1/29/1994

FINAL

DATA EVALUATION REPORT

L-656,748

Study Type:
Subchronic Oral Toxicity Study in Dog

Study Title:
L-656,748 Fourteen-Week Oral Toxicity Study in Dogs.
TT #88-060-0

Prepared for:

Office of Pesticide Programs
U.S. Environmental Protection Agency
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DATA EVALUATION REPORT

STUDY TYPE: Subchronic oral toxicity study in dogs

TEST MATERIAL: L-656,748

SYNONYM: Deoxy avermectin; MK-0243

P.C. NO.: 122806

TOX. CHEM. NO.: New chemical (not assigned)

MRID NO.: 427436-23
427436-22 (3 week range-finding study)

STUDY NO.: Laboratory Project Identification 618-244-TOX20
(TT #88-060-0)

SPONSOR: Agricultural Research and Development
Merck Research Laboratories
Merck & Co., Inc.
Three Bridges, NJ

TESTING FACILITY: Merck Research Laboratories
Merck & Co., Inc.
West Point, PA and Three Bridges, NJ

TITLE OF REPORT: L-656,748 Fourteen-Week Oral Toxicity Study in Dogs.
TT #88-060-0

AUTHOR: Jeanne M. Manson, Ph.D.

REPORT ISSUED: December 18, 1992

QUALITY ASSURANCE: A signed Quality Assurance Statement (not dated) and a signed GLP Certification Statement (dated January 14, 1993) were provided. The study was conducted in compliance with OECD guidelines and GLP regulations.

CONCLUSIONS: L-656,748 was administered to male and female Beagle dogs (4/sex/group) by gavage in water at doses of 0, 0.5, 1.0, or 1.5 mg/kg/day for

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the first 2 weeks of a 14-week study. Dose levels were reduced to 0, 0.25, 0.5, or 1.0 mg/kg/day for the rest of the study because of clinical signs of excessive toxicity.

NOEL = 0.25 mg/kg/day

LOEL = 0.5 mg/kg/day based on microscopic pathological signs of neurotoxicity consisting of skeletal muscle atrophy and white matter multifocal degeneration in the brains of both sexes and white matter multifocal degeneration in the spinal cords of males.

In addition, at 1.0 mg/kg/day, ataxia, tremors, mydriasis, and recumbency occurred in both sexes. Decreased food consumption was observed in males and females prior to reduction of dose level. Thymus atrophy, decreased number of erythropoietic cells in the bone marrow, neuronal degeneration in the brain, and sciatic nerve and optic nerve degeneration were observed in both sexes. White matter multifocal degeneration in the spinal cord occurred in both sexes.

CORE CLASSIFICATION: Core Minimum. This study satisfies the minimum requirements for a subchronic oral toxicity study in dogs. However, the study failed to examine all of the clinical chemistry parameters recommended by Subdivision F Guidelines. Also, a large discrepancy in dose concentrations existed between the tests to verify concentration of doses and the test for stability analysis, doses were reduced during the study, and study authors did not do appropriate calculations and statistics for the parameters examined (e.g., body weight).

A. MATERIALS, METHODS, AND RESULTS

1. Test Article Description

Name: L-656,748

Composition: 4"-epi-methylamino-avermectin derivative

Batch number: L-656,748-010V003

Purity: 96.9%

Physical Property: Not reported

Stability: Stable for 24 hours in aqueous solution (storage conditions not described).

2. Test Substance Analyses for Purity and Stability

The test article was dissolved in deionized water to achieve the desired concentration in a 2-mL/kg solution and administered by gavage for 14 weeks. Purity of 96.9% was confirmed by HPLC analysis before study initiation. Control animals received deionized water as a treatment. Dose solutions were prepared fresh daily and were based on the most recent individual body weight data. Verification of test

compound concentration was conducted during study weeks 1, 8, and 14. The sample concentrations were within an acceptable range and were as follows:

Dosing Group	Target Concentration (mg/mL)	Mean of Actual Concentration (mg/mL)[a]
Low	0.25	0.25 (100.0%)
	0.125[b]	0.126 (92.0-108.8%)
Mid	0.5	0.50 (104.2%)
	0.25[b]	0.245 (93.6-102.0%)
High	0.75	0.751 (100.1%)
	0.5[b]	0.489 (94.0-101.4%)

[a]Numbers in parentheses indicate percentage of nominal concentration; given in range of analysis values.
[b]Doses were reduced for the mid- and high-dose groups at the end of week 2 and for the low-dose groups at the beginning of week 3.

The stability of the test solutions for 24 hours was analyzed in duplicate one time during the study. The report does not describe the storage conditions of the compound before analysis for stability. No determination of the stability of the test compound for the duration of the study was provided. The concentrations of the test solutions before and after being stored for 24 hours were as follows:

Dosing Group	Target Concentration (mg/mL)	Actual Concentration (mg/mL)
Low		
day 1	0.26	0.115
day 2	0.26	0.119
High		
day 1	0.78	0.479
day 2	0.78	0.483

The results of the stability analysis show the dosing solution to be stable for at least 24 hours; however, the actual concentrations measured were only 44-62% of the target concentration. The analyses for concentration show that the actual concentrations in the other samples were 97-104% of the target concentrations.

3. Animals

Beagle dogs, (16 males and 16 females) were received from Marshall Research Animals, Inc., North Rose, NY. Upon arrival, animals were housed in individual cages in an environmentally controlled room. Animals were selected on the basis of pretest body weight, physical appearance, ophthalmic and electrocardiographic examinations, and clinical chemistry parameters. The length of the acclimatization period was not reported. The animals were then randomly assigned to the four treatment groups (4/sex/group) and adjusted so that litter mates were not in the same dosage groups. Animals were uniquely identified by tattoos. The dogs were 28-31 weeks of age at the initiation of dosing, and body weight ranges were 7.0-9.6 kg for males and 6.1-8.9 kg for females.

Purina Certified Dog Chow (350 g/day) and tap water (*ad libitum*) were provided throughout the study periods. Selected high-dose animals were occasionally administered one can of Big Bet® Canned pet food/day because of poor food consumption of the regular food. Caging and sanitary conditions were maintained in accordance with the SOPs of the testing facility.

The dogs (4/sex/group) were randomly assigned to the following test and control groups:

Group	Dose Levels (mg/kg/day)	Number of Animals (14 weeks) Males	Females
1 Control	0	4	4
2 Low	0.5/0.25[a]	4	4
3 Mid	1.0/0.5[a]	4	4
4 High	1.5/1.0[a]	4	4

[a]Dose levels were reduced for mid- and high-dose groups on the last day of study week 2 and for low-dose groups on the first day of study week 3 because of signs of excessive toxicity.

4. Rationale for Dose Selection

Doses were based on the results from a 3-week oral range-finding study in dogs (Study no. TT #88-047-0; laboratory project I.D. 618-244-TOX19; MRID no. 427436-22). The range-finding study was originally designed as a 3-week dietary study rather than a gavage study, but, because of poor food consumption (probably due to unpalatability, especially at highest doses), dietary administration was terminated on study day 4. The route of administration was

changed to oral gavage and dosing resumed on study day 8. Five groups of 2/sex/group were administered daily doses of 0.5, 2.5, 12.5 or 25 mg/kg/day. The dose levels for the 12.5- and 25-mg/kg/day groups were lowered to 5 and 7.5 mg/kg/day, respectively, after day 9. Mydriasis and ataxia and/or tremors occurred in animals at all doses, but the time of onset of these symptoms was dose-dependent. Dosing was terminated on day 10 for all animals in the 7.5-mg/kg/day group and in one female in the 5-mg/kg/day group because of severe ataxia and lateral recumbency. Dosing was terminated on day 11 for the remaining 5-mg/kg/day animals and for two 2.5-mg/kg/day animals. For the remaining 2.5-mg/kg/day animals, dosing was terminated on day 16. Treatment- related changes seen in the 2.5-, 5-, and 7.5-mg/kg/day groups also include decreases in food consumption and body weight. Decreases in lymphocyte count and slight increases in erythrocyte count and hematocrit value were observed in one 2.5-mg/kg/day animal at week 3. Slight increases in serum glucose and serum protein levels were found in two animals in the 2.5 mg/kg/day group at week 3; a decrease in serum creatinine was also observed in one of these animals. The study author attributed clinical chemistry changes to stress and anorexia rather than to exposure. No treatment-related effects were seen in the low-dose animals; therefore, the NOEL for this study was determined to be 0.5 mg/kg/day. The LOEL was 2.5 mg/kg/day.

5. Statistical Analyses

Statistical analyses were not performed in this study. The reviewers performed ANOVA and Scheffe's test on quantitative data to determine significant differences between control and exposed groups.

6. General Observations

(a) Mortality/moribundity/survival

Animals were observed daily for mortality/moribundity.

Results: Because of tremors, mydriasis, anorexia, lethargy, and recumbency, one high-dose female and one high-dose male were sacrificed during study week 3, and one high-dose female was sacrificed during week 6. All other animals survived until study termination.

(b) Clinical signs

Observations for adverse clinical effects were made once daily throughout the study. Electrocardiograms were taken on all dogs prior to initiation of the study and during study weeks 4, 8, and 12 at approximately 3-5 hours following dose administration.

Results: As seen in the following table (Table 1), the incidence of ataxia, mydriasis, tremors, and recumbency was increased in high-dose animals. A higher incidence of tremors, ataxia, and mydriasis occurred in females than in males. Three animals

(two females and one male) were sacrificed before study termination because of the severity of their clinical signs. Mydriasis was only noted in the three early sacrifice animals. Recumbency was noted in all three early sacrifice animals, and only one occurrence was seen in the animals that survived until study termination. Mydriasis, tremors, and recumbency occurred as early as week 2 (onset of these symptoms began before doses were lowered from 1.5 mg/kg/day to 1.0 mg/kg/day) in the animals sacrificed before study termination. Tremors and ataxia were observed as early as week 2 (onset of these symptoms began before doses were lowered from 1.5 mg/kg/day to 1.0 mg/kg/day) and persisted throughout the study in one high-dose female that survived until study termination, however, occurrences of neurological signs did not begin in the other surviving animals until week 4 (tremors and ataxia only seen at week 4) and week 10 (recumbency only seen at week 10, tremors seen from week 10 until study termination). These symptoms did not occur in the control, low-dose, or mid-dose groups.

Table 1. Incidence of Treatment-Related Clinical Symptoms[a]

	Incidence			
Clinical Sign	Males (mg/kg/day)		Females (mg/kg/day)	
	0	1.5/1.0[b]	0	1.5/1.0[b,c]
Tremors	0/4	2/4	0/4	4/4
Ataxia	0/4	1/4	0/4	3/4
Mydriasis	0/4	1/4	0/4	2/4
Recumbency	0/4	2/4	0/4	2/4

[a]Data extracted from Table A-3 (pp. 34-37).
[b]One animal sacrificed at end of week 3.
[c]One animal sacrificed at end of week 6.

The study author reported that there were no treatment-related changes in electrocardiograms; however, no individual or group data were reported in the study to confirm this conclusion.

(c) Body weights/food consumption

Body weights--Body weights were recorded three times before study initiation and once weekly thereafter throughout the study.

Results: No statistically significant changes (as calculated by reviewers) were observed in body weights (Table 2). However, by the end of week 3, weight losses were observed in high-dose males

and females (87% and 84% of control values in males and females, respectively). Although weight losses in the high-dose groups were reversed with the early sacrifice of three animals and reduction of dose, the body weight gain of the high-dose groups continued to lag behind that of the other groups; cumulative body weight gain at study termination was 75% of control value in males and 41% of control value in females).

Food consumption--Food consumption was measured four times weekly throughout the study except during weeks 4, 8, and 12 during which it was measured three times weekly.

Results: The only significant changes observed were in high-dose females during weeks 2 and 3 (Table 3). Food consumption was 42% and 27% of control value in high-dose females during weeks 2 and 3, respectively (one high-dose female was sacrificed after study week 2). However, the two females that consumed abnormally small amounts of food during weeks 2 and 3 were sacrificed before study termination (and compound dose was decreased), so mean food consumption returned to normal for the remainder of the study. No other significant changes were observed, however, at study week 2 food consumption in high-dose males was only 66% of control value. Two males consumed abnormally small amounts of food during week 2; one was sacrificed at end of week 3 and food consumption in the other increased after the dose reduced from 1.5 to 1.0 mg/kg/day.

(d) Ophthalmoscopic examination

Ophthalmic examinations were conducted on all animals prior to the initiation of dosing and during weeks 4 and 12 of the study. Before examination, 1-2 drops of Mydriacyl® were placed in each eye.

Results: No treatment-related ocular lesions were observed.

7. Clinical Pathology

Prior to the study and during study weeks 4, 8, and 12, blood samples were collected from the jugular veins of all surviving animals. Animals were fasted overnight prior to collection of blood samples.

The hematology and clinical chemistry parameters indicated by an "X" below were examined:

(a) Hematology

X Hematocrit (HCT)*
X Hemoglobin (HGB)*
X Leukocyte count (WBC)*
X Erythrocyte count (RBC)*
X Platelet count*
Heinz-body determinations
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)
X Prothrombin time
X Activated partial thromblastin time

*Recommended by Subdivision F (November 1984) Guidelines

Results: No treatment-related effects were observed. Changes that did occur were minor and within the laboratory's historical ranges.

(b) Blood (clinical) chemistry

Electrolytes

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

Enzymes

X Alkaline phosphatase (ALP)
X Serum alanine aminotransferase (SGPT)*
X Serum aspartate aminotransferase (SGOT)*

Other

X Albumin*
Albumin/globulin ratio
X Blood creatinine*
X Blood urea nitrogen*
X Cholesterol
Globulins
X Glucose*
Total bilirubin*
Direct bilirubin
X Total protein*
X Triglycerides

*Recommended by Subdivision F (November 1984) Guidelines

Results: No treatment-related changes were observed. The study failed to examine calcium, phosphorous, and total bilirubin levels as recommended by Subdivision F Guidelines.

(c) Urinalysis

Urine samples were collected from all surviving animals prior to study initiation and during study weeks 8 and 12. The parameters indicated by an "X" were examined:

Appearance	X Sediment (microscopic)	X Bilirubin
X Volume	X Protein	X Blood
X Specific gravity	X Glucose	Nitrate
X pH	X Ketone (acetoacetic acid)	X Urobilinogen

Results: An increase in the incidence of urinary bilirubin was observed at week 12 in all treated males. The incidence were 2/4 in low-dose males, 4/4 in mid-dose males, and 2/3 in high-dose males compared to 1/4 in controls. However, in the absence of any liver pathology (see below) and with no dose-response relationship, the biological significance of this finding is unclear. No other treatment-related changes were observed.

8. Sacrifice and Pathology

Complete gross examinations were performed on all animals at terminal sacrifice, as well as on the animals that were sacrificed during the study. All animals were sacrificed by exsanguination under barbiturate anesthesia. Most tissues were preserved in 10% neutral buffered formalin. Testes were preserved in Bouin's solution and eyes were preserved in Zenker's acetic fixative. Tissues marked with an "X" below were examined histologically in high-dose and control animals. Organs indicated by "XX" below were also weighed for all animals. In addition, the brain, spinal cord, optic nerve, sciatic nerve, skeletal muscle, and bone marrow were examined in all low- and mid-dose animals. Selected sections of the brain and peripheral nerve were stained with Sevier-Munger or Luxol-Fast Blue/Periodic Acid Schiff and examined for all animals.

Digestive System

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

Respiratory

X Trachea*
XX Lung*
X Nasal Turbinates

Cardiovascular/Hematologic

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

Urogenital

XX Kidneys*
X Urinary bladder*
XX Testes*
Epididymides
XX Prostate
Seminal vesicle
XX Ovaries
XX Uterus

Neurologic

XX Brain
X Peripheral nerve (sciatic nerve)*
X Spinal cord (three levels)
XX Pituitary*
X Eyes (optic nerve)*

Glandular

XX Adrenals*
Lacrimal gland
X Mammary gland
XX Thyroids*
X Parathyroids*
Harderian glands

Other

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

*Recommended by Subdivision F (November 1984) Guidelines

Note: The Subdivision F Guidelines recommend full histopathology in all nonrodents. However, only target organs were examined in the low- and mid-dose groups.

(a) Organ weights and organ-to-body-weight ratios

No treatment-related changes were observed in absolute or relative organ weights.

(b) Macroscopic pathology

No treatment-related macroscopic lesions were observed.

(c) Microscopic pathology

Histopathologic analysis showed treatment-related changes in nervous system tissues and in skeletal muscle (Table 3). High-dose males and females showed increased incidence of thymus atrophy, decreased number of erythropoietic cells in the bone marrow, neuron degeneration in the brain, and sciatic nerve and optic nerve degeneration when compared to controls. The brain lesions consisted of very slight to moderate degeneration.

Spinal cord, sciatic nerve, and optic lesions were judged to be very slight to slight in degree. Skeletal muscle atrophy was judged to be very slight to moderate in degree. Mid- and high-dose animals showed increased incidence of skeletal muscle atrophy and white matter multifocal degeneration in the brain. Mid-dose males and high-dose males and females showed increased incidence of white matter multifocal degeneration in the spinal cord. No other treatment-related microscopic changes were observed.

Slight to moderate neuron degeneration in the brain was localized primarily to the pontine and accessory cuneate nuclei and reticular formation of the brainstem. Swollen neurons in sections stained with Sevier-Munger stain contained cytoplasmic aggregates of granular and fibrillar material; this finding is associated with collections of neurofilaments. Neuronal degeneration was most prominent in the early sacrifice animals but was also observed in three of the five high-dose animals that survived until scheduled termination.
White matter degeneration of the brain was most prominent in the cerebellar peduncles; however, vacuoles containing cell debris and pyknotic nuclei were also observed in sections of the midbrain, medulla, and optic tract. Much of the debris seen in the vacuoles consisted of myelin or myelin breakdown products. This lesion was most prominent in the animals that survived until scheduled termination (five high-dose animals and four mid-dose animals).

Spinal cord lesions consisted of scattered vacuoles containing cell debris and pyknotic nuclei. These lesions were most prominent in the ventral and ventromedial regions of spinal cord white matter. Similar changes were noted in the sciatic and optic nerve lesions. All spinal cord, sciatic nerve, and optic nerve lesions were judged to be slight. The skeletal muscle atrophy observed was consistent with the neurogenic atrophy seen in the central and peripheral nervous systems. Degenerative changes in the nerve fibers within sections of the affected muscle were occasionally seen.

B. DISCUSSION

A review of the final report and supporting data indicates that the conduct of the study was adequate and that the reporting of the results was accurate. The reviewers' conclusions were in accordance with the conclusions made by the study authors. Thus, despite the lack of examination of all recommended clinical chemistry parameters and proper data tabulation with statistical analysis, the study satisfies the intent of the guidelines and is classified as Core Minimum.

The data presented in this study show that both the peripheral and central nervous system was the principal target organ of L-656,748 toxicity in beagle dogs. The compound produced neurotoxic effects in mid- and high-dose animals. Treatment-related clinical signs of neurotoxicity including

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ataxia, tremors, mydriasis, and recumbency were observed in high-dose males and females. These effects were most severe in the three animals that were sacrificed before study termination and were consistent with the types of neurohistopathologies observed. Histopathological examination of nervous system tissues showed localized neuron degeneration in the pontine and accessory cuneate nuclei and reticular formation in the brainstem of both high-dose males and females. Neuronal degeneration was most prominent in the three animals that were sacrificed before study termination. White matter degeneration in the cerebellar peduncles, midbrain, medulla, and optic tract was observed in mid- and high-dose animals. White matter degeneration was more prominent in the animals that survived until study termination. Degeneration in the ventral and ventromedial portions of the spinal cord was observed in mid-dose males and high-dose males and females. Similar degeneration was observed in the sciatic and optic nerves of high-dose males and females. Skeletal muscle (location not identified) atrophy consistent with neurogenic atrophy was observed in mid- and high-dose males and females.

An increased incidence of urinary bilirubin was observed in low-, mid-, and high-dose males; however, since no histopathologic lesions indicating hepatic toxicity were observed, this was not considered to be biologically significant. Urinalysis also showed increases in bilirubin without any liver pathology at the high-dose (0.75 mg/kg/day) in the 1-year dog study (MRID no. 427636-24); the biological significance of this finding is unclear. Decreased food consumption was observed in high-dose females, but this was reversed when two females were sacrificed before study termination. High-dose males and females also showed increases in the incidence of thymus atrophy and decreases in the number of erythropoietic tissue in the bone marrow when compared to controls. The changes in the thymus and erythropoietic tissue may be stress related. The study authors considered these effect to be secondary to systemic toxic effects.

The LOEL, based on microscopic pathology signs of neurotoxicity consisting of skeletal muscle atrophy and white matter multifocal degeneration in the brains of both sexes and white matter multifocal degeneration in the spinal cords of males, was determined to be 0.5 mg/kg/day. The NOEL was 0.25 mg/kg/day.

TABLE 2. Mean Body Weight at Representative Intervals in Dogs Administered L-656,748 by Gavage for 14 Weeks[a,b,c]

Dose (mg/kg/day)	Mean Body Weight (kg ± S.D.) at Week: -1	3	7	11	13	Total change
			Males			
0	8.2±0.9	8.7±1.0	9.5±1.1	10.3±1.1	10.6±1.1	2.7±0.8
0.5/0.25	9.1±0.6	9.7±0.7	10.6±0.9	11.6±1.0	11.7±1.1	2.6±0.5 (96%)
1.0/0.5	7.9±0.7	8.3±0.8	9.1±1.0	10.0±1.1	10.1±1.1	2.2±0.6 (81%)
1.5/1.0[d]	8.2±0.9	7.6±0.2	8.7±0.5	9.7±0.7	9.8±0.7	2.0±0.4 (74%)
			Females			
0	7.7±0.5	8.1±0.5	9.0±0.5	10.1±0.9	10.3±0.9	2.7±0.8
0.5/0.25	7.1±0.7	7.5±0.9	8.4±0.9	9.2±1.0	9.1±1.1	2.0±0.7 (74%)
1.0/0.5	7.5±0.6	8.0±0.6	9.0±0.7	9.9±1.1	10.1±1.1	2.5±0.7 (93%)
1.5/1.0[d,e]	7.6±0.9	6.8±1.5	8.4±1.5	9.3±2.5	9.3±2.4	1.1±1.4 (41%)

[a]Data extracted from Study No. 618-244-TOX20, Table A-1 (pp. 16-19). Means ± S.D. calculated by reviewers.
[b]Doses were reduced for the mid- and high-dose groups at the end of week 2 and for the low-dose groups at the beginning of week 3.
[c]Value in parentheses represent percent of control value.
[d]One animal sacrificed at end of week 3.
[e]One animal sacrificed at end of week 6.

TABLE 3. Mean Food Consumption at Representative Intervals in Dogs Administered L-656,748 by Gavage for 14 Weeks[a,b]

Dose (mg/kg/day)	Mean Food Consumption (g/animal/day ± S.D.) at Week: 1	2	3	7	11	13
			Males			
0	350.0±0	332.9±34.1	341.3±17.5	350.0±0	333.9±32.3	350.0±0
0.5/0.25	350.0±0	350.0±0	350.0±0	350.0±0	334.3±31.5	350.0±0
1.0/0.5	342.0±16.0	315.3±55.7	321.9±32.4	333.8±32.5	291.1±55.4	332.5±23.6
1.5/1.0[c]	342.0±16.0	220.9±123.3	321.7±42.3	335.7±24.8	335.3±25.4	336.9±22.7
			Females			
0	308.8±49.2	283.2±73.8	314.7±55.1	328.8±30.7	298.0±83.4	293.8±70.8
0.5/0.25	333.0±28.9	330.8±16.7	313.7±43.8	343.9±8.0	309.0±32.4	308.3±61.4
1.0/0.5	332.3±20.5	333.3±25.6	345.8±8.5	338.8±22.5	325.3±30.6	322.5±42.2
1.5/1.0[c,d]	327.8±28.5	119.8±60.8*	84.7±113.3*	275.5±105.4	267.0±14.1	287.5±88.4

[a]Data extracted from Study No. 618-244-TOX20, Table A-2 (pp. 20-33). Means ± S.D. calculated by reviewers.
[b]Doses were reduced for the mid- and high-dose groups at the end of week 2 and for the low-dose group at the beginning of week 3.
[c]One animal sacrificed at end of week 3.
[d]One animal sacrificed at end of week 6.

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

TABLE 4. Incidence of Selected Microscopic Observations in Dogs Administered 1.0 mg/kg/day L-656,748 by Gavage for 14 Weeks[a,b]

Site/ Lesion	Incidence							
	Males (mg/kg/day)				Females (mg/kg/day)			
	0	0.25	0.5	1.0	0	0.25	0.5	1.0
Thymus								
Atrophy	0/4	-	-	1/4	0/4	-	-	2/4
Bone marrow								
Erythropoietic cells, decreased number	0/4	0/4	0/4	1/4	0/4	0/4	0/4	2/4
Skeletal muscle								
Atrophy	0/4	0/4	1/4	3/4	0/4	0/4	0/4	4/4
Brain								
White matter, multifocal degeneration	0/4	0/4	3/4	3/4	0/4	0/4	1/4	3/4
Neuron, degeneration	0/4	0/4	0/4	3/4	0/4	0/4	0/4	3/4
Spinal cord								
White matter, multifocal degeneration	0/4	0/4	1/4	4/4	0/4	0/4	0/4	4/4
Sciatic nerve								
Degeneration	0/4	0/4	0/4	4/4	0/4	0/4	0/4	3/4
Optic nerve								
Degeneration	0/4	0/4	0/4	2/4	0/4	0/4	0/4	3/4

[a]Data extracted from Study No. 618-244-TOX20 Table B-5 (pp. 275-278).
[b]Doses were reduced for the mid- and high-dose groups at the end of week 2 and for the low-dose group at the beginning of week 3.
- Not examined