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FINAL

009677

DATA EVALUATION RECORD

THIRAM

Study Type: Chronic Feeding Study in Dogs

Prepared for:

Healths Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency

Prepared by:

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Contract Number: 68D10075
Work Assignment Number: 1-36
Clement Number:
Project Officer: James Scott

Guideline Series 83-1: Chronic Toxicity

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Date: 8/7/92

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STUDY TYPE: Chronic feeding study in dogs

EPA IDENTIFICATION NUMBERS

TOX CHEM NUMBER:

MRID NUMBER: 419679-0

TEST MATERIAL: Tetramethylthiuram disulfide; purity: 97.5%

SYNONYMS: Thiram, AAtack, Aules, Chipco Thiram 75, Fermide 850, Fernasan, FMC 2070, Hexathir, Mercuram, Micropearls, Nomersan, Polyram-Ultra, Spotrete, Thioknock, Thiodex, Thiramad, Thirasan, Thiuramin, Tirampa, TMTC, TMTDS, Trametan, Tuads

SPONSOR: Uniroyal Chemical Company, Inc., Bethany, Connecticut

STUDY NUMBER: HLA 6111-112

PROTOCOL NUMBER: TP7209

TESTING FACILITY: Hazleton Laboratories America, Madison, Wisconsin

TITLE OF REPORT: 52-Week Dietary Chronic Toxicity Study with Thiram in Dogs

AUTHOR: D. Kehoe

REPORT ISSUED: June 28, 1991

CONCLUSIONS: Thiram was fed to groups of six beagle dogs/sex for 52 weeks at dosage levels of 0, 30, 90, or 250 ppm (for males: 0, 0.84, 2.61, or 7.35 mg/kg/day; for females: 0, 0.90, 2.54, or 7.23 mg/kg/day). Compound-related systemic toxicity was evidenced in dosage-related trends of reduced levels of total protein and albumin, increased levels of cholesterol, and significantly increased liver-to-body weight ratios in males of all dosage groups, with similar findings in females at 90 and 250 ppm. In addition, male body weight was slightly affected at 250 ppm. Based on these results, the LOEL values for systemic toxicity were 30 ppm (0.84 mg/kg/day) in males and 90 ppm (2.54 mg/kg/day) in females. A NOEL was not determined for males; for females it was 30 ppm (0.90 mg/kg/day)

Core Classification: This study is Core Supplementary for chronic toxicity (Guideline 83-1) as a NOEL was not determined for males.

A. MATERIALS:

1. Test Compound: Thiram

Description: off-white powder
Stability: stable
Solubility: insoluble
Lot no.: 117
Purity: 97.5%
Received: May 15, 1987

2. Test Animals

Species: dog
Strain: beagle
Age: four to five months at start of study
Weight: males--5.4-6.8 kg and females--4.0-6.3 kg at start of study
Source: Hazleton Research Products, Inc.

B. STUDY DESIGN

1. Animal Assignment

Animals were acclimated to laboratory conditions for 3 weeks and were assigned by sex to the following test groups (using a computer-generated randomization procedure):

Test group	Dosage in Diet (ppm)	Males	Females
Control	0	6	6
Low	30	6	6
Medium	90	6	6
High	250	6	6

Animals were housed individually. Temperature and relative humidity were controlled at 73° ± 6°F and 50% ± 20%, respectively. A 12-hour dark/light cycle was maintained.

Dosage levels were selected based on the results of a 13-week chronic feeding study performed at Hazleton Laboratories America in which male and female dogs received thiram in their diets at dosage levels of 0, 75, 250, and 500 ppm (Study No. HLA 6111-121). In that study, body weights in both sexes were affected at 250 and 500 ppm. Therefore, for this study, the highest dosage was set at 250 ppm.

2. Diet Preparation

Diets were prepared weekly and frozen. Animals were given fresh food every day (with two exceptions). A premix was first prepared in a

Waring blender consisting of the required amount of test material and approximately 50 g of basal diet (Certified Canine Diet #5007). The premix was then placed into a Hobart mixing bowl and basal diet was added to achieve the final concentration of test material in the diet. Homogeneity was determined for all dosage levels from the first week's diets. Stability was analyzed on samples from the first week's diets after 7 days of storage in the freezer and 1 day at room temperature. Concentrations of the dosages were analyzed every week for the first 4 weeks and every fourth week thereafter.

Results: Purity of the test material was confirmed at 97.6%. Homogeneity analyses revealed concentrations between 83% and 92% of target. Stability analyses revealed concentrations between 100% and 105% of target. Concentrations of the test material in the diet ranged from 81% to 107% of target.

3. Food and Water Consumption

Animals received food (Certified Canine Diet #5007; Purina Mills, Inc.) and water ad libitum through week 24. Thereafter, the food was offered for 3-6 hours per day.

4. Statistics

The following procedures were utilized in analyzing body weight, food consumption, clinical chemistry, hematology, urinalysis, and organ weight data: Levene's test for variance homogeneity (transformations were used on heterogeneous variances); ANOVA or ANCOVA; and Dunnett's t-test or Games and Howell Modified Tukey-Kramer test for pairwise comparisons between groups if ANOVA or ANCOVA was significant.

5. Quality Assurance

A signed quality assurance statement, dated June 28, 1991, was provided

C. METHODS AND RESULTS

1. Observations

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

Results: No compound-related mortalities or clinical signs were observed. Two females, one at 90 ppm and one at 250 ppm, were sacrificed moribund during weeks 25 and 26, respectively. Death, considered to be unrelated to treatment, was preceded by clonic convulsions with pulmonary congestion (caused by meningoencephalitis) and clonic seizures with opisthotonos (caused by hydrocephalus). Clinical signs, including soft/mucoid stool, ocular discharge, alopecia, erythema, and oily coat, were frequently noted in all groups.

2. Body Weight

Body weights were recorded weekly during weeks 1-16, and once every fourth week thereafter. Weight gain data were not provided.

Results: Table 1 summarizes data on mean body weight. No significant compound-related effects were observed in body weight or body weight change. However, at 250 ppm, a pattern of decreasing body weight with increasing time on the test diet was observed in males and may have been a compound-related effect. During weeks 2-16, 20-32, and 36-52, the average decreases at this dosage level were approximately 5%, 8%, and 14%, respectively. This pattern was not observed in the females; over the entire dosing period, their average decrease was <5% at 250 ppm.

Net weight gain (data not shown; calculated by the reviewers) for males was 81%, 114%, and 69% of control at 30, 90, and 250 ppm, respectively. Net weight gain for females was 113%, 87%, and 93% of controls at 30, 90, and 250 ppm, respectively.

3. Food Consumption and Compound Intake

Food consumption (g/week) was recorded weekly during weeks 1-16 and every fourth week thereafter. Water consumption was not recorded.

Results: Table 2 summarizes data on mean food consumption. No compound-related effects were observed. At 250 ppm during week 20, a significant decrease was noted in females and was considered to be an incidental finding.

Average compound intake was 0.84, 2.61, and 7.35 mg/kg/day for males and 0.90, 2.54, and 7.23 mg/kg/day for females at nominal dietary levels of 30, 90, and 250 ppm, respectively.

4. Ophthalmological Examinations

Ophthalmologic examinations were performed on all animals before initiation of the study and during week 51 using an indirect ophthalmoscope after the pupils were dilated with 1.0% Mydriacyl.

Results: No lesions were observed in any animal. No individual data were submitted for this endpoint.

5. Hematology and Clinical Chemistry

Animals were fasted overnight and blood was collected from the jugular vein from all animals during weeks -2, 13, 26, and 52. The parameters checked (X) below were determined.

a. Hematology

X Hematocrit (HCT)[a]
X Hemoglobin (HGB)[a]
X Leukocyte count (WBC)[a]
X Erythrocyte count (RBC)[a]
X Nucleated erythrocyte count (RBC)
X Platelet count[a]
Reticulocyte count (RETIC)
X Red cell morphology
X Lymphocyte count (LYMP)
X Eosinophil count (EOSN)
Atypical lymphocyte count (ATYP)
Leukocyte differential count
X Mean corpuscular HGB (MCH)
X Mean corpuscular HGB concentration (MCHC)
X Segmented neutrophil count (N-SEG)
X Mean corpuscular volume (MCV)
X Prothrombin time (PT)
X Basophil count (BASO)
X Monocyte count (MONO)
X Band leucocyte (BAND)

[a]Recommended by Subdivision F (October 1982) Guidelines

Results: Table 3 summarizes results for selected hematologic endpoints. Possible compound-related effects included a significant decrease in RBC in males at 250 ppm during weeks 13 and 52 and increases (frequently significant, see Table 3 for details) in MCV and MCH in both sexes at all dosage levels during all weeks when assayed. In addition, the following parameters (not shown in the table) were significantly different from controls: HGB in males during week 52 at 250 ppm; MCHC in females at 30 and 90 ppm during week -2; PT in males at 250 ppm during week 13; and NRBC in females at 250 ppm during week 52. These changes, however, were considered to be incidental since they occurred without a dosage-related response or consistent pattern with regard to sex and time.

b. Clinical Chemistry

Electrolytes

X Calcium[a]
X Chloride[a]
Magnesium
X Phosphorus[a]
X Potassium[a]
X Sodium

Enzymes

X Alkaline phosphatase (ALP)
Cholinesterase
X Creatinine phosphokinase[a]
Lactic acid dehydrogenase (LDH)
X Alanine aminotransferase (ALT/SGPT)[a]
X Aspartate aminotransferase (AST/SGOT)[a]

Other

X Albumin[a]
Albumin/globulin ratio
X Creatinine[a]
X Urea Nitrogen[a]
X Cholesterol[a]
X Globulins
X Glucose
X Total bilirubin[a]
Direct bilirubin
X Total protein[a]
Triglycerides

[a]Recommended by Subdivision F (October 1982) Guidelines

Results: Table 4 summarizes results for selected blood chemistry endpoints. Compound- and dosage-related effects at weeks 13, 26,

and 52 included decreases in total protein and albumin, and increases in cholesterol in males of all dosage groups and in females at 90 and 250 ppm (frequently significant in males at 90 and 250 ppm and in females at 250 ppm). In addition, the following endpoints were significantly different from controls: AST/SGOT in males at 30 and 90 ppm during week 26 and in females at 250 ppm during week 13; ALT/SGPT in males at 90 and 250 ppm during week 52 and in females at 30 ppm during week 26; calcium (data not shown) in males at 250 ppm during week 26; phosphorus (data not shown) in females at 90 and 250 ppm during week 52; sodium (data not shown) in males at 30 and 90 ppm during week 13; and chloride (data not shown) in males at 30 ppm during week 13 and in females at 30 and 90 ppm during week 52. These changes, however, were considered to be incidental since they occurred without a dosage-related response or consistent pattern with regard to sex and time.

6. Urinalysis

Urinalysis was performed on all animals during weeks -2, 13, 26, and 52. Animals were fasted overnight prior to urine collection which went on for a period of 16 hours. The parameters checked (X) below were examined.

X Appearance[a]	X Glucose[a]
X Volume[a]	X Ketones[a]
X Specific gravity[a]	X Bilirubin[a]
X pH X	Blood[a]
X Sediment (microscopic)[a]	Nitrate
X Protein[a]	X Urobilinogen

[a]Recommended by Subdivision F (October 1982) Guidelines.

Results: No compound-related effects were observed for any endpoint at any time for either sex.

7. Sacrifice and Pathology

All animals (found dead or sacrificed) were subjected to gross pathological examination. Following overnight fasting, surviving animals at term were weighed, anesthetized with pentobarbital, exsanguinated, and necropsied. Gross examination included the external surface of the body; all orifices; the cranial cavity; external surfaces of brain and spinal cord; nasal cavity; paranasal sinuses; and the thoracic, abdominal, and pelvic cavities. The tissues checked (X) below were collected and preserved in 10% phosphate-buffered formalin for histological examination. In addition, the double-checked (XX) organs were weighed.

Digestive System	Cardiovasc./Hemat.	Neurologic
Tongue	X Aorta	XX Brain
X Salivary glands[a]	X Heart[a]	X Peripheral nerve (sciatic nerve)[a]
X Esophagus[a]	X Bone marrow[a]	X Spinal cord (3 levels)
X Stomach[a]	X Lymph nodes[a]	X Pituitary[a]
X Duodenum[a]	X Spleen	X Eyes, optic nerve
X Jejunum[a]	X Thymus	
X Ileum[a]		
X Cecum[a]		
X Colon[a]		
X Rectum	**Urogenital**	**Glandular**
XX Liver[a]	XX Kidneys[a]	X Adrenals[a]
X Gall bladder[a]	X Urinary bladder[a]	Lacrimal gland
X Pancreas[a]	XX Testes[a]	X Mammary glands[a]
	X Epididymides	XX Thyroids[a](with parathyroids[a])
	X Prostate gland	Harderian glands
	Seminal vesicles	Parotid gland
Other	XX Ovaries	Sublingual gland
X Skeletal muscle[a]	X Uterus	Submaxillary gland
X Skin[a] - Subcutaneous tissue	X Cervix	**Respiratory**
	Renal pelvis	X Trachea[a]
X All gross lesions	X Vagina	X Lungs[a]
X Bone (femur)[a]		

[a]Recommended by Subdivision F (October 1982) Guidelines.

Results

- Organ Weights: Table 5 summarizes liver weights in animals sacrificed at term. Compound-related effects included increases in absolute liver weight in males of all dosage groups (significant at 90 and 250 ppm), in females at 90 and 250 ppm, liver-to-body weight percentages in males of all dosage groups (significant at 30, 90, and 250 ppm), and in females at 90 and 250 ppm (significant at 250 ppm). There were dosage-related trends involving increased liver-to-brain weight ratios in both males and females, but this increase was statistically significant only in 250 ppm males.

- Gross Pathology: Table 6 summarizes gross findings in animals sacrificed at term. No compound-related lesions were observed in either sex. Incidental lesions, including the GI tract, brain, lungs, heart, kidneys, liver, skin, lymph nodes, ovaries, and prostate, were noted in most dosage groups (see table for details).

- Microscopic Pathology: Tables 7 and 8 summarize the most frequent microscopic lesions and severity of liver lesions in animals sacrificed at term. No compound-related lesions were observed in either sex (Table 7). Extramedullary hemopoiesis (EMH) of the liver was noted in all dosage groups; however, a few of the treated animals had a slightly higher severity score (2 or 3) of EMH (Table 8) when compared to control animals, which were all minimal (1). No lesion in any animal, however, was graded "moderately severe" (4) or "severe" (5). Tubular mineralization in the kidney

and microgranulomas and mononuclear cell infiltrate in the liver were observed in most animals, including those in the control group. Pituitary cysts occurred in more males than females. Inflammation of the mandibular lymph node as well as hemorrhage in the mesenteric lymph node occurred in approximately half of all animals. These incidences were not dosage related and were considered to be spontaneous in origin. Additional incidental lesions in various organs, including the brain, lungs, spleen, thyroid, salivary gland, spinal cord, and uterus, were noted in all dosage groups (see Table 8 for details).

D. STUDY AUTHOR'S CONCLUSIONS

Technical grade thiram was administered in the diet to beagle dogs at nominal concentrations of 0, 30, 90, or 250 ppm for 52 weeks. Significant compound-related changes were observed in several clinical chemistry parameters at 90 and/or 250 ppm in both sexes. They included total protein, albumin, and cholesterol. In addition, absolute liver weights, liver-to-body weight percentages, and liver-to-brain weight ratios were significantly affected in males at 90 and/or 250 ppm; liver-to-body weight % was also affected in females at 250 ppm. Significant changes were also observed in selected hematology parameters (RBC, MCV, and MCH). However, because of differences between groups in these hematology parameters before treatment started, these effects are inconclusive. No compound-related effects were observed on clinical signs, mortality, body weight, food consumption, ophthalmology, urinalysis, or gross and microscopic lesions. Although sporadic changes were noted in food consumption and body weight, these were considered to be normal variations.

Based on changes in liver function and size, the NOEL and LOEL values for systemic toxicity were 30 and 90 ppm, respectively, for males and 90 and 250 ppm, respectively, for females. These effects may, however, be more a physiologic adaptation to the compound than a toxicologic reaction.

E. REVIEWERS' DISCUSSION AND INTERPRETATION OF RESULTS

The data reporting was acceptable and the summary means that were validated were supported by the individual animal data. The reviewers agree with the study author that the changes in liver function and size (manifested as a change in levels of total protein, albumin, and cholesterol and increased liver weight) were compound-related effects and the sporadic changes in food consumption and hematology were normal variations. However, the reviewers believe that a NOEL was not observed in males as indications of liver function changes were observed even in low dosage (30 ppm) males. These included decreases in total protein and albumin, and increases in cholesterol. While these were not statistically significant at 30 ppm, there was a consistent dosage-related trend involving these parameters and this dosage level at weeks 13, 26, and 52. In addition, at termination in 30 ppm males there was a non-significant increase in mean liver weight, and this was again part of a well-defined dosage-related trend. Further, the increased liver-to-body weight percentages were statistically significant for all male dosage groups. The reviewers believe that the 12.8% decrement (albeit statistically nonsignificant) in terminal body weight in males at 250 ppm was an effect

of the test compound and is in concordance with the male gender being more sensitive to thiram than the female gender.

The study is classified as Core Supplementary. The LOEL value for systemic toxicity in males was 30 ppm (lowest dosage tested); in females it was 90 ppm. The NOEL in females was 30 ppm.

TABLE 1. Mean Body Weight at Representative Intervals in Dogs Fed Thiram for 52 Weeks[a]

Mean Body Weight (kg ± S.D.) at Week:	Dietary Level (ppm) 0	30	90	250
		Males		
0	6.3 ± 0.39	6.2 ± 0.48	6.0 ± 0.36	6.3 ± 0.34
1	6.5 ± 0.44	6.5 ± 0.45	6.5 ± 0.37	6.6 ± 0.40
7	8.7 ± 0.75	8.2 ± 0.82	8.7 ± 0.52	8.1 ± 0.55
14	9.9 ± 0.89	9.4 ± 1.09	10.3 ± 0.95	9.3 ± 0.71
20	10.5 ± 1.27	9.8 ± 1.22	11.0 ± 1.11	9.7 ± 0.80
36	10.6 ± 1.45	9.9 ± 1.29	11.0 ± 1.40	9.2 ± 0.73
44	10.7 ± 1.58	9.9 ± 1.44	11.1 ± 1.39	9.3 ± 0.70
52	10.9 ± 2.01	10.0 ± 1.31	11.4 ± 1.64	9.5 ± 0.80
		Females		
0	5.2 ± 0.78	5.3 ± 0.58	5.1 ± 0.62	5.2 ± 0.56
1	5.6 ± 0.83	5.6 ± 0.70	5.4 ± 0.63	5.5 ± 0.52
7	7.1 ± 1.22	7.4 ± 0.95	7.1 ± 0.90	6.9 ± 0.84
14	8.2 ± 1.34	8.6 ± 1.24	8.1 ± 1.04	7.9 ± 0.97
20	8.6 ± 1.27	9.1 ± 1.22	8.4 ± 0.92	8.0 ± 1.11
36	8.7 ± 1.35	9.0 ± 1.18	7.8 ± 0.79	8.2 ± 1.30
44	8.7 ± 1.20	9.3 ± 1.37	7.8 ± 0.51	8.4 ± 1.47
52	8.7 ± 1.25	9.4 ± 1.42	8.2 ± 0.77	8.5 ± 1.55

[a]Data were extracted from Study No. HLA 6111-112, Tables 6 and 7.

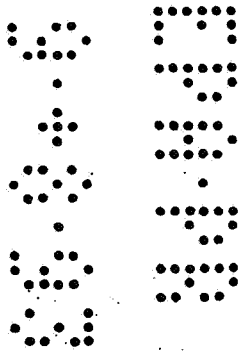

TABLE 2. Mean Food Consumption at Representative Intervals in Dogs Fed Thiram for 52 Weeks[a]

Mean Food Consumption (g/week ± S.D.) at Week:	Dietary Level (ppm) 0	30	90	250
		Males		
1	1861 ± 297	1462 ± 341	1514 ± 192	1707 ± 198
2	2018 ± 355	1786 ± 333	1775 ± 222	1684 ± 256
7	2160 ± 339	1805 ± 429	2038 ± 274	2102 ± 195
14	1799 ± 249	1692 ± 205	1923 ± 232	1884 ± 348
20	1873 ± 405	1711 ± 275	1882 ± 258	1648 ± 264
36	1788 ± 310	1703 ± 258	1616 ± 203	1571 ± 339
44	1646 ± 397	1529 ± 312	1576 ± 218	1722 ± 296
52	1589 ± 518	1434 ± 182	1690 ± 229	1598 ± 145
		Females		
1	1496 ± 226	1552 ± 249	1182 ± 157	1448 ± 229
2	1532 ± 200	1643 ± 214	1378 ± 138	1386 ± 173
7	1754 ± 273	1677 ± 307	1617 ± 261	1612 ± 200
14	1736 ± 220	1936 ± 123	1820 ± 330	1808 ± 372
20	1668 ± 208	1664 ± 242	1474 ± 137	1300 ± 311*
36	1595 ± 90	1641 ± 173	1384 ± 125	1477 ± 328
44	1326 ± 327	1480 ± 244	1190 ± 141	1293 ± 372
52	1293 ± 312	1408 ± 303	1398 ± 287	1377 ± 291

[a]Data were extracted from Study No. HLA 6111-112, Tables 8 and 9.

*Significantly different from control ($p \leq 0.05$).

TABLE 3. Selected Mean Hematology Values in Dogs Fed Thiram for 52 Weeks[a]

Dietary Level (ppm)	RBC (E6/UL)	MCV (FL)	MCH (PG)	MCHC (%)
Males Week -2				
0	5.80	62	20.0	32.6
30	6.40	61	19.9	32.7
90	5.83	65	21.0	32.2
250	5.56	64	20.9	32.5
Males Week 13				
0	6.94	66	20.8	31.7
30	6.75	68	21.7	32.2
90	6.87	70*	22.1	31.4
250	6.19*	71*	22.9*	32.2
Males Week 26				
0	7.21	64	19.7	30.6
30	6.84	67*	20.4	30.4
90	6.99	69*	20.4	29.7
250	6.60	69*	20.7	29.8
Males Week 52				
0	7.64	68	21.1	31.0
30	7.60	69	21.4	30.8
90	7.31	71*	21.9	31.0
250	6.77*	70*	21.7	30.9
Females Week -2				
0	5.92	61	20.1	33.0
30	5.56	68*	21.3	31.6*
90	5.51	67*	21.6	32.2*
250	5.81	66*	21.5	32.5
Females Week 13				
0	7.04	62	20.2	32.3
30	6.92	68*	21.8*	31.8
90	6.35	70*	22.4*	32.0
250	6.36	71*	23.2*	32.5
Females Week 26				
0	7.33	62	19.2	30.9
30	6.98	69*	20.8	30.3
90	6.87	69*	20.9	30.5
250	6.81	70*	21.9*	31.2
Females Week 52				
0	7.27	67	20.6	30.8
30	6.98	70	21.2	30.5
90	7.02	71	22.2*	31.3
250	7.25	72*	22.5*	31.2

[a]Data were extracted from Study No. MLA 6111-112, Tables 11-18.

*Significantly different from control ($p \leq 0.05$).

TABLE 4. Selected Mean Clinical Chemistry Values in Dogs Fed Thiram for 52 Weeks[a]

Dietary Level (ppm)	CREAT (mg/dL)	TPRO (g/dL)	ALB (g/dL)	CHOL (mg/dL)	AST/ SGOT (IU/L)	ALT/ SGPT (IU/L)
Males Week -2						
0	0.6	5.2	3.2	154	34	32
30	0.7	5.2	3.3	160	32	30
90	0.7	5.2	3.2	184	30	25
250	0.6	5.4	3.2	166	29	29
Males Week 13						
0	0.8	6.1	3.4	133	39	47
30	0.9	5.9	3.4	172	32	40
90	1.0*	5.8	3.4	191*	34	38
250	0.8	5.6	3.2*	195*	35	41
Males Week 26						
0	1.0	6.7	3.8	140	44	56
30	1.0	6.6	3.6	182	38	49
90	1.0	6.1*	3.5	200*	32*	38
250	0.9	5.9*	3.3*	206*	36*	39
Males Week 52						
0	1.0	7.0	4.0	136	41	60
30	1.1*	6.9	3.8	173	32	45
90	1.1*	6.3*	3.6	199*	37	41*
250	1.0	6.2*	3.4*	212*	36	40*
Females Week -2						
0	0.7	5.2	3.3	132	35	34
30	0.7	5.2	3.2	147	35	33
90	0.7	5.2	3.2	137	32	36
250	0.7	5.1	3.2	150	32	32
Females Week 13						
0	0.8	5.9	3.3	129	42	57
30	0.9	6.2	3.5	174	38	37
90	0.9	5.7	3.3	159	37	42
250	0.9	5.4	3.0	210*	30*	40
Females Week 26						
0	0.9	6.0	3.5	132	37	44*
30	0.9	6.4	3.6	209*	32	32
90	0.9	6.0	3.4	180	33	40
250	0.9	5.6	3.0*	258*	28	32
Females Week 52						
0	1.0	6.4	3.6	148	37	38
30	1.1	6.8	3.9	194	38	34
90	1.0	6.1	3.4	192	33	37
250	1.0	5.9	3.3	237*	33	31

[a]Data were extracted from Study No. HLA 6111-112, Tables 19-26.

*Significantly different from control ($p \leq 0.05$).

TABLE 5. Selected Liver Weights at Termination in Dogs Fed Thiram for 52 Weeks[a]

Organ	Dietary Level (ppm) 0	30	90	250
		Males		
Total no. examined	6	6	6	6
Absolute liver weight (g)	227.9	253.0	288.6*	295.0*
Absolute brain weight (g)	77.7	73.8	79.3	74.2
Liver-to-body weight (%)	2.2	2.5*	2.6*	3.1*
Liver-to-brain weight	3.0	3.5	3.6	4.0*
		Females		
Total no. examined	6	6	5	5
Absolute liver weight (g)	207.1	222.8	241.7	265.9
Absolute brain weight (g)	76.5	70.8	69.5	73.1
Liver-to-body weight (%)	2.4	2.4	2.9	3.1*
Liver-to-brain weight	2.8	3.2	3.5	3.6

[a]Data were extracted from Study No. HLA 6111-112, Tables 35 and 37.

*Significantly different from control ($p \leq 0.05$).

TABLE 6. Macroscopic Observations at Termination in Dogs Fed Thiram for 52 Weeks[a]

	Dietary Level (ppm)							
	Males				Females			
Observation	0	30	90	250	0	30	90	250
Total no. of animals examined	6	6	6	6	6	6	6	6
GI Tract								
Dark fluid content	0	0	0	1	0	0	0	0
Brain								
Large ventricles	0	1	0	0	0	0	0	0
Lung								
Light foci areas	0	0	0	0	0	0	2	0
Red foci areas	0	0	0	0	0	0	1	0
Mottled	0	1	0	0	0	0	0	0
Heart								
Cysts	0	0	0	1	0	1	0	0
Light raised areas	0	0	0	0	0	1	0	0
Liver								
Diffusely dark	0	0	0	0	0	0	1	0
Duodenum								
Thickened walls	0	0	0	0	0	0	0	1
Colon								
Raised foci areas	0	0	0	0	0	0	0	1
Skin								
Diffuse alopecia	1	0	0	0	0	0	0	0
Focal alopecia	1	0	0	0	0	0	0	0
Mesenteric Lymphnode								
Mottled	1	1	0	0	0	0	1	0
Ovary								
Large	-	-	-	-	0	1	0	0
Prostate								
Cysts	0	0	0	1	-	-	-	-

[a]Data were extracted from Study No. HLA 6111-112, Table 38 and Appendix D.

TABLE 7. Microscopic Observations at Termination in Dogs Fed Thiram for 52 Weeks[a,b]

Observation	Dietary Level (ppm)							
	Males				Females			
	0	30	90	250	0	30	90	250
Total no. of animals examined	6	6	6	6	6	6	5	5
Brain								
Inflammation, nonsuppurative	0	0	1	0	1	0	0	0
Lung								
Hyperplasia, intimal artery	1	0	0	1	0	0	0	0
Hyperplasia, perivascular/ peribronchial lymphoid	1	0	2	0	1	0	1	0
Inflammation, granulomatous	0	0	1	0	2	2	0	2
Histiocytosis, alveolar	0	0	0	0	1	0	1	0
Fibrosis, pleural/subpleural	0	0	1	0	0	0	1	0
Kidney								
Mineralization, tubular	6	5	5	5	5	5	5	4
Mononuclear infiltration, focal	1	0	1	0	0	1	0	0
Proteinaceous casts	0	1	1	0	1	0	1	0
Liver								
Microgranulomas	6	3	5	5	5	4	3	5
Congestion	0	0	0	0	0	0	2	0
Infiltrate, mononuclear cell	6	5	5	5	3	6	5	5
Hematopoiesis, extramedullary	2	3	4	1	1	2	3	2
Pigmentation, sinusoidal cell	0	0	0	1	1	0	0	1
Inflammation, acute	1	1	1	1	2	0	0	1
Spleen								
Hematopoiesis, extramedullary increased	1	0	0	2	2	0	0	2
Siderotic plaque/nodule	0	0	1	1	0	0	0	0
Pituitary								
Cysts	3	2	3	2	3	1	0	0
Thyroid								
Hyperplasia, "C" Cell	1	0	1	0	0	1	0	0
Cyst, thyroglossal duct	1	2	0	0	0	0	0	0
Salivary gland								
Mononuclear infiltration	0	1	2	1	1	1	2	0
Mandibular lymph node								
Inflammation, suppurative	2	1	1	1	2	3	1	1
Inflammation, eosinophilic	0	3	4	0	2	2	2	2
Mesenteric lymph node								
Hemorrhage	2	3	3	3	1	3	3	2
Spinal cord								
Mineralization	1	0	1	0	0	0	0	0
Uterus								
Dilatation	-	-	-	-	0	1	0	1

[a]Data were extracted from Study No. HLA 6111-112, Table 39 and Appendix D.

[b]Includes incidences that occurred in two or more animals (sexes combined).

TABLE 8. Severity of Microscopic Liver Lesions in Dogs Fed Thiram for 52 Weeks[a]

	Dietary Level (ppm)							
	Males				Females			
Observation/Score	0	30	90	250	0	30	90	250
Total no. of animals examined	6	6	6	6	6	6	5	5
Microgranulomas								
Finding not present	0	3	1	1	1	2	2	0
Grade 1	6	1	4	3	4	4	3	5
Grade 2	0	2	1	2	1	0	0	0
Mononuclear cell infiltrate								
Finding not present	0	1	1	1	3	0	0	0
Grade 1	5	4	4	5	3	6	5	4
Grade 2	1	1	1	0	0	0	0	1
Extramedullary hematopoiesis								
Finding not present	4	3	2	5	5	4	2	3
Grade 1	2	2	3	0	1	2	3	0
Grade 2	0	0	1	0	0	0	0	2
Grade 3	0	1	0	1	0	0	0	0

[a]Data were extracted from Study No. HLA 6111-112, Table 40.

[b]Grading scale: 1 (minimal) to 5 (severe)