg								
0	10.1	10.1	10.1	10.2	8.2	8.2	8.1	8.2
13	12.1	12.7	12.1	11.6	9.7	10.3	9.7	9.4
26	13.0	13.6	12.8	12.3	10.6	11.0	10.2	10.0
39	13.6	14.0	13.1	11.9	11.6	11.1	10.4	9.7
52	14.3	14.4	13.7	12.1	12.2	11.9	10.9	10.2
Body Weight Gain-kg								
0-13	2.0	2.6	2.0	1.4	1.5	2.2	1.5	1.2
0-52	4.2	4.2	3.6	2.0*	4.0	3.7	2.8	2.1*

Number of dogs = 5/sex/group

Statistical Significance: * = $p \leq 0.05$

Data extracted from Report Appendix E, pages 198-218. [Individual weights on Report pages 219-246.]

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A statistically significant ($p \leq 0.05$) decrease in body weight gain was reported for males (Report page 213) and females (Report page 39) administered the test article at 500 mg/kg/day. Over the 52-week period, for females at 150 mg/kg/day, individual dogs gained 2.0, 2.1, 2.2, 3.2 and 4.4 kg compared with control values of 2.1, 2.6, 2.9, 5.5 and 7.0 kg.

C. Food Consumption

There did not appear to be a distinct test article effect on food consumption.

D. Ophthalmology

There were no findings that were considered to have been related to test article administration.

E. Clinical Pathology

1. HEMATOLOGY

The administration of CHLOROTHALONIL did not appear to have an effect on any of the above parameters.

2. CLINICAL CHEMISTRY (See Table 2)

NOTE: No week 13 data were included in the Report.

Group mean alanine aminotransferase values for males and females of all doses were ≤ 2 IU/L compared with control means of 20-26 IU/L for the 26/27 and 52 week intervals.

Cholesterol values (group means) for females appeared to be elevated for all dose groups at the 26/27 and 52-week intervals with significance ($p \leq 0.01$) for the 500 mg/kg/day dogs at the 26/27 week interval. Group mean male values for 150 and 500 mg/kg/day animals were above controls at the 26/27 and 52-week determinations, but were essentially similar to pretreatment levels.

Group mean total protein values for males at 26/27 and 52 weeks were less than respective controls at all 3 doses with statistical significance ($P \leq 0.05$ or 0.01) for all doses at 26/27 and only 500 mg/kg/day at 52 weeks. However, these group means were similar to or greater than both pretreatment values.

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Albumin group mean values for males and females at 500 mg/kg/day were less ($p \leq 0.01$) than controls at both treatment intervals, but were similar to pretreatment values.

Table 2

CLINICAL CHEMISTRY PARAMETERS WHICH APPEARED TO HAVE BEEN ALTERED IN A 1-YEAR DOG STUDY WITH CHLOROTHALONIL ADMINISTERED ORALLY BY GELATIN CAPSULE

Parameter (weeks)	Males (mg/kg/day)				Females (mg/kg/day)			
	0	15	150	500	0	15	150	500
Alanine aminotransferase								
Pretest I	18	14*	14	15	17	15	15	16
Pretest II	16	13	13	13	17	15	18	15
26/27	24	2	1**	0	23	1*	0**	0
52	26	2	0**	0**	20	1*	1*	0
Cholesterol								
Pretest I	209	215	204	210	168	184	174	178
Pretest II	202	195	197	204	169	177	162	177
26/27	176	177	207	221	171	221	224	293**
52	161	158	208	219	181	220	223	256
Total Protein								
Pretest I	5.6	5.5	5.5	5.5	5.5	5.4	5.5	5.5
Pretest II	5.5	5.3	5.5	5.5	5.6	5.4	5.4	5.5
26/27	6.5	6.1*	5.8**	5.6**	5.9	5.9	5.8	5.7
52	6.4	6.2	6.0	5.5**	6.1	5.9	5.9	6.2
Albumin								
Pretest I	3.4	3.3	3.3	3.4	3.3	3.4	3.4	3.3
Pretest II	3.4	3.3	3.4	3.4	3.4	3.3	3.5	3.3
26/27	3.7	3.6	3.5	3.2**	3.7	3.5	3.5	3.2**
52	3.6	3.4	3.4	3.0**	3.7	3.4	3.5	3.1**

Number of dogs = 5/sex/group

Alanine aminotransferase = IU/L; Cholesterol = mg/dl; Total Protein = g/dl; Albumin = g/dl

Statistical Significance: * = $p \leq 0.05$; ** = $p \leq 0.01$

Data extracted from Report Appendix I, pages 324-404.

3. URINALYSIS

There were no apparent test article effects on any of the parameters.

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F. Sacrifice and Pathology**1. MACROSCOPIC**

No findings appeared to have been related to test article administration.

2. ORGAN WEIGHTS (See Table 3)

Individual female dog absolute liver weights (g) were as follows: 0 mg/kg/day = 228, 263, 268, 270 and 297; 15 mg/kg/day = 225, 271, 307, 308 and 337; 150 mg/kg/day = 243, 253, 307, 321 and 397; and 500 mg/kg/day = 285, 308, 312, 350 and 439.

Table 3**ABSOLUTE AND RELATIVE GROUP MEAN LIVER WEIGHTS IN A 1-YEAR DOG STUDY WITH CHLOROTHALONIL ADMINISTERED ORALLY BY GELATIN CAPSULE**

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	15	150	500	0	15	150	500
Terminal BW-kg	13.9	14.0	13.5	11.9	11.9	11.5	10.6	9.9
Absolute wt-g	323	327	379	337	265	290	304	339
Relative-to-BW	2.33	2.34	2.81**	2.85**	2.29	2.52	2.89	3.44**
Relative-to-brain wt	3.94	3.72	4.61*	4.06	3.43	3.50	3.71	4.13

Number of dogs = 5/sex/group

Statistical Significance: * = $p \leq 0.05$; ** = $p \leq 0.01$

Data extracted from Report Appendix K, pages 416-441.

3. MICROSCOPIC

The only finding considered to be possibly attributed to test article administration was renal tubular cell pigmentation where the incidence was as follows:

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Table 4RENAL TUBULAR CELL PIGMENTATION IN A 1-YEAR DOG STUDY WITH
CHLOROTHALONIL ADMINISTERED ORALLY BY GELATIN CAPSULE

Severity	Males (mg/kg/day)				Females (mg/kg/day)			
	0	15	150	500	0	15	150	500
Minimal ...	3	3	3	1	3	4	1	0
Slight/Mild	0	0	2	3	0	0	4	3
Moderate ..	0	0	0	1	0	0	0	2

Number of dogs = 5/sex/group

Data extracted from the Pathology Report, Report pages 445-483.

At least 3/5 dogs/sex had renal tubular pigmentation. There appeared to be a dose response concerning severity as only some of the 150 and 500 mg/kg/day males and females were reported to have slight/mild and only some of the 500 mg/kg/day dogs of both sexes had moderate severity.

III. DISCUSSION

Test article purity and stability data were within acceptable limits.

There was no mortality. No clinical signs appeared to be the result of test article administration. Individual dog incidences of emesis did not reveal a distinct difference between treated and control animals. In a 90-day dog study, an increase in the incidence of emesis was reported for dogs of both sexes at 500 mg/kg/day when compared with controls.

Statistically significant ($p \leq 0.05$) decreases in body weight gains were noted over the 52 weeks in males and females treated with 500 mg/kg/day. The non-significant decrease in gain seen for 150 mg/kg/day females was not considered to have been test-article related because of individual animal variation regarding this parameter.

Test article treatment did not appear to have an effect on food consumption, ophthalmoscopy, hematology or urinalysis parameters.

As was reported in the 90-day and the 30-day studies, alanine aminotransferase levels of all treated dogs were lower at all levels compared with control and pretest values. In this 52-week study, treated dog values were ≤ 2 IU/L compared with control and pretest values of 13-26 IU/L.

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Female group mean cholesterol values were above control and pretreatment levels for 500 mg/kg/day animals at the 26/27 and 52-week intervals.

Total protein and albumin values were below respective controls, primarily in 500 mg/kg/day males (both parameters) and females (albumin only). However, these observations are not considered to be of toxicological significance as they are similar to pretreatment levels and are within the expected range.

Absolute liver weights for females appeared to be above control values in a dose-response fashion (no statistical significance). Although group mean body weights for females were essentially the same at week 0 (8.1-8.2 kg for all 4 groups), final weights were 12.2, 11.9, 10.9 and 10.2 kg for the 0, 15, 150 and 500 mg/kg/day groups. Statistically significant ($p \leq 0.01$) higher relative liver weights in 500 mg/kg/day males and females were attributed to a decrease in body weight gain. Even though it appeared that there was a test article effect on absolute liver weights in females (500 mg/kg/day), the lack of effects on relevant clinical chemistry or microscopic pathology indicates that there does not appear to be a definitive toxicological effect on this tissue.

The severity of renal tubular cell pigmentation was increased in both males and females at both 150 and 500 mg/kg/day. Control and 15 mg/kg/day dogs of both sexes had 3-4 out of 5 with "minimal" severity; whereas, the two higher dose groups had 2-4/5 dogs with "slight/mild". One male and two females at 500 mg/kg/day had a "moderate" amount of pigmentation. Report page 22 stated, "The presence of this pigment had no adverse effect on the tubular epithelial cells."

IV. CONCLUSIONS

In a chronic toxicity study (MRID No. 43653603), CHLOROTHALONIL (98.3% purity) was administered orally by gelatin capsules to Marshall beagle dogs (5/sex/group) at doses of 0 (empty capsules), 15, 150 and 500 mg/kg/day for 52 weeks. The following parameters were examined: mortality, clinical signs, body weights, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, macroscopic pathology, organ weights and microscopic pathology.

There were decreases in body weight gains in males and females at 500 mg/kg/day. Alanine aminotransferase levels were reduced about 90% in all dosed animals compared with controls as well as with pretreatment levels. There were no effects on the following parameters: mortality, clinical signs, food consumption, ophthalmology, hematology, urinalysis, macroscopic pathology, organ weights and microscopic pathology.

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Chlorothalonil

Chronic Dog study S83-1

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The Systemic Toxicity NOEL = 150 mg/kg/day
The Systemic Toxicity LOEL = 500 mg/kg/day, based on decreased
body weight gains in both sexes

This study is Acceptable and satisfies the data requirement
(S83-1) for a chronic toxicity study in dogs.