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

APR 2 8 1993

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Subject: EPA ID# 018301, Chlorpropham: CIC Review of the One-Year Chronic Dog Feeding Study with Chlorpropham/393J-502-640-89 (MRID# 421895-01).

Shaughnessy #: 018301.
Caswell#: 510A.
Cas #: 101-21-3.
DP Barcode: D174543.
Case#: 81637.
Submission#: S4116442.
Action Code: 627.

From: David G Anderson, PhD David G Anderson 12/3/92
Section 3, Toxicology Branch-1
HED (H7509C)

To: Walter Waldrop/Venus Eagle, PM-71.
Reregistration Branch
SRRD (H7508W)

Thru: Karen Hamernik, PhD Karl D. Hamernik for 4/26/93
Acting Section 3 Head
Toxicology Branch-1,
HED (H7509C)

Data Reviewed:
MRID# 421895-01. J.H. Wedig. January 20, 1992. One Year Chronic Study of Chlorpropham in Dogs. Conducted at T.P.S., Inc. for Chlorpropham Task Force, John Wise & Associates, Ltd. Lab ID 393J-502-640-89.

CONCLUSIONS: Chlorpropham was administered via the diet to 4 Beagle dogs per sex per group for 60-weeks at target dose levels of 0, 5, 50, 350 or 500 mg/kg/day.

NOEL: 5 mg/kg/day (LDT).

LOEL: 50 mg/kg/day for thyroid toxicity in males and females; absolute and relative thyroid weight increase and enlargement determined under histological examination occurred with irregular shaped follicles lined with medium to high cuboidal epithelium containing clear to pale staining colloid. Thyroxine (T_4) and T_3 levels were decreased in animals with enlarged thyroids. TSH

stimulation tests indicated that chlorpropham administration resulted in reduced stimulation. Marked and moderate thyroid lesions and relative liver weight increases occurred at 350 and 500 mg/kg/day. Male and female dogs weights were decreased at 350 and 500 mg/kg/day. Treatment related effects occurred at 350 and 500 mg/kg/day in decreased erythrocyte counts, hemoglobin concentration, hematocrit levels as well as increases in cholesterol levels.

Core Classification: Minimum. The study is acceptable under guideline 83-1 for a 1-year study in dogs. ~~Stability of the chlorpropham in feed should be submitted~~. KB 4/26/93

CMemo on a CIC-DER for a 1-year study in dogs/MRID# 421895-01/B:\CHLORV25.10A\CMD1YDOG.CIC/DANDERSON/12/7/92.*

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CHLORPROPHAM TASK FORCE

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1. **NAME AND ADDRESS OF SUBMITTER:**

CHLORPROPHAM TASK FORCE
c/o John Wise & Associates, Ltd
5 Victory Lane Suite 201
Liberty, MO 64068
Consortium No: 64592

421895-00

Submitted on Behalf Of the Following Members:

Aceto Agricultural Chemicals Corporation: EPA No. 2749
Atochem North America, Inc.: EPA No. 2792

In Support of the Following Registrations:
All registrations for the above companies containing the active ingredient Chlorpropham (018301).

* Chlorpropham Task Force will act as sole agent for all submitters.

2. **REGULATORY ACTION IN SUPPORT OF WHICH THIS PACKAGE IS SUBMITTED:**

GUIDANCE FOR THE REREGISTRATION OF PESTICIDE PRODUCTS CONTAINING CHLORPROPHAM (OPP NUMBER 018301) AS THE ACTIVE INGREDIENT, CASE NUMBER 0271, ISSUED DECEMBER, 1987.

3. **TRANSMITTAL DATE:** January 30, 1991

4. **LIST OF SUBMITTED STUDIES:**

Vol I of III, Pages 1 - 252
Vol II of III, Pages 253 - 657
Vol III of III, Pages 658 - 897
One Year Chronic Study of Chlorpropham in Dogs
40 CFR 158.340
FIFRA Guideline No. 83-1(b)

421895 01

COMPANY OFFICIAL: John M. Wise, Chairman _____
Name Signature

COMPANY NAME: Chlorpropham Task Force

COMPANY CONTACT: John M. Wise (816) 781-1763
Name Phone No.

DOC930167

FINAL

DATA EVALUATION REPORT

CHLORPROPHAM

Study Title:

One Year Chronic Study of Chlorpropham in Dogs

Prepared for:

Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

August 10, 1992

Principal Author: _____ Date 11/16/92
John Piccione, Ph.D.

Reviewer: _____ Date 11/16/92
William McLellan, Ph.D.

QA/QC Manager: _____ Date 11/16/92
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 1-43.3
Clement Number: 93-55
Project Officer: James Scott

EPA Reviewer: David G. Anderson, Ph.D.
Toxicology Branch I
Health Effects Division

Signature: David G. Anderson
Date: 12/7/92

EPA Section Head: Karen Hamernik, Ph.D.
Section Head
Toxicology Branch I
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Signature: _____
Date: _____

DATA EVALUATION REPORT

STUDY TYPE: Chronic feeding dog study

Shaughnessy NO: 018301

MRID Number: 421895-01

TOX CHEMICAL NO: 510 A

Caswell Number: 101-21-3

PC barcode: D174543

TEST MATERIAL: Chlorpropham

SYNONYM: Chlorprophame; Isopropyl N-(3-chlorophenyl)carbamate

STUDY NUMBER: 393J-502-640-89

SPONSOR: CHLORPROPHAM TASK FORCE, John Wise & Associates, Ltd., Liberty, MD.

TESTING FACILITY: T.P.S., Inc., Mt. Vernon, Indiana

TITLE OF REPORT: One Year Chronic Study of Chlorpropham in Dogs

AUTHOR: J.H. Wedig, Ph.D., DABT

REPORT ISSUED: January 20, 1992

CONCLUSIONS: Chlorpropham was fed to groups of four Beagle dogs/sex for 60 weeks at dietary levels to provide dose levels of 0, 5, 50, 350 or 500 mg/kg/day . Marked decreases in food consumption were noted in dogs receiving 350 or 500 mg/kg/day during week 1 indicating unpalatability of the test diets at these dose levels. Food consumption in dogs receiving 350 mg/kg/day returned to normal during week 2, whereas food consumption in the high-dose dogs returned to normal after adjustment of the concentration of the test material in the diets between weeks 4 and 8. Decreases in body weight gain (compared to those of controls) were noted in dogs receiving 350 or 500 mg/kg/day throughout the treatment period. Assessment of pathology and clinical chemistry data indicate the thyroid as a target organ. Moderate-to-severe histopathological findings in the thyroid (irregularly shaped follicles lined by medium-to-high cuboidal epithelium containing clear-to-pale staining colloid) were observed in dogs receiving 50, 350 or 500 mg/kg/day. Gross findings in these dogs included slight-to-moderate enlargement of the thyroid. Also, absolute and relative thyroid weights were increased in these dogs. Results of thyroid hormone analyses showed decreases in T_3 and T_4 levels in dogs receiving 50, 350 or 500 mg/kg/day. Other changes noted in dogs receiving 350 or 500 mg/kg/day included increases in cholesterol levels,

platelets and mean corpuscular volume, and decreases in red blood cell count, hemoglobin and hematocrit levels, and mean corpuscular hemoglobin concentration.

The LOEL is 50 mg/kg/day based on thyroid effects. The NOEL is 5 mg/kg/day.

CORE CLASSIFICATION: Core Minimum. ~~Although~~ This study is acceptable under the guidelines (83-1) for a chronic study in dogs. ~~test material stability data in the feed should be submitted~~. KBH/26/93

A. MATERIALS, METHODS, AND RESULTS

1. Test Article Description

Name: Chlorpropham

Chemical Name: Isopropyl N-(3-chlorophenyl)carbamate

Lot number: 14065-L-89

Purity: 96.2±2% (Sponsor analysis)

Physical property: White crystalline solid

Stability: Not reported

2. Test Article Analyses for Purity and Stability

Test diets were prepared weekly. Prior to use, the crystalline solid was completely melted in a constant temperature cabinet at 45-47°C. In some instances a liquid aliquot containing test material was used, while in other instances the chlorpropham was allowed to harden and then ground into a powder with a mortar and pestle before addition to the test diets. Appropriate amounts of the material were then dissolved in Mazola corn oil (doses calculated to correct the test material to 100%) and the solution was mixed with approximately 2.5-6.5 kg of Purina Certified Canine Diet Meal no. 5007 in a Univex M-20 mixer for 15 minutes in order to prepare a preblend. Control diets without test material were prepared in the same manner. Final test diet concentrations were achieved by mixing the preblend with the appropriate amount of dog chow in either a PK V-blender or a Hobart Model V1401 mixer.

Samples of 100 g were taken from the top, middle, and bottom of all test diets and were analyzed by high performance liquid chromatography for test material concentration at weeks 1 through 7, and at weeks 9, 16, 28, 40, 50 and 60. Mean results for verification of chlorpropham levels in the diets at 190, 210, 2000, 2100, 14500, and 20500 ppm dose levels were within ±6% of target dose. The distribution of the test material in the feed was homogeneous. The purity and stability of the test material was determined by the sponsor prior to study initiation. The purity was reported to be

96.2±2%. ~~Results of stability analyses were not presented in the study report.~~ KB 4/28/93

3. Animals

Species: Dog
Strain: Beagle
Age and weight at study initiation: 7 Months; Males -- 9.6-14.8 kg; Females -- 8.1-13.3 kg.
Source: Hazleton/LRE Research Products
Kalamazoo, MI

Animals were acclimated to laboratory conditions for approximately 2 months and were assigned to groups using a computer generated randomization list.

Group Number	Dose Level (mg/kg/day)	Number of Animals (60 weeks) Males	Females
1	0	4	4
2	5	4	4
3	50	4	4
4	350	4	4
5	500	4	4

The health status of each animal was determined by a pretest physical examination including ophthalmology and clinical pathology. The dogs were housed individually in stainless steel cages in an isolated animal room with controlled temperature (58-84°F) and humidity (40-83%), and with 10-15 air changes/hour and a 12 hour light/dark cycle. Tap water and test diets were provided ad libitum.

Rationale for dose selection: A rationale for dose selection was not discussed in the study report. However, a 4-week range-finding study in dogs (MRID# 418990-01) was available for review. In the range-finding study, chlorpropham was fed to male and female dogs at dose levels of 0, 5, 50 or 500 mg/kg/day for 28 days. Moderate-to-severe histopathological changes in the thyroid (irregularly shaped follicles lined by medium-to-high cuboidal epithelium containing clear-to-pale staining colloid) were observed in the mid- and high-dose dogs. Slight splenic lymphoid atrophy and decreased body weight gains were seen in the high-dose dogs. Absolute and relative spleen weights were decreased in the mid- and high-dose dogs. There were no significant effects on mortality, clinical signs, hematology, clinical chemistry, or ophthalmology.

4. Statistics

Dunnett's test was utilized to evaluate body weight, food consumption, hematology and clinical chemistry data.

5. Quality Assurance

A statement of compliance with Good Laboratory Practice Standards and a Quality Assurance Statement, both signed and dated, were provided in the study report.

B. METHODS AND RESULTS

1. General Observations: All dogs were observed twice daily for clinical signs of toxicity and mortality. Each animal received a weekly general physical examination. A veterinary clinical assessment was performed when necessary.

Results: One male (ID # ANT3M03) receiving 50.9 mg/kg/day was sacrificed following several violent episodes of clonic-tonic convulsions on day 146. Animals in group 4 and 5 did not exhibit convulsions. All remaining animals survived to the scheduled terminal sacrifice.

Results of physical examinations revealed that dogs receiving 350 mg/kg/day (2 males; 3 females) or 500 mg/kg/day (4 male; 3 females) were thin; the thinness was regarded by the study author to be reflective of unpalatability of the diets (discussed below) at these dose levels.

2. Body Weight and Food Consumption:

Individual body weights were recorded at pretest, prior to dosing on test day 1, approximately weekly thereafter, and prior to necropsy. Individual food consumption was determined weekly throughout the treatment period.

Results:

Body Weight: Table 1 summarizes body weight gain data. Significant decreases in mean body weight gain (>10% when compared to those of controls) were noted in males and females receiving 350 or 500 mg/kg/day during week 1. The loss in body weight was apparently due to unpalatability of the test diets. Between weeks 1 and 3, males receiving 50 or 350 mg/kg/day exhibited gradual increases in body weights, while the high-dose males showed gradual increases in body weights following week 4 and after adjustment of chlorpropham concentration in the high-dose diets between weeks 4 and 8 (discussed below). However, mean body weight gains in group 4 (350 mg/kg/day) and group 5 (500 mg/kg/day) males remained lower than the weight gains of control animals throughout the treatment period. Overall mean body weight gain in males receiving 350 mg/kg/day was 37.1% lower than those of controls at week 60. Overall mean body weight

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TABLE 1. Mean Body Weight Gain (kg) at Selected Intervals for Dogs Fed Chlorpropham for 60 Weeks[a]

Week(s)	Dose Groups (mg/kg/day) 0	5	50	350	500
			Males		
1	0.12±0.1	0.23±0.2	-0.03±0.1	-0.92±0.9*	-1.31±0.2*
13	1.40±0.7	1.39±0.5	1.04±0.3	0.62±1.3	-0.37±0.9*
25	1.70±0.6	1.70±0.5	1.17±0.1	0.85±1.2	-0.03±1.1**
52	2.41±1.1	2.20±0.7	2.03±0.6	1.55±1.5	0.60±1.8
60	2.72±1.1	2.41±0.8	2.30±0.6	1.71±1.5	0.32±1.6*
			Females		
1	0.04±0.2	0.09±0.3	0.06±0.1	-1.21±0.4**	-1.04±0.4
13	0.50±0.6	0.74±0.6	0.49±0.2	-0.23±1.0	0.52±0.4
25	0.45±0.2	0.31±0.6	0.84±0.2	0.46±0.8	0.89±0.3
52	2.09±0.8	2.53±1.9	1.40±0.5	1.18±1.0	1.16±1.3
60	2.01±0.6	3.01±2.4	1.54±0.4	1.30±0.7	1.44±1.1

[a]Data extracted from tables 5 and 6 of the study report.

*Significantly different from control value, $p<0.05$.
**Significantly different from control value, $p<0.01$.

gain in the high-dose males was 88.2% lower than those of controls at week 60. Between weeks 3 and 4, group 4 females showed increases in body weight, whereas group 5 females showed increases in body weights at weeks 4 and 5. Mean body weight gains in group 4 females remained lower (nonsignificantly) than those of controls throughout the study; examination of individual animal data revealed that the body weight decrement was particularly evident in 2 females (# ANT4F01 and ANT4F04). Mean body weight gains in the high-dose females were roughly similar or slightly lower (nonsignificantly) than controls throughout the treatment period. Overall mean body weight gain in females receiving 350 mg/kg/day was 35.3% lower than those of controls at week 60. Overall mean body weight gains in the high-dose females was 28.4% lower (nonsignificantly) than those of controls at weeks 13 and 52, respectively.

Food Consumption: Table 2 summarizes food consumption data. There was an apparent palatability problem with the 350 and 500 mg/kg/day test diets because the group 4 (350 mg/kg/day) and group 5 (500 mg/kg/day) animals consumed very little food during the first week. Food consumption improved in dogs receiving 350 mg/kg/day (except male # ANT4M03 which consumed very little food up to week 4) during week 2; mean food intake of these animals was higher than that of controls during weeks 4 (males and females) and 5 (males), and thereafter returned to expected levels. In order to encourage food intake in male # ANT4M03, the dietary concentration of test material was reduced from 13700 ppm to 5000 ppm during week 4; 750 ppm at week 5; and increased to 10000 ppm at week 6; and 14000 ppm at week 7.

Compound Intake: Mean actual compound intakes calculated over the 60 week period in males were 0 mg/kg/day (Group 1), 5.5 mg/kg/day (Group 2), 50.9 mg/kg/day (Group 3), 351.9 mg/kg/day (Group 4), and 465.2 mg/kg/day (Group 5). In females, the mean compound intakes were 0 mg/kg/day (Group 1), 5 mg/kg/day (Group 2), 51.6 mg/kg/day (Group 3), 365 mg/kg/day (Group 4) and 447.8 mg/kg/day (Group 5).

3. Ophthalmologic examinations:

Examinations were performed on all dogs with an ophthalmoscope prior to treatment and prior to necropsy. The pupils of each animal were dilated with a mydriatic before examination.

Results: There were no treatment-related effects on ophthalmoscopic findings.

4. Clinical Pathology:

Hematological and clinical chemical analyses were performed on all dogs prior to study initiation and at weeks 9, 13, 26, 52 and 60. Blood was collected from the jugular vein. All animals were fasted overnight prior to blood collections. The checked (X) parameters were examined:

(a) Hematology

TABLE 2. Mean Food Consumption (g/kg/day ± SD) at Selected Intervals for dogs Fed Chlorpropham[a]

	Dose Group (mg/kg/day)				
Week(s)	0	5	50	350	500
			Males		
1	24.6±2.9	26.7±2.1	26.2±5.3	11.8±15.6	3.7±5.3
4	27.8±2.4	28.6±2.9	28.1±5.2	35.7±4.9	48.3±10.8
13	24.5±2.9	28.9±1.3	23.1±3.9	26.6±6.0	24.0±6.7
52	22.1±4.4	25.8±5.5	18.9±0.3	21.1±5.7	18.8±4.4
60	17.2±0.8	21.7±1.4	18.7±7.2	20.8±5.6	16.7±1.3
			Females		
1	27.4±4.2	28.8±1.4	27.4±4.7	5.0±7.9	5.0±8.2
4	31.1±1.9	30.7±109	27.9±4.0	38.1±9.9	51.3±13.8
13	27.0±2.9	24.6±2.5	23.8±3.4	31.2±5.4	20.6±2.7
52	22.8±2.1	19.5±2.1	20.8±2.2	22.9±2.4	23.1±2.5
60	16.0±6.1	15.4±3.5	17.6±2.5	21.5±2.6	17.5±6.1

[a]Data extracted from Tables 7 and 8 of the study report.

X Hematocrit (HCT)*
X Hemoglobin (HGB)*
X Leukocyte count (WBC)*
X Erythrocyte count (RBC)*
X Platelet count*
Reticulocyte count (RETIC)
Red cell morphology
X Leukocyte differential count
X Mean corpuscular HGB (MCH)
X Mean corpuscular HGB concentration (MCHC)
X Mean corpuscular volume (MCV)
Coagulation: thromboplastin time (PT)

* = Recommended by Subdivision F (November 1984) Guidelines

Results: Table 3 summarizes selected hematology data. Decreases in red blood cell count, hemoglobin and hematocrit levels, and mean corpuscular hemoglobin concentration were noted in group 4 (350 mg/kg/day) and group 5 (500 mg/kg/day dogs); the decreases reached statistical significance ($p<0.05$ or $p<0.01$) at various intervals of the study. In addition, an increase in platelet levels and mean corpuscular volume was observed in group 4 and 5 males and females at weeks 9, 13, 26, 52 and 60. The alterations in hematology parameters were treatment related.

(b) Blood (clinical) chemistry

Electrolytes

X Calcium*
X Chloride*
Magnesium*
X Phosphorus*
X Potassium*
X Sodium*

Enzymes

Alkaline phosphatase (ALP)
X Cholinesterase
X Creatinine phosphokinase
Lactic acid dehydrogenase
Serum alanine aminotransferase (SGPT)*
X Serum aspartate aminotransferase (SGOT)*
X Gamma glutamyltransferase (GGT)

Other

X Albumin*
X Albumin/globulin ratio
X Blood creatinine*
X Blood urea nitrogen*
X Cholesterol*
Globulins
X Glucose*
X Total bilirubin*
Direct bilirubin
X Total protein*
Triglycerides
Phospholipid
X Thyroid hormones (T_3, T_4)

* = Recommended by Subdivision F (November 1984) Guidelines

In addition, a TSH Stimulation test was performed on each dog. Serum was collected for T3 and T4 from each dog just prior to TSH injection at pretest and during weeks 14, 26, 54 and 60. TSH was given IV in the cephalic vein at a rate of 1 mL/minute. Serum was again collected four hours post injection for T4 assay.

Results: Alterations in thyroid hormone levels were noted in males and females (Table 4a). Significant decreases in

TABLE 3. Representative Hematological Parameters (Mean±S.D.) in Dogs Fed Chlorpropham for One Year[a,b]

Parameter/ Weekly Interval	Dose Groups (mg/kg/day)									
	Males					Females				
	0	5	50	350	500	0	5	50	350	500
RBC (10^6/mm^3)										
Week - 0	7.29±0.27	7.54±0.60	7.65±0.76	7.49±0.79	7.58±0.33	7.39±0.88	8.27±0.56	7.76±0.38	7.28±0.49	7.63±0.56
9	7.90±0.34	7.80±0.36	7.71±0.79	6.23±1.00**	6.27±0.42**	7.51±0.34	7.79±0.57	7.38±0.30	5.76±0.49**	6.23±0.79*
13	6.85±0.23	7.42±0.33	7.30±0.75	5.69±0.92*	5.63±0.25*	7.17±0.31	6.87±0.77	6.89±0.06	5.55±0.72**	5.63±0.82**
26	7.63±0.22	7.91±0.65	8.32±0.62	6.37±0.51	6.36±0.63*	7.52±0.38	7.42±0.98	7.10±1.34	5.80±0.45*	6.29±0.68
52	7.96±0.41	8.37±0.32	8.05±0.93	6.81±0.76	6.87±0.88	7.12±0.55	7.40±0.95	8.11±0.36	6.16±0.97	6.74±0.43
60	7.85±0.23	8.20±0.63	7.81±0.69	6.47±0183	6.40±1.19	6.85±0.28	7.71±0.73	7.30±0.38	5.34±0.72*	5.85±1.05
Hemoglobin (g/dL)										
Week - 0	15.6±0.5	15.7±1.1	15.9±1.5	15.5±1.2	16.0±0.9	15.9±0.8	17.1±1.1	16.4±0.4	15.4±1.0	15.7±1.2
9	17.0±0.9	16.5±0.3	16.6±1.6	13.5±1.6**	14.2±0.3**	15.7±0.7	16.3±0.9	15.6±0.9	12.4±1.0**	13.5±1.4*
13	15.2±0.6	15.8±0.7	15.7±1.4	12.9±1.7*	13.0±0.6*	15.8±1.0	15.2±1.7	15.3±0.4	12.5±1.3	12.7±1.8*
26	16.8±0.3	17.0±1.0	17.5±1.1	13.8±0.6**	14.4±1.3**	16.9±0.8	16.4±2.0	15.7±2.5	13.0±0.8*	14.0±1.6
52	18.1±0.9	18.5±0.5	17.7±1.6	15.4±1.4	15.9±2.1	16.4±1.1	17.1±1.9	18.3±0.5	14.4±1.9	15.3±1.0
60	17.8±0.5	18.0±1.0	17.2±1.4	14.7±1.5	14.9±2.7	15.9±0.7	17.4±1.3	16.4±0.5	12.4±1.6*	13.2±2.2
Hematocrit (%)										
Week - 0	45.2±1.5	45.2±2.6	45.9±4.4	45.0±2.4	47.4±2.3	45.3±4.2	49.6±3.1	47.3±1.8	44.2±2.9	45.5±3.4
9	48.3±2.4	46.8±1.0	47.1±4.2	39.7±4.5**	41.8±0.9*	46.1±1.7	47.5±3.6	45.3±2.7	37.2±3.2**	40.4±3.3*
13	44.0±2.2	45.9±1.5	45.9±4.0	37.9±4.9	38.8±1.8	46.0±2.2	43.5±4.8	44.3±1.5	36.8±3.6*	37.9±5.2*
26	48.5±1.4	48.9±2.6	51.1±3.4	41.5±2.0*	43.4±3.9	48.5±1.9	47.4±5.3	45.3±6.9	39.0±2.4*	41.5±3.8
52	51.7±3.1	52.2±1.0	51.3±5.1	45.0±4.7	47.5±6.6	47.'±2.8	49.4±6.3	52.1±1.2	42.3±5.5	45.3±2.1
60	51.3±2.0	51.4±2.8	49.8±3.1	44.8±4.3	44.5±7.9	45.5±2.0	50.2±3.1	47.3±0.9	36.7±4.6*	39.5±5.6

TABLE 3 (Continued)

Parameter/ Weekly Interval	Dose Groups (mg/kg/day)									
	Males					Females				
	0	5	50	350	500	0	5	50	350	500
MCHB (g/dL)										
Week - 0	34.6±0.2	34.7±1.0	34.7±0.5	34.4±0.8	33.8±0.2	35.3±1.7	34.5±0.2	34.6±0.6	34.8±0.3	34.5±0.7
9	35.2±0.7	35.4±0.3	35.2±0.3	34.1±0.6*	33.9±0.2**	34.1±0.4	34.4±1.0	34.4±0.1	33.2±0.1	33.4±0.7
13	34.5±0.3	34.3±0.4	34.3±0.3	33.9±0.6	33.5±0.3*	34.4±0.5	34.9±0.2	34.5±0.6	34.0±0.4	33.4±0.6*
26	34.7±0.8	34.8±0.4	34.2±0.3	33.4±0.4**	33.3±0.4**	34.8±0.6	34.6±0.5	34.7±0.6	33.4±0.2**	33.6±0.7*
52	35.0±0.3	35.4±0.9	34.6±0.6	34.3±0.6	33.4±0.6**	34.8±0.6	34.7±0.7	35.1±0.4	34.1±0.1	33.8±0.6
60	34.7±0.4	34.9±0.6	34.4±0.8	32.7±0.6**	33.4±0.7*	34.9±0.2	34.5±0.4	34.6±0.5	33.9±0.8	33.4±1.1*

[a]Data extracted from Table 10 of the study report.
[b]Data based on 4 dogs/sex/group except for group 3 (50 mg/kg/day) males at weeks 26, 52, and 60 in which data are based on 3 dogs.

*Significantly different from control values, $p<0.05$.
**Significantly different from control values, $p<0.01$.

TABLE 4a. Mean Levels (±S.D.) of Thyroid Hormones in Dogs Fed Chlorpropham for 52 Weeks[a,b]

Paramter/ Weekly Interval	Dose Group (mg/kg/day)				
	0	5	50	350	500
Males					
T_3 (ng/dL)					
Week - 0	0.47±0.1	0.33±0.2	0.44±0.2	0.39±0.1	0.42±0.1
14	0.85±0.3	0.83±0.2	1.05±0.2	0.64±0.2	0.60±0.1
26	0.99±0.2	0.83±0.3	1.00±0.3	0.58±0.2	0.59±0.1
54	1.21±0.4	0.81±0.2	0.91±0.1	0.60±0.2	0.59±0.0*
60	1.28±0.4	1.04±0.2	1.20±0.1	0.68±0.2*	0.80±0.2*
T_4 (µg/dL)					
Week - 0	4.68±1.0	4.40±0.8	5.00±0.3	4.60±0.7	4.05±0.7
14	4.66±1.2	4.09±0.5	3.37±0.4*	2.62±0.4*	2.45±0.2*
26	5.25±1.1	5.27±1.3	4.13±0.6	3.59±0.2	2.99±0.5*
54	3.86±0.9	4.02±0.7	2.96±0.3	2.70±0.3	2.37±0.5*
60	3.89±1.0	4.12±0.7	2.87±0.6	2.66±0.1*	2.58±0.2*
Females					
T_3 (ng/dL)					
Week - 0	0.34±0.1	0.48±0.2	0.36±0.1	0.40±0.1	0.32±0.0
14	1.56±0.5	1.85±0.3	1.15±0.2	0.97±0.1*	0.86±0.2*
26	0.62±0.2	0.85±0.2	0.54±0.1	0.41±0.1	0.38±0.2
54	0.66±0.2	1.19±0.6	0.90±0.2	1.25±1.0	0.54±0.1
60	0.98±0.2	1.38±0.3*	1.21±0.2	0.80±0.1	0.94±0.1
T_4 (µg/dL)					
Week - 0	4.17±0.8	5.90±1.4	4.87±1.3	5.24±1.3	4.46±1.0
14	3.96±0.9	6.16±1.3*	2.64±0.9	2.37±0.5	2.70±0.4
26	4.49±1.1	6.18±1.6	3.65±1.3	3.28±0.1	3.64±0.4
54	4.47±1.3	5.16±1.2	3.28±0.1	2.69±0.3*	3.14±0.3
60	4.00±0.8	5.10±1.6	3.64±0.4	2.69±0.3	2.88±0.2

[a]Data extracted from Tables 11 and 12 of the study report.
[b]Data based on 4 dogs/sex/group except for group 3 (50 mg/kg/day) males at weeks 26, 54, and 60 in which data are based on 3 males.

*Significantly different from control values, $p<0.05$.

triiodothyronine (T_3) levels were seen in group 4 (350 mg/kg/day) and group 5 (500 mg/kg/day) males at weeks 54 and 60. A decreasing trend in T_3 levels was noted in females receiving 50, 350, or 500 mg/kg/day. Significant decreases in thyroxine (T_4) levels were seen in males receiving 50, 350 or 500 mg/kg/day at week 14. Significant decreases in T_4 levels were observed in the high-dose males at weeks 26, 54 and 60. T_4 levels were also significantly reduced in males receiving 350 mg/kg/day at week 60. A decreasing trend in T_4 levels was seen in females receiving 50, 350 or 500 mg/kg/day, although statistical significance was generally not reached. The effects on thyroid hormone levels were treatment related. Results of T4 determinations made before and after TSH stimulation are summarized in Table 4b. Following 14 weeks of treatment, T4 levels were significantly ($p<0.05$) decreased in males receiving 50, 350, or 500 mg/kg four hours after TSH stimulation. T4 levels after TSH stimulation remained significantly reduced in the high-dose males at weeks 26, 54, and 60. A decreasing trend in T4 levels after TSH stimulation was also noted in females receiving 50, 350, or 500 mg/kg; however, the decreases for the most part did not reach statistical significance. Total cholesterol levels were for the most part significantly increased in group 4 and 5 males and females at each interval (data not shown). The study author considered the increase in cholesterol levels and decreases in thyroid hormone levels to be a possible treatment related secondary hypothyroidism effect. Test results on cholinesterase failed to detect any dose related effects.

(c) Urinalysis

Urinalysis was performed on all animals prior to initiation of treatment and at weeks 13, 26, and 60. The checked (X) parameters were examined:

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

* = Recommended by Subdivision F (November 1984) Guidelines

Results: Bilirubin levels were increased in the urine from week 13 to the end of the study in Groups 3 and 4 males. There were no changes of toxicological significance in the urinalysis parameters.

5. Sacrifice and Pathology

All dogs, including the group 3 male sacrificed on day 146, received a complete necropsy. Tissues were fixed with 10% buffered formalin. The checked (X) tissues were examined histologically. In addition, the (XX) organs were weighed:

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TABLE 4b. Mean Levels T4 Levels Before and After TSH Stimulation in Dogs Fed Chlorpropham for 52 Weeks

Weekly Interval	Dose Group (mg/kg/day) 0	5	50	350	500
			Males		
Week 0					
Before	0.80	0.83	1.04	1.04	0.82
After	4.68	4.40	5.00	4.60	4.05
Week 14					
Before	1.76	1.30	1.84	1.61	1.50
After	4.66	4.09	3.37*	2.62*	2.45*
Week 26					
Before	2.11	1.79	1.69	2.29	1.82
After	5.25	5.27	4.13	3.59	2.99*
Week 54					
Before	1.49	1.17	1.50	1.60	0.99
After	3.86	4.02	2.96	2.70	2.37*
Week 60					
Before	1.14	1.12	1.44	1.40	1.44
After	3.89	4.12	2.87	2.66*	2.58*
			Females		
Week 0					
Before	1.09	1.10	0.97	1.21	1.19
After	4.17	5.90	4.87	5.24	4.46
Week 14					
Before	1.77	2.44	1.57	1.80	1.58
After	3.96	6.16*	2.64	2.37	2.70
Week 26					
Before	1.71	2.89*	2.29	2.14	2.19
After	4.49	6.18	3.65	3.28	3.64
Week 54					
Before	2.03	2.49	1.70	1.56	1.62
After	4.47	5.16	2.76*	2.69*	3.14
Week 60					
Before	1.69	2.33	1.81	1.78	2.01
After	4.00	5.10	2.84	2.69	2.88

*Significantly different from control values, $p<0.05$.

Digestive System	Cardiovascular/Hematologic	Neurologic
Tongue	X Aorta*	XX Brain
X Salivary glands*	XX Heart*	X Peripheral nerve (sciatic nerve)*
X Esophagus*	X Bone marrow*	X Spinal cord (three levels)
X Stomach*	X Lymph nodes*	XX Pituitary*
X Duodenum*	XX Spleen	X Eyes (optic nerve)*
X Jejunum*	X Thymus	
X Ileum*		Glandular
X Cecum*	Urogenital	
X Colon*		XX Adrenals*
X Rectum	XX Kidneys*	Lacrimal gland
XX Liver*	X Urinary bladder*	X Mammary gland
X Gallbladder*	XX Testes*	XX Thyroids*
X Pancreas*	X Epididymides	X Parathyroids*
	X Prostate	Harderian glands
Respiratory	Seminal vesicle	
	XX Ovaries	
X Trachea*	X Uterus	
X Lung*	Vagina	

Other

X Bone (sternum and femur)*
X Skeletal muscle*
X Skin
X All gross lesions and masses

* = Recommended by Subdivision F (November 1984) Guidelines

(a) Organ Weights:

Table 5 presents thyroid and liver weight data in dogs fed chlorpropham for 60 weeks. Absolute and relative (to body weight) thyroid weights of males and females receiving 50, 350 or 500 mg/kg/day were significantly increased when compared with controls. The increases were treatment related. A significant increase in relative liver weight was noted in males and females receiving 350 or 500 mg/kg/day; however, the increases did not correspond to any elevations in serum liver enzymes or hepatic histological lesions.

(b) Gross pathology:

Slight-to-moderate enlargement of the thyroid glands was noted in dogs receiving 50 mg/kg/day (2 males; 3 females), 350 mg/kg/day (3 males; 4 females), or 500 mg/kg/day (4 males; 4 females).

(c) Microscopic pathology:

TABLE 5. Absolute and Relative Thyroid and Liver Weights (Mean±S.D.) for Dogs Fed Chlorpropham for One Year[a,b]

Sex/Dose Level (mg/kg/day)	Thyroid	Liver
	Organ Weights (g)	
Male		
0	1.06±0.31	308.1±51.8
5	1.21±0.19	316.3±63.9
50	2.07±0.68*	295.8±47.9
350	3.24±0.59**	383.1±43.7
500	2.39±0.34	404.9±53.5
Female		
0	0.79±0.10	264.9±45.0
5	0.96±0.04	247.0±37.6
50	1.84±0.22*	273.8±30.9
350	3.12±0.63**	356.4±49.4
500	3.34±0.82	396.0±68.7**
	Organ-to-body weight ratios (%)	
Male		
0	0.0074±0.0020	2.154±0.17
5	0.0089±0.0017	2.290±0.29
50	0.0157±0.0042**	2.264±0.24
350	0.0260±0.0020**	3.098±0.16**
500	0.0199±0.0042**	3.320±0.36**
Female		
0	0.0066±0.0013	2.186±0.30
5	0.0083±0.0019	2.080±0.23
50	0.0175±0.0010**	2.631±0.33
350	0.0295±0.0041**	3.378±0.24**
500	0.0276±0.0052**	3.304±0.66**

[a]Data extracted from Tables 13 and 14 of the study report.
[b]Data based on 4 dogs/sex/dose level except for group 3 (50 mg/kg/day) males in which data are based on 3 males.

*Significantly different from control values, $p<0.05$.
**Significantly different from control values, $p<0.01$

Histopathological findings in the thyroid gland (characterized by irregular shaped follicles lined by medium-to-high cuboidal epithelium and containing clear-to-pale staining colloid), were observed in dogs receiving 50, 350, or 500 mg/kg/day. Marked thyroid lesions were observed in dogs receiving 350 mg/kg/day (1 males; 4 females). The lesions were moderate in dogs receiving 50 mg/kg/day (3 males; 4 females), 350 mg/kg/day (2 males; 1 female), or 500 mg/kg/day (3 males). Slight thyroid lesions were noted in control dogs (4 males; 4 females) and in dogs receiving 5 mg/kg/day (4 males; 4 females) or 50 mg/kg/day (1 male).

C. DISCUSSION

The design and conduct of the study were adequate for a chronic oral study in dogs. Results of stability analyses of the test material (conducted prior to initiation of the study) were not presented for review.

Unpalatability of the 350 and 500 mg/kg/day test diets was apparent during the first week of the study. Dogs receiving 350 or 500 mg/kg/day consumed very little food during the first week; as a result, body weight loss was also evident in these animals. Group 4 (350 mg/kg/day) dogs eventually adapted to their diets; whereas, adjustment of the concentration of the test material in the group 5 (500 mg/kg/day) diets was necessary in order to encourage feeding among the group 5 dogs. Mean body weight gains in the groups 4 and 5 dogs remained lower than those of controls throughout the treatment period. Unpalatability of chlorpropham in the test diet (500 mg/kg/day) was also noted in a previous 28-day repeated oral study in dogs.

The results of gross and histologic examinations indicated the thyroid as a target organ, consistent with the findings of a previous repeated oral study in dogs. There was an increase in the severity of thyroid lesions (i.e., irregularly shaped follicles lined by medium-to-high cuboidal epithelium containing clear-to-pale staining colloid) in dogs receiving 50, 350 or 500 mg/kg/day. In addition, T_3 and T_4 levels were decreased and thyroids were enlarged in these animals. Results of the TSH stimulation test indicated that chlorpropham directly affected the ability of the thyroid to respond to hormone stimulation, i.e., direct toxicity rather than indirectly through the pituitary. Also, absolute and relative thyroid weights were increased in dogs receiving 50, 350, or 500 mg/kg/day. Cholesterol levels were increased in dogs receiving 350 or 500 mg/kg/day, suggesting a possible hypothyroidism effect.

Treatment-related hematological effects in dogs receiving 350 or 500 mg/kg/day consisted of decreases in red blood cell count, hemoglobin and hematocrit levels, and mean corpuscular hemoglobin concentration and increases in platelets and mean corpuscular volume.

Based on effects in the thyroid, the LOEL is 50 mg/kg/day, and the NOEL is 5 mg/kg/day.