FINAL REPORT

TOXICITY OF THALLIUM(I) SULFATE (CAS NO. 7446-18-6) IN SPRAGUE-DAWLEY RATS

VOLUME ONE: RANGE-FINDING (14-DAY) STUDY

Project No. 8702-L(18)

Work Assignment No. 111148-008

Prepared for

U.S. Environmental Protection Agency
Office of Solid Waste
401 M Street, S.W.
Washington, DC 20460

Through

Dynamac Corporation
The Dynamac Building
11140 Rockville Pike
Rockville, MD 20852

November 21, 1986

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Study Initiation: April 8, 1986
Study Termination: April 23, 1986

By:

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RANGE-FINDING (14-DAY) TOXICITY OF THALLIUM(I) SULFATE (CAS NO. 7446-18-6) IN SPRAGUE-DAWLEY RATS

November 21, 1986

Maxine L. Stoltz, B.S.
Study Director

Monaem El-hawari, Ph.D.
Task Manager

QUALITY ASSURANCE STATEMENT

RANGE-FINDING (14-DAY) TOXICITY OF THALLIUM(I) SULFATE
(CAS NO. 7446-186) IN SPRAGUE-DAWLEY RATS

This study was inspected by the Quality Assurance Unit of MRI and reports were submitted to management as follows:

Animal receipt, quarantine records	3/27/86
Chemical analyses	4/14/86
Dosing, body weights, observations	4/14/86
Clinical observations	4/16/86
Data audit	4/21/86
Necropsy	4/23/86
*Tissue trimming	5/02/86
*Processing, embedding	5/07/86
*Microtomy	5/08/86
Interim report review	5/12/86
*Staining, coverslipping	5/19/86
*Labeling	5/20/86
*Date audit, data entry	5/22/86
*Final pathology report	5/22/86
Interim report review	6/03/86
Final report review/audit	11/17-19/86

* Conducted by the PAI Quality Assurance Unit

This study was conducted in compliance with the EPA TSCA GLP Standards (FR 48 53922-53944, November 29, 1983). The report accurately presents the methods followed and the data generated during the study. This report incorporates the comments provided by the sponsor on the interim reports submitted May 12, 1986 and June 4, 1986.

The raw data and final report are stored in the MRI archives. Slides, blocks, and tissue specimens are stored at PAI.

Eugene H. Pabreburaa
Manager, Quality Assurance Unit

I. INTRODUCTION

EPA's Office of Solid Waste (OSW) is currently developing a framework for a regulatory program to restrict the continued land disposal of hazardous wastes at facilities regulated under Subtitle C of the Resource Conservation and Recovery Act (RCRA) of 1976, as amended by the Hazardous and Solid Waste Amendments of 1984. Under OSW's proposed framework, EPA will establish health-based thresholds for individual chemical constituents in leachates emanating from land disposal units (or their equivalents for release to air and surface water). The leachate thresholds will be established through a back calculation that starts from a point of potential exposure and estimates an acceptable leachate concentration at release from a land disposal unit using fate and transport models. The data provided from the subchronic toxicity study with thallium(I) sulfate will assist in developing maximum acceptable concentrations for this compound in leachates emanating from land disposal units.

II. OBJECTIVE

The primary objective of this range-finding study was to obtain preliminary information on thallium(I) sulfate toxicity and to determine doses for the 90-day subchronic toxicity study.

III. MATERIALS AND METHODS

A. Test Compound

1. Source, receipt, and storage: Thallium(I) sulfate (CAS No. 7446-18-6), Lot No. 03631JL, was purchased from Aldrich Chemical Company, Milwaukee, Wisconsin, and Midwest Research Institute (MRI) received 500 g on February 18, 1986. Upon receipt, the compound was stored at room temperature. Later, however, the compound was transferred to refrigerated conditions (~ 4°C) due to a lack of information regarding thallium sulfate stability.

2. Identity analysis: Elemental analysis for thallium, sulfur, and oxygen and analysis for water using Karl Fischer water analysis confirmed the identity of the test compound.*

* "Chemical Characterization and Dosage Formulation Studies for Thallium(I) Sulfate," Midwest Research Institute, Project No. 8702-L(18), Final Report, April 22, 1986

3. Purity: Purity of thallium sulfate was performed by spark source mass spectrometry. The results indicated that the compound was greater than 99.9% pure,* consistent with the manufacturer's stated purity. Since lead content was shown to be > 100 ppm, studies are underway to quantify these amounts by inductively coupled argon plasma (ICAP) techniques.

4. Dose formulation: Dosing solutions were prepared by dissolving thallium sulfate in water, once per week. At each preparation, an appropriate amount of the test compound was weighed into a volumetric flask, dissolved in Milli-Q® purified water, and used as a stock solution. Serial dilutions were performed volumetrically to obtain the desired dose concentration.

5. Dose verification: Dosing solutions were analyzed using a titration methodology described in MRI report of April 22, 1986.*

B. Animals

1. Source: Male and female Sprague-Dawley rats were used in this study. This species and strain was selected by the sponsor. The rats were purchased from Charles River Breeding Laboratories, Portage Facility, Portage, Michigan.

2. Arrival and quarantine: A total of 85 males and 84 females were received March 25, 1986; they were 30 days old upon receipt. All animals were received in good condition and were immediately housed in quarantine for a 2-week period. During the quarantine period, the animals were ear-tagged with unique identification numbers. They were examined by the attending veterinarian and determined to be in good health as evidenced by normal growth and appearance.

During the test period, the rats were housed individually in clear polycarbonate cages (19 x 10.5 x 8 in.) containing Ab-Sorb-Dri® (Ab-Sorb-Dri Company, Garfield, New Jersey) hardwood chip bedding. Certified Purina Lab Mash (No. 5002, Ralston Purina Company, St. Louis, Missouri) and tap water** were administered ad libitum. The animals were kept in environmentally controlled rooms (temperature, 72 ± 3°F; humidity, 50 ± 10%) maintained on a 12-hr light/dark cycle.

General procedures for animal care and housing were in accordance with DHEW Publication No. (NIH) 85-23, 1985, Guide for the Care and Use of Laboratory Animals, and MRI Manual for Animal Care. Cages, bedding, and

* "Chemical Characterization and Dosage Formulation Studies for Thallium(I) Sulfate," Midwest Research Institute, Project No. 8702-L(18), Final Report, April 22, 1986.

** Monthly records from the Kansas City Water and Pollution Control Department are kept in the MRI Quality Assurance Office.

feeding containers were changed in accordance with MRI standard operating procedures.

C. Experimental Procedures

1. Randomization and group assignment: In order to obtain groups that were comparable by weight, the rats were weighed and randomized for each test group using a computer-based body weight stratification procedure. Randomization was performed 1 day before initiation of dosing. One additional group (10 males and 10 females) were randomized and kept nontreated. These rats were to have been used if an additional dose group had been needed. All rats were 45 days old at the initiation of dosing. The males weighed 161 to 209 g and the females weighed 132 to 160 g.

2. Dosing procedures: Ten rats per sex were assigned to one of five dose groups and one vehicle control group (VCTL). The five doses used were 0.1, 1.0, 2.5, 5.0, and 10.0 mg/kg/day. These dose levels were selected by the sponsor based on available literature information. Each vehicle control animal received doses of Milli-Q® purified water.

The compound was administered daily by gavage for 14 days and the dose volume was based on body weights taken on Days 0, 3, 7, and 10 of the study. A dose volume of 5.0 mL/kg body weight was used for all rats.

3. Clinical observations: Animals were checked twice daily (morning and afternoon) for viability. A detailed clinical observation was performed at dosing and at approximately 1 hr after dosing. Observations were recorded once per day.

4. Body weights and food consumption: Body weights were determined on Days 0, 3, 7, 10, and 15 (termination) or when found dead. Body weight changes were computed. Food consumption was measured during the following intervals: Days 0-3, 3-7, 7-10, and 10-15 and the grams consumed per rat per day was calculated. When an animal was found dead, the feeder was weighed.

5. Necropsy: All animals dying spontaneously and those sacrificed at the scheduled necropsy were subjected to detailed macroscopic examinations. All necropsies were performed under the supervision of a pathologist. For the scheduled necropsy, the rats were sacrificed on study day 15 using carbon dioxide gas.

6. Organ weights: After examination of the animal, the liver, kidneys, brain, gonads (testes or ovaries), spleen, heart, and adrenals were excised and weighed.

7. Histopathology: Tissues showing gross lesions were preserved for microscopic evaluation. These tissues were fixed in 10% neutral buffered formalin and were sectioned, mounted, stained with hematoxylin and eosin (H&E) and examined by light microscopy.

8. Statistical analyses: Body weights, body weight gain, food consumption, absolute organ weights, and relative organ weights were statistically evaluated using the Dunnett's t-test. For evaluation of mean differences, a level of probability of $p < 0.05$ was used.

IV. RESULTS

A. Dose Concentration Analyses

Table 1 shows the results obtained from analyses of dosing solutions used for this study. The results indicate that the nominal and analytical values did not differ by more than ± 7.5%.

B. Mortality

Daily cumulative mortality is shown in Table 2. Total mortality occurred in male and female rats treated at the 10 mg/kg dose level. These animals died after receiving six to eight doses of the test compound. Nine of the ten males treated with the 5 mg/kg dose died before study termination; seven were found dead after the 11th dose, one after receiving 12 doses and one following the 13th dose. Only two females treated with the 5 mg/kg dose died during the course of the study; one after the 10th dose and one after the 13th dose.

C. Clinical Observations

The clinical observations are summarized in Table 3.

Vehicle controls (0 mg/kg dose group): Some of the male rats exhibited a slight decrease in grooming behavior which was reflected in reddish staining around the eyes and nares thought not to be related to treatment or handling. The partial closure of the eyes in three rats, the piloerection in one rat and the rough coat in one rat were all slight in severity.

The female rats treated with the vehicle showed no clinical signs.

0.1 mg/kg dose group: The major clinical signs observed in male rats of this dose group were lacrimation, exophthalmos, and piloerection. These signs became evident between Days 4 and 6 of the study. As dosing continued, these signs became less apparent and dryness or erythema around the eyes, partial closure of the eyes and rough coat became more frequent. Two animals showed signs of shedding.

The female rats showed similar signs as the males, i.e., lacrimation and exophthalmos, but displayed less incidence of piloerection.

1.0 mg/kg dose group: The male rats of this dose group showed similar signs as those described for the males treated at the 0.1 mg/kg dose level. Additional observations included rales, unstable gait, hypoactivity, and self-biting behavior in one animal.

All the female rats of this dose group displayed lacrimation and piloerection early in the study. Four rats showed erythema around the eyes and one rat showed hair loss.

2.5 mg/kg dose group: The male rats of this dose group displayed lacrimation and piloerection early in the study. Exophthamos was observed in eight of the ten rats. Lacrimation progressed to a higher incidence of erythema or dryness around the eyes and partial closure of the eyes. Piloerection also progressed to rough coat, balding in spots, and the development of areas of erythema on the skin.

All female rats of this dose group showed lacrimation, exophthalmos, and piloerection early in the study. The progression of erythema around the eyes, discharge, and closure was less apparent than in the males. Seven animals displayed shedding and two showed late signs of erythema in patches on the skin.

5.0 mg/kg dose group: Male rats of this dose group showed similar early signs (lacrimation, exophthalmos, and piloerection) as described for the 2.5 mg/kg males. Progression of these signs, however, was more severe. All of these rats showed shedding and balding with areas of erythema on the skin. Death was usually preceded by severe diarrhea. Other signs observed occassionally were hypoactivity, hunched posture, cyanosis in the limbs, tremors, and decreased body temperature.

The female rats showed similar signs as the males but displayed a higher incidence in self-biting behavior and changes (either increases or decreases) in body temperature. Only one animal had diarrhea.

10.0 mg/kg dose group: Males showed a very rapid onset of lacrimation and piloerection, progressing to rough coat, diarrhea, and death. Clinical signs in the females were similar to those observed in males. Of interest was the higher incidence of self-biting behavior in the female rats.

D. Body Weights and Body Weight Changes

Average body weights and body weight gains are shown in Tables 4 and 5. Individual animal data are contained in Appendix I, Tables I-1 to I-4. Significant decreases in body weights were apparent in the surviving male rats treated with the 10 mg/kg dose on Day 7 and in males receiving the 5 mg/kg dose on Day 10 (Table 4). Weight loss, however, was demonstrated in males treated with the 5 mg/kg dose between Days 3 and 7 (Table 5). Significant weight losses were also apparent in males treated at the 2.5 mg/kg dose level between Days 10 and 15.

Surviving female rats treated with the 10 mg/kg dose showed significant decreases in body weights and body weight gain between Days 3 and 7. Females receiving the 5 mg/kg dose showed these changes between Days 7 and 15. Between Days 0 and 3, females treated with the 0.1 mg/kg dose showed a significant increase in body weight; this, however, is considered incidental.

E. Food Consumption

Average amounts of food consumed by rats treated with thallium sulfate are shown in Table 6. Individual food consumption data are contained in Appendix I, Tables I-5 and I-6. Significantly decreased food intake was apparent in male and female rats treated at the 10 mg/kg dose level between Days 3 and 7 and in male and female rats treated with the 5 mg/kg dose between Days 7 and 15.

F. Absolute and Relative Organ Weights

Absolute organ weights are presented in Table 7 while relative organ weights, expressed as percent of organ to body weight, are shown in Table 8. Individual animal data are contained in Appendix I, Tables I-7 to I-10. Organ weight data from only those animals surviving the study were used for statistical analyses.

For absolute organ weights of males, only one rat survived the 5 mg/kg and none survived the 10 mg/kg dose, therefore, no statistical analyses could be performed on these groups of data. The only other finding was that males treated with the 2.5 mg/kg dose showed a significant decrease in absolute liver weight.

No females survived the 10 mg/kg dose. However, following treatment with the 5 mg/kg dose, significant decreases were observed in liver, ovaries, spleen, and heart weight and an increase in kidney weight. Females treated with the 2.5 mg/kg dose also showed an increased absolute kidney weight.

Relative organ weights of rats treated with thallium sulfate are shown in Table 8. Of the surviving males, no significant differences from controls were observed. Females treated with the 5 mg/kg dose showed a significant decrease in liver and an increase in kidneys, brain, and adrenals relative weight.

G. Gross Pathology Findings

The gross lesions observed in rats following treatment with thallium sulfate are summarized in Table 9.

With the exception of darkening of various organs, the lesions observed were randomly distributed and appeared to be incidental. The orange hue detected in the lungs of two rats treated with the 10 mg/kg dose was unusual but its significance is not known. Mottling or dark foci in the lungs of several rats in the 5.0, 2.5, and 1.0 mg/kg groups could be the result of CO_2 euthanasia. The red areas or foci in the thymus of four rats in the 0.1 mg/kg group could also be related to CO_2 euthanasia. The occurrence of this lesion in only one rat in higher dose groups (5.0 mg/kg) suggests that it is not a dose-related lesion and probably not a chemical-related lesion. Although a few samples of skin from rats with alopecia were taken, this lesion was not consistently recorded at necropsy as it was recorded in detail as a clinical sign.

A note of caution is warranted in interpretation of organ color changes in "found dead" animals. The color of organs, especially abdominal viscera, may intensify or darken as a result of post-mortem pooling of blood. The actual length of time between death and necropsy was unknown in most cases and the degree of color change owing to post-mortem changes can not be exactly assessed. In early death rats, this was taken into account and only distinct changes were recorded. Darkening of organs usually indicates vascular congestion and, when multiple organs are involved, indicates generalized congestion associated with cardiovascular weakness or collapse. These are rather non-specific changes. Other findings occurring in only one rat in a group should certainly be considered incidental findings.

H. Histopathology

Microscopic lesions detected in tissues are summarized in Table 10. All tissues examined for histopathological changes are shown in Appendix I, Table I-11.

The degeneration of heart muscle observed in one male treated at the 5.0 mg/kg level was minimal and may be treatment-related. Although several lung lesions were present, none are likely to be toxic effects. Congestion and alveolar edema in rats treated with the 5.0 and 10.0 mg/kg dose probably resulted from cardiovascular compromise or collapse. The perivascular edema is likely to have resulted from the method of sacrifice or the lung perfusion technique. The interstitial inflammation is equivocal as it occurred in lungs that were incompletely inflated, thus making interpretation difficult. Other minimal lesions of the lung are incidental. The adrenal lesions of congestion and hemorrhage occurred in one rat treated with the 5.0 and one at the 10.0 mg/kg doses. These lesions are probably reflective of cardiovascular collapse in these rats (both early deaths) rather than of a direct toxic effect of thallium sulfate.

Lesions occurred in several organs of the lymphopoietic system (thymus, spleen, lymph nodes), but none were considered a toxic change. Plasma cell hyperplasia of lymph nodes can occur as a response to localized inflammations, and thymic hemorrhage is a relatively common agonal effect of CO_2 sacrifice. There was no apparent dose relationship. Marked lymphoid depletion of the spleen occurred in one female rat (early death) treated with the 5.0 mg/kg dose and was most likely associated with the stress of dying. Lymphoid depletion can occur in stressful conditions associated with increased glucocorticoid secretion. More commonly, the thymus is involved; however, the thymus was not sampled from this rat.

Acute necrosis of renal tubules occurred in the kidneys of two rats treated at the 10.0 mg/kg level. The necrosis was very recent, have elicited little or no response, and may have contributed to the early deaths of these rats. The necrotic tubules were in the inner cortex or at the corticomedullary junction and were probably the distal straight portion (pars recta) of the proximal convoluted tubule. This lesion was not seen in lower dose groups even though kidneys were also examined from two rats in both the 5.0 and 2.5 mg/kg groups. A subtle increase in cells in the interstitium of the medulla was noted in two rats in the 5.0 mg/kg group and was diagnosed as inflammation, interstitial. Although the latter lesion is somewhat equivocal, the tubular necrosis is not and, therefore, the kidney is concluded to be a target organ. The presence of a mucous plug in the urinary bladder is considered to be incidental even though it occurred in a high dose rat. Similar plugs are common background findings in rats, therefore, it is not considered to be chemical-related.

Liver lesions occurred only in rats treated at the 5.0 and 10.0 mg/kg doses. However, most of these lesions are occasionally seen as background lesions in rats and may or may not be chemical-related. The liver of one male rat treated with the 5.0 mg/kg dose had necrosis, fibrosis, and mineralization. These are less frequently occurring lesions and should be suspected of being treatment-related.

The ceca of two females receiving the 5.0 mg/kg dose had distinct inflammatory lesions which should be considered treatment-related. Other parts of the intestinal tract were not sampled but they should also be considered as potential target organs. All sections of skin examined (three animals treated at the 5.0 mg/kg level and one at the 2.5 mg/kg level) had some degree of alteration of hair follicles. Much lesser involvement of the surface epithelium (acanthosis of epidermis) was noted in two of the rats. These lesions correspond to the grossly described alopecia and are treatment-related.

Most lesions, especially those thought to be related to thallium sulfate toxicity, occurred in the two highest dose groups (5.0 and 10.0 mg/kg). Sampling of tissues for microscopic examination was of gross lesions only, therefore, those microscopic lesions that were not visible grossly might not be fairly represented. Further, all gross lesions did not necessarily have a corresponding microscopic lesion especially when the gross lesions were marginally present, when the gross lesion was related to blood supply,

or when the tissues were autolytic. Fortunately, none of the rats that were found dead had severe post-mortem autolysis although some degree of change was noticed.

V. SUMMARY AND CONCLUSIONS

A range-finding study was conducted to obtain preliminary information on the toxicity of thallium(I) sulfate and to determine doses for the subchronic study. Six groups containing 10 male and 10 female Sprague-Dawley rats each were treated with 14 daily oral doses of the test compound at levels of 0 (vehicle control), 0.1, 1.0, 2.5, 5.0, and 10.0 mg/kg.

Daily oral administration of the compound at a dose of 10 mg/kg caused total mortality in male and female rats following 6 to 8 doses. Doses of 5 mg/kg caused death in 9 of 10 male rats and 2 of 10 female rats. Deaths in this group occurred following 10 to 13 doses. No mortality occurred in the lower dose groups or in the vehicle control group. However, animals treated at levels of 0.1, 1.0, and 2.5 mg/kg showed clinical signs of toxicity including varying degrees of lacrimation, exophthalmos, and piloerection. These toxic signs, which were most apparent in the 2.5 mg/kg dose group, progressed to erythema around the eyes, partial closure of the eyes, rough coat, shedding, and areas of erythema on the skin where loss of hair had occurred. In general, male rats were more severely affected than females.

Significant body weight losses were observed in males and females treated at the 10 mg/kg level and in males treated at the 5 mg/kg level between days 3 and 7 of the study. Males treated at the 2.5 mg/kg level showed significant weight loss between days 10 and 15. In general, decreased food consumption paralleled the weight losses.

Since all males and females treated with the 10 mg/kg dose and nine of ten males treated with the 5 mg/kg dose were found dead, differences in absolute and relative organ weights could not be assessed. In females treated with the 5 mg/kg dose, significant decreases in relative liver weights and significant increases in kidney, brain, and adrenals weights were demonstrated. Most gross tissue lesions detected at necropsy were randomly distributed and were considered incidental. However, upon microscopic examination of these lesions, direct toxic effects of thallium sulfate were detected in the kidneys, cecum, and skin. Probable toxic effects also occurred in the heart. In addition, the liver lesions may possibly be related to thallium sulfate toxicity. Other lesions were considered incidental or related to cardiovascular compromise rather than direct toxicity.

Based on the preliminary results of this study, daily doses for the subchronic (90-day) toxicity study were selected to be 0.25, 0.05, and

0.01 mg/kg, with a control group receiving the vehicle as well as a non-

0.01 mg/kg, with a control group receiving the vehicle as well as a non-treated control group. The subchronic study, which was initiated on April 30, 1986, is now in progress.

VI. ACKOWLEDGEMENTS

Acknowledgement of the principal contributors participating in the performance of this study is presented in the following list:

M. El-hawari	Head, Pharmacology and Toxicology
M. Stoltz	Senior Toxicologist
M. Stedham	Principal Pathologist (PAI)
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L. Laber	Senior Technician
P. Alm	Senior Technician
M. Easton	Senior Technician (PAI)

TABLE 1

CONCENTRATION ANALYSES OF DOSING SOLUTIONS USED IN THE THALLIUM SULFATE RANGE-FINDING STUDY

Date of Analysis	Dose (mg/kg)	Nominal Conc. (mg/mL)	Actual Conc. (mg/mL)	Percent Nominal[a]
April 7, 1986	0	0	0	-
	0.1[b]	0.02	0.0189	94.5
	1.0	0.20	0.205	102.5
	2.5	0.50	0.50	100.0
	5.0	1.00	1.04	104.0
	10.0	2.00	2.03	101.5
April 14, 1986	0	0	0	-
	0.1	0.02	0.0215	107.5
	1.0	0.20	0.196	98.0
	2.5	0.50	0.503	100.6
	5.0	1.00	1.00	100.0
	10.0	2.00	2.00	100.0

[a] Percent nominal = $\frac{\text{Actual Concentration}}{\text{Nominal Concentration}} \times 100$.

b Analyzed April 14, 1986.

TABLE 2

DAILY CUMULATIVE MORTALITY OF SPRAGUE-DAWLEY RATS TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY

Dose (mg/kg)	Number of Doses Received													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Males														
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10.0	0	0	0	0	0	6	8	10	10	10	10	10	10	10
Females														
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10.0	0	0	0	0	0	3	8	10	10	10	10	10	10	10

TABLE 3

INCIDENCE OF CLINICAL OBSERVATIONS IN SPRAGUE-DAWLEY RATS TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY[a]

Observation	Dose (mg/kg)					
	0	0.1	1.0	2.5	5.0	10.0
	Males					
Lacrimation/Eye discharge	3(8)	10(4)	10(5)	10(4)	10(4)	10(2)
Exophthalmos	1(12)	9(6)	7(6)	8(6)	9(6)	0
Dryness/Erythema around eyes	3(8)	8(8)	8(8)	7(6)	6(7)	0
Partial closure of eyes	3(8)	7(8)	7(8)	7(6)	3(9)	2(7)
Discharge from nose/mouth	0	1(5)	2(6)	3(4)	6(5)	4(5)
Rales	0	0	1(12)	0	0	1(6)
Erythema around nose/mouth	1(8)	0	1(8)	1(4)	3(10)	0
Piloerection	1(12)	10(4)	10(3)	10(3)	10(3)	10(3)
Rough coat	1(9)	4(6)	3(7)	8(6)	7(7)	8(5)
Shedding/Balding/Erythema of skin	0	2(9)	2(13)	8(7)	10(8)	2(6)
Hunched posture	0	0	0	0	2(12)	2(6)
Unstable gait	0	0	1(13)	0	1(12)	1(6)
Tremors	0	0	0	0	1(12)	1(6)
Cyanotic limbs	0	0	0	0	2(11)	2(6)
Paralysis in limbs	0	0	0	0	0	1(8)
Hyperactive	0	0	0	0	0	0
Hypoactivity			1(13)	0	1(11)	2(6)
Walking backward	0	0	0	0	0	1(7)
Convulsions	0	0	0	0	0	0
Self-biting	0	0	1(7)	0	0	3(5)
Diarrhea	0	0	0	0	8(9)	5(5)
Increased body temperature	0	0	0	1(13)	0	0
Decreased body temperature	0	0	0	0	1(10)	2(6)

TABLE 3 (Concluded)

Dose (mg/kg)

TABLE 3 (Concluded)

Observation	Dose (mg/kg) 0	0.1	1.0	2.5	5.0	10.0
			Females			
Lacrimation/Eye discharge	0	10(6)	10(5)	10(3)	10(3)	10(2)
Exophthalmos	0	10(6)	0	10(6)	10(6)	0
Dryness/Erythema around eyes	0	2(8)	4(8)	4(8)	4(8)	1(8)
Partial closure of eyes	0	1(8)	1(8)	0	0	1(8)
Discharge from nose/mouth	0	0	0	2(8)	6(10)	6(5)
Rales	0	0	0	0	0	0
Erythema around nose/mouth	0	1(8)	0	0	3(8)	4(7)
Piloerection	0	6(6)	10(3)	10(3)	10(3)	10(3)
Rough coat	0	1(6)	0	1(7)	9(8)	10(6)
Shedding/Balding/Erythema of skin	0	0	1(13)	7(10)	9(7)	2(7)
Hunched posture	0	0	0	0	2(10)	2(7)
Unstable gait	0	0	0	0	1(10)	0
Tremors	0	0	0	0	0	2(5)
Cyanotic limbs	0	0	0	0	1(10)	3(7)
Paralysis in limbs	0	0	0	0	1(10)	0
Hyperactive	0	0	0	0	0	1(6)
Hypoactivity	0	0	0	0	0	1(7)
Walking backward	0	0	0	0	0	0
Convulsions	0	0	0	0	0	2(7)
Self-biting	0	0	0	0	3(10)	5(5)
Diarrhea	0	0	0	0	1(7)	6(6)
Increased body temperature	0	0	0	0	3(13)	0
Decreased body temperature	0	0	0	0	3(10)	2(7)
Vaginal discharge	0	0	0	0	0	1(7)

a Listed as the number of animals that were observed with the sign at least once. Numbers in parenthesis indicate the first day the sign was observed.

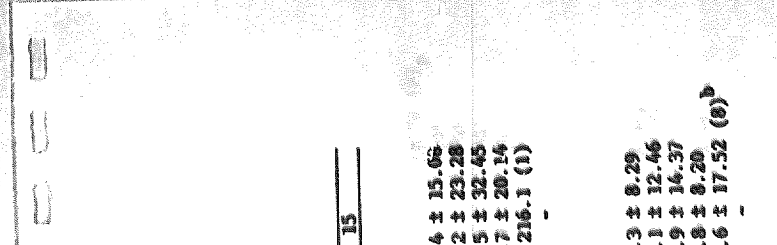

TABLE 4

BODY WEIGHTS OF SPRAGUE-DAWLEY RATS TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY[a]

Dose (mg/kg)	Day of Study 0	3	7	10	15
			Males		
0	185.8 ± 9.95	205.1 ± 10.07	234.2 ± 10.93	253.7 ± 11.63	291.4 ± 15.08
0.1	184.8 ± 12.91	205.2 ± 13.70	236.4 ± 15.96	257.1 ± 17.83	294.2 ± 23.28
1.0	185.6 ± 11.12	202.3 ± 14.03	233.0 ± 16.85	253.1 ± 24.29	283.5 ± 32.45
2.5	186.1 ± 10.85	204.3 ± 13.75	235.1 ± 15.71	255.2 ± 16.63	270.7 ± 20.14
5.0	184.6 ± 12.14	203.8 ± 14.35	224.4 ± 16.30	207.2 ± 18.29[b]	216.1 (1)
10.0	185.5 ± 9.84	203.4 ± 11.64	179.9 ± 28.70 (3)[b]	-	-
			Females		
0	145.6 ± 7.67	151.7 ± 7.89	167.0 ± 8.80	178.4 ± 9.06	193.3 ± 8.29
0.1	145.8 ± 7.12	155.7 ± 6.60	171.7 ± 8.02	185.0 ± 8.15	201.1 ± 12.46
1.0	146.4 ± 9.06	155.1 ± 9.50	169.3 ± 10.56	181.0 ± 12.23	195.9 ± 14.37
2.5	145.0 ± 7.93	153.8 ± 6.68	169.3 ± 7.91	180.1 ± 9.47	189.8 ± 8.20
5.0	145.2 ± 7.61	154.4 ± 8.01	165.6 ± 10.27	168.0 ± 9.93 (9)[b]	151.6 ± 17.52 (8)[b]
10.0	145.9 ± 7.23	155.1 ± 8.49	127.1 ± 11.71 (6)[b]	-	-

a Mean ± SD (in grams) of 10 rats per group except as indicated in parentheses.
b Significantly different ($p < 0.05$) from the control group.

TABLE 5

BODY WEIGHT GAIN IN SPRAGUE-DAWLEY RATS TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY[a]

Dose Level (mg/kg)	Day of Study 0-3	3-7	7-10	10-15
		Males		
0	19.3 ± 3.95	29.1 ± 4.36	19.6 ± 2.06	37.7 ± 5.28
0.1	20.5 ± 4.15	31.1 ± 2.83	20.8 ± 3.58	37.1 ± 6.52
1.0	16.7 ± 3.81	30.7 ± 4.09	20.1 ± 10.04	30.4 ± 11.16
2.5	18.2 ± 4.79	30.8 ± 3.52[b]	20.1 ± 4.86	15.4 ± 8.75[b]
5.0	19.2 ± 4.61	20.6 ± 4.00[b]	-17.1 ± 11.15[b]	-35.7 (1)
10.0	18.0 ± 3.31	-30.9 ± 16.00 (3)[b]	-	-
		Females		
0	6.1 ± 1.92	15.3 ± 2.30	11.4 ± 3.11	14.8 ± 3.95
0.1	9.9 ± 3.13[b]	16.0 ± 2.56	13.3 ± 2.43	16.1 ± 6.21
1.0	8.6 ± 2.46	14.2 ± 2.24	11.7 ± 2.40	14.9 ± 4.28
2.5	8.8 ± 2.50	15.5 ± 2.57	10.8 ± 3.70	9.7 ± 4.76
5.0	9.2 ± 3.31	11.3 ± 5.31	0.7 ± 4.07 (9)[b]	-17.2 ± 14.29 (8)[b]
10.0	9.2 ± 3.57	-26.6 ± 9.88 (6)[b]	-	-

a Mean ± SD (in grams) of 10 rats per group except as indicated in parentheses.
b Significantly different ($p < 0.05$) from the control group.

TABLE 6

FOOD CONSUMPTION OF SPRAGUE-DAWLEY RATS TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY[a]

Dose (mg/kg)	Day of Study 0-3	3-7	7-10	10-15
		Males		
0	21.9 ± 1.56	22.4 ± 1.40	22.7 ± 1.41	23.4 ± 1.90
0.1	22.5 ± 1.52	23.2 ± 1.40	23.4 ± 2.07	24.1 ± 2.12
1.0	21.6 ± 1.59	22.7 ± 1.79	23.2 ± 4.83	22.9 ± 4.61
2.5	21.5 ± 2.21	22.8 ± 2.08	22.5 ± 2.08	20.3 ± 2.25
5.0	21.7 ± 1.84	21.7 ± 1.52	13.5 ± 2.83[b]	10.8 (1)
10.0	19.5 ± 4.99	10.3 ± 3.07 (3)[b]	-	-
		Females		
0	16.6 ± 1.13	17.3 ± 1.09	17.7 ± 1.72	17.3 ± 1.08
0.1	17.5 ± 0.98	18.0 ± 1.79	17.9 ± 1.07	17.7 ± 1.49
1.0	16.2 ± 0.77	17.1 ± 1.43	17.6 ± 1.57	17.4 ± 1.57
2.5	17.3 ± 0.92	18.1 ± 1.54	17.9 ± 1.56	16.6 ± 1.14
5.0	17.0 ± 0.91	17.1 ± 1.51	13.3 ± 1.83 (9)[b]	8.4 ± 2.74 (8)[b]
10.0	17.1 ± 1.35	7.2 ± 2.24 (6)[b]	-	-

a Mean ± SD (in grams per rat per day) of 10 rats per group except as indicated in parentheses.
b Significantly different ($p < 0.05$) from the control group.

TABLE 7

ABSOLUTE ORGAN WEIGHTS (IN GRAMS) OF SPRAGUE-DAWLEY RATS TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY[a]

Dose (mg/kg)	Liver	Kidneys	Brain	Gonads	Spleen	Heart	Adrenals
				Males			
0	13.26 ± 1.17	2.79 ± 0.21	1.89 ± 0.07	2.72 ± 0.17	0.65 ± 0.07	1.03 ± 0.05	0.043 ± 0.006
0.1	12.91 ± 1.78	2.73 ± 0.31	1.92 ± 0.09	2.67 ± 0.20	0.60 ± 0.09	1.02 ± 0.08	0.046 ± 0.022
1.0	12.30 ± 2.26	2.77 ± 0.39	1.87 ± 0.05	2.59 ± 0.16	0.66 ± 0.14	1.03 ± 0.16	0.045 ± 0.021
2.5	11.36 ± 1.70	2.99 ± 0.32	1.89 ± 0.10	2.77 ± 0.24	0.62 ± 0.09	0.97 ± 0.10	0.039 ± 0.007
5.0	8.45 (1)	2.90 (1)	1.90 (1)	2.71 (1)	0.35 (1)	0.90 (1)	0.053 (1)
10.0	-	-	-	-	-	-	-
				Females			
0	8.58 ± 0.51	1.79 ± 0.16	1.77 ± 0.10	0.091 ± 0.019 (9)	0.45 ± 0.09	0.75 ± 0.06	0.052 ± 0.011
0.1	8.87 ± 0.91	1.89 ± 0.17	1.85 ± 0.25	0.082 ± 0.023 (9)	0.50 ± 0.07	0.75 ± 0.06	0.054 ± 0.006 (9)
1.0	8.50 ± 1.17	1.83 ± 0.12	1.81 ± 0.08	0.088 ± 0.016	0.45 ± 0.07	0.75 ± 0.10	0.051 ± 0.010
2.5	7.81 ± 0.73	2.00 ± 0.19	1.62 ± 0.30	0.086 ± 0.024	0.44 ± 0.06	0.71 ± 0.04	0.050 ± 0.007 (9)
5.0	5.79 ± 0.69 (8)[b]	2.04 ± 0.13 (8)[b]	1.73 ± 0.06 (8)	0.065 ± 0.012 (8)[b]	0.32 ± 0.09 (8)[b]	0.60 ± 0.06 (8)[b]	0.054 ± 0.009 (8)
10.0	-	-	-	-	-	-	-

a Mean ± SD of 10 rats per group except as indicated in parentheses.
b Significantly different ($p < 0.05$) from the control group.

TABLE 8

RELATIVE ORGAN WEIGHT (IN PERCENT OF BODY WEIGHT) OF SPRAGUE-DAWLEY RATS TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY

Level (mg/kg)	Liver	Kidneys	Brain	Gonads	Spleen	Heart	Adrenals
				Males			
0	4.6 ± 0.41	1.0 ± 0.11	0.6 ± 0.05	0.9 ± 0.07	0.2 ± 0.03	0.4 ± 0.05	0.01 ± 0.005
0.1	4.4 ± 0.39	0.9 ± 0.12	0.7 ± 0.05	0.9 ± 0.07	0.2 ± 0.03	0.4 ± 0.05	0.01 ± 0.010
1.0	4.3 ± 0.45	1.0 ± 0.07	0.6 ± 0.10	0.9 ± 0.09	0.2 ± 0.05	0.4 ± 0.05	0.02 ± 0.007
2.5	4.2 ± 0.51	1.1 ± 0.10	0.7 ± 0.06	1.0 ± 0.09	0.2 ± 0.05	0.4 ± 0.05	0.01 ± 0.005
5.0	4.0 (1)	1.3 (1)	0.9 (1)	1.3 (1)	0.2 (1)	0.4 (1)	0.02 (1)
10.0	-	-	-	-	-	-	-
				Females			
0	4.4 ± 0.24	0.9 ± 0.06	0.9 ± 0.07	0.04 ± 0.012 (9)	0.2 ± 0.05	0.4 ± 0.00	0.03 ± 0.007
0.1	4.4 ± 0.30	0.9 ± 0.07	0.9 ± 0.14	0.04 ± 0.009 (9)	0.2 ± 0.04	0.4 ± 0.03	0.03 ± 0.005 (9)
1.0	4.3 ± 0.32	0.9 ± 0.07	0.9 ± 0.08	0.04 ± 0.010	0.2 ± 0.05	0.4 ± 0.05	0.02 ± 0.007
2.5	4.1 ± 0.33	1.0 ± 0.08	0.8 ± 0.17	0.04 ± 0.012	0.2 ± 0.04	0.4 ± 0.00	0.02 ± 0.005 (9)
5.0	3.8 ± 0.37 (8)[b]	1.4 ± 0.24 (8)[b]	1.2 ± 0.12 (8)[b]	0.04 ± 0.007 (8)	0.2 ± 0.05 (8)	0.4 ± 0.04 (8)	0.04 ± 0.007 (8)[b]
10.0	-	-	-	-	-	-	-

a Mean ± SD of 10 rats per group except as indicated in parentheses.
b Significantly different ($p < 0.05$) from the control group.

TABLE 9

GROSS PATHOLOGICAL OBSERVATIONS IN TISSUES OF SPRAGUE-DAWLEY RATS TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY

Lesion	Dose (mg/kg) 0 M	0 F	0.1 M	0.1 F	1.0 M	1.0 F	2.5 M	2.5 F	5.0[a] M	5.0[a] F	10.0[b] M	10.0[b] F
Heart, Atria												
Enlarged and/or black									2		2	
Lungs												
Orange											2	
Firm											1	
Mottled					1	2		1	1	1		
Red or darkened foci or areas										1		
Yellow area			1									
Adrenals												
Enlarged										1		
Dark											1	
Thymus												
Red area or foci			2	2						1		
Spleen												
Small										1		
Mandibular lymph node												
Enlarged or red	1						1					
Kidneys												
Dark and/or mottled			1		1		2		1	1	2	
Bladder												
Plug											1	
Liver												
Dark									1	2	2	
Yellow foci									1			
Small intestine												
Distended with red-brown fluid											1	
Cecum												
Small										2		
Brain												
Dark and/or bloody										1	2	
Skin												
Alopecia							1		0	3		
Fat												
Scant										1		

a Includes 11 early deaths.
b All early deaths.

TABLE 10

HISTOPATHOLOGICAL LESIONS DETECTED IN TISSUES OF SPRAGUE-DAWLEY RATS TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY[a]

Organ	Lesion	Dose (mg/kg) 0 M	0.1 M	0.1 F	1.0 M	1.0 F	2.5 M	2.5 F	5.0 M	5.0 F	10.0 M
Heart	Degeneration, Myocardium, Atrium								1		
Lungs	Congestion, Acute								3	1	2*2*
	Edema, Alveolar								2		
	Edema, Perivascular					3,1				3,2	
	Hemorrhage, Acute					1					
	Histiocytosis, Alveolar		1								
	Inflammation, Interstitial		1		1						1*1*
Adrenals	Congestion, Acute										4*
	Hemorrhage, Acute									3*	1*
Thymus	Hemmorrhage, Acute			1,1							
Spleen	Depletion, Lymphoid									4*	
Mandibular Lymph Node	Hyperplasia, Plasma Cell	4					2				
Kidneys	Congestion, Acute				1		1		2		2*
	Inflammation, Interstitial, Medulla								2	1	1*
	Necrosis, Acute Tubules										3*3*
Bladder	Mucous Plug										P*
Liver	Congestion, Acute								2	1,1	3*2*
	Inflammation, Subacute Multifocal									1,2	
	Necrosis, Chronic								2*		
	Fibrosis								2*		
	Mineralization								2*		
Cecum	Inflammation, Necrotizing									2,4*	
Skin	Acanthosis, Epidermis							1		1	
	Dystrophy, Hair Follicle							3		2,3,3	

a Each numerical entry represents a diagnosis in one rat.
P = present; 1 = minimal; 2 = mild; 3 = moderate; 4 = marked; * = early death.

APPENDIX I

INDIVIDUAL ANIMAL DATA

TABLE I-1

TABLE I-1

INDIVIDUAL BODY WEIGHTS (IN GRAMS) OF MALE SPRAGUE-DAWLEY RATS TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY

Dose (mg/kg)	Rat No.	Day of Study 0	3	7	10	15
0	RF684	170.6	195.4	232.1	255.5	2[illegible]7.7
	RF685	181.6	196.2	221.9	240.2	1[illegible]6.8
	RF686	188.4	205.4	231.2	251.7	2[illegible]6.4
	RF697	177.2	195.7	222.4	239.2	272.7
	RF699	190.4	209.2	238.7	257.0	300.8
	RF714	202.0	217.5	239.6	261.6	308.5
	RF728	174.4	191.3	219.5	238.3	268.9
	RF734	191.4	218.4	252.8	271.6	311.0
	RF742	196.6	215.7	246.5	267.3	300.6
	RF745	185.0	205.9	237.0	254.8	292.5
	Mean ± S.D.	185.8 ± 9.95	205.[illegible] ± 10.07	234.2 ± 10.93	253 7 ± 11.63	291.4 ± 15.08
0.1	RF687	191.2	210.3	241.7	265.7	308.7
	RF691	208.9	228.3	262.9	283.5	326.5
	RF711	186.5	201.4	228.4	244.5	284.1
	RF712	180.6	198.8	229.4	251.6	282.3
	RF726	195.1	217.0	251.7	278.8	314.2
	RF727	182.1	204.4	236.5	260.8	299.1
	RF740	173.2	189.2	215.8	235.8	271.4
	RF746	191.2	215.1	247.2	265.7	304.2
	RF754	162.5	181.6	210.6	227.3	269.9
	RF756	176.4	205.7	239.3	257.6	293.9
	Mean ± S.D.	184.8 ± 12.91	205.2 ± 13.70	236.4 ± 15.96	257.1 ± 17 83	294.2 ± 23.28
1.0	RF688	185.1	206.3	238.9	260.1	291.0
	RF690	192.6	211.3	240.1	261.3	299 1
	RF694	184.5	199.5	232.0	255.2	288.9
	RF700	173.8	187.2	211.6	204.1	206.7
	RF705	190.7	206.1	242.3	267.9	310.5
	RF708	181.9	199.0	229.8	252.4	288.0
	RF719	204.0	224.3	254.2	281.6	314.4
	RF741	198.6	217.3	253.1	277.8	300.3
	RF751	176.5	195.0	226.8	251.3	287.7
	RF758	168.5	176.8	201.0	219.3	248.2
	Mean ± S.D.	185.6 ± 11.12	202.3 ± 14.03	233.0 ± 16.85	253.1 ± 24.[illegible]9	283.5 ± 32.45
2.5	RF698	174.8	181.9	210.9	228.3	240.3
	RF707	196.2	215.3	249.4	277.0	2[illegible]7.8
	RF715	205.3	229.2	262.6	274.0	29[illegible].3
	RF723	194.2	210.2	246.9	270.1	290.2
	RF725	180.1	197.3	224.7	246.9	279.0
	RF738	188.4	205.9	238.8	258.9	267.2
	RF739	184.7	203.5	234.4	256.1	273.1
	RF750	169.9	186.9	215.2	230.1	234.0
	RF752	189.9	211.9	236.9	254.6	262.0
	RF759	177.4	200.8	231.2	256.2	281.7
	Mean ± S.D.	186.1 ± 10.85	204.3 ± 13.75	235.1 ± 15.71	255.2 ± 16.63	270.7 ± 20.14
5.0	RF692	176.4	196.9	211.3	201.2	-
	RF709	186.9	213.9	240.4	217.1	-
	RF710	174.1	192.2	215.2	198.2	-
	RF713	197.3	218.9	241.8	205.4	-
	RF722	180.4	200.4	220.6	206.3	-
	RF729	201.8	226.2	246.3	251.8	216.1
	RF731	161.0	176.2	192.7	182 8	-
	RF749	193.6	210.9	230.1	2[illegible]8 8	-
	RF753	184.3	201.1	227.0	2[illegible]7.9	-
	RF761	190.2	201.1	218.2	1[illegible]2.9	-
	Mean ± S.D.	184.6 ± 12.14	203.8 ± 14.35	224.4 ± 16.30	207.2 ± 18.29[a]	
10.0	RF681	179.5	194.3	151.4	-	-
	RF682	181.5	200.3	-[b]	-	-
	RF695	174.1	193.7	153.6[b]	-	-
	RF717	197.5	216.5	179.5	-	-
	RF718	198.6	221.6	208.8[b]	-	-
	RF730	194.3	209.8	165.1[b]	-	-
	RF732	183.3	196.3	-[b]	-	-
	RF743	169.1	184.0	152.7[b]	-	-
	RF748	190.1	209.3	159.3[b]	-	-
	RF760	186.6	208.7	160.7[b]	-	-
	Mean ± S.D.	185.5 ± 9.84	203.4 ± 11.64	179.9 ± 28.70[a]		

a Significantly different ($p < 0.05$) from the control group.
b Found dead on Day 7; not included in mean ± S.D.

TABLE I-2

INDIVIDUAL BODY WEIGHT GAINS (IN GRAMS) OF MALE SPRAGUE-DAWLEY RATS TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY

Dose		Day of Study				
(mg/kg)	Rat No.	0-3	3-7	7-10	10-15	

TABLE I-2

INDIVIDUAL BODY WEIGHT GAINS (IN GRAMS) OF MALE SPRAGUE-DAWLEY® RATS TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY

Dose (mg/kg)	Rat No.	Day of Study 0-3	3-7	7-10	10-15
0	RF684	24.8	36.7	23.4	42.2
	RF685	14.6	25.7	18.3	34.6
	RF686	17.0	25.8	20.5	34.7
	RF697	18.5	26.7	16.8	33.5
	RF699	18.8	29.5	18.3	43.8
	RF714	15.5	22.1	22.0	46.9
	RF728	16.9	28.2	18.8	30.6
	RF734	27.0	34.4	18.8	39.4
	RF742	19.1	30.8	20.8	33.3
	RF745	20.9	31.1	17.8	37.7
	Mean ± S.D.	19.3 ± 3.95	29.1 ± 4.36	19.6 ± 2.06	37.7 ± 5.28
0.1	RF687	19.1	31.4	24.0	43.0
	RF691	19.9	34.1	20.6	41.0
	RF711	14.9	27.0	16.1	39.6
	RF712	18.2	30.6	22.2	30.7
	RF726	21.9	34.7	27.1	45.4
	RF727	22.3	32.1	24.3	38.3
	RF740	16.0	26.6	20.0	35.6
	RF746	23.9	32.1	18.5	38.5
	RF754	19.1	29.0	16.7	22.6
	RF756	29.3	33.6	18.3	36.3
	Mean ± S.D.	20.5 ± 4.15	31.1 ± 2.83	20.8 ± 3.58	37.1 ± 6.52
1.0	RF688	21.2	32.6	21.2	30.9
	RF690	18.7	28.8	21.2	37.8
	RF694	15.0	32.5	23.2	33.7
	RF700	13.4	24.4	-7.5	2.6
	RF705	15.4	36.2	25.6	42.6
	RF708	17.1	30.8	22.6	35.6
	RF719	20.3	29.9	27.4	32.8
	RF741	18.7	35.8	24.7	22.5
	RF751	18.5	31.8	24.5	36.4
	RF758	8.3	24.2	18.3	28.9
	Mean ± S.D.	16.7 ± 3.81	30.7 ± 4.09	20.1 ± 10.04	30.4 ± 11.1[a]
2.5	RF698	7.1	29.0	17.4	12.0
	RF707	19.1	34.1	27.6	10.8
	RF715	23.9	33.4	11.4	17.3
	RF723	16.0	36.7	23.2	20.1
	RF725	17.2	27.4	22.2	32.1
	RF738	17.5	32.9	20.1	8.3
	RF739	18.8	30.9	21.7	17.0
	RF750	17.0	28.3	14.9	3.9
	RF752	22.0	25.0	17.7	7.4
	RF759	23.4	30.4	25.0	25.5
	Mean ± S.D.	18.2 ± 4.79	30.8 ± 3.52	20.1 ± 4.86	15.4 ± 8.75[a]
5.0	RF692	20.5	14.4	-10.1	-
	RF709	27.0	26.5	-23.3	-
	RF710	18.1	23.0	-17.0	-
	RF713	21.6	22.9	-36.4	-
	RF722	20.0	20.2	-14.3	-
	RF729	24.4	20.1	5.5	-35.7
	RF731	15.2	16.5	-9.9	-
	RF749	17.3	19.2	-21.3	-
	RF753	16.8	25.9	-19.1	-
	RF761	10.9	17.1	-25.3	-
	Mean ± S.D.	19.2 ± 4.61	20.6 ± 4.00[a]	-17.1 ± 11.15[a]	
10.0	RF681	14.8	-42.9	-	-
	RF682	18.8	-[b]	-	-
	RF695	19.6	-40.1[b]	-	-
	RF717	19.0	-37.0	-	-
	RF718	23.0	-12.8	-	-
	RF730	15.5	-44.7[b]	-	-
	RF732	13.0	-	-	-
	RF743	14.9	-31.3[b]	-	-
	RF748	19.2	-50.0[b]	-	-
	RF760	22.1	-48.0[b]	-	-
	Mean ± S.D.	18.0 ± 3.31	-30.9 ± 16.00		

a Significantly different ($p < 0.05$) from the control group.
b Found dead on Day 7; not included in mean ± S.D.

TABLE I-3

INDIVIDUAL BODY WEIGHTS (IN GRAMS) OF FEMALE SPRAGUE-DAWLEY RATS TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY

Dose (mg/kg)	Rat No.	Day of Study 0	3	7	10	15
					178.1	194.8

TABLE I-3

INDIVIDUAL BODY WEIGHTS (IN GRAMS) OF FEMALE SPRAGUE-DAWLEY RATS TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY

Dose (mg/kg)	Rat No.	Day of Study 0	3	7	10	15
0	BF769	140.8	149.0	163.3	176.3	194.6
	BF813	136.8	145.6	160.7	178.6	1[illegible].5
	BF819	142.4	150.5	162.8	172.9	1[illegible].1
	BF828	144.8	149.9	167.7	176.6	1[illegible].0
	BF830	149.8	155.0	168.0	177.9	1[illegible].3
	BF832	155.1	162.2	181.4	188.8	203.6
	BF834	141.5	146.4	159.5	169.9	188.8
	BF835	158.4	164.8	179.7	193.8	208.4
	BF840	135.4	138.3	154.1	163.4	179.7
	BF843	150.6	155.0	172.7	186.0	195.4
	Mean ± S.D.	145.6 ± 7.67	151.7 ± 7.89	167.0 ± 8.80	178.4 ± 9.06	193.3 ± 8.29
0.1	BF766	142.3	152.0	169.8	184.9	197.1
	BF796	146.4	157.2	177.7	192.2	215.4
	BF802	138.4	152.0	168.3	183.9	198.0
	BF818	138.4	146.7	158.6	171.9	184.7
	BF822	147.1	159.6	176.0	189.1	204.8
	BF823	151.6	162.4	175.9	191.4	204.9
	BF824	156.4	167.7	186.3	196.7	215.9
	BF827	155.9	158.8	174.2	188.3	197.9
	BF837	136.7	148.6	162.4	175.9	186.4
	BF838	144.6	151.6	167.9	175.8	195.7
	Mean ± S.D.	145.8 ± 7.12	155.7 ± 6.60	171.7 ± 8.02	185.0 ± 8.15	201.1 ± 12.46
1.0	BF767	153.8	162.6	180.4	191.5	208.9
	BF772	142.9	150.3	164.9	178.0	192.2
	BF763	159.5	166.6	183.3	198.8	213.2
	BF774	153.2	167.1	179.2	191.2	211 8
	BF783	139.8	148.7	162.7	175.2	183.1
	BF788	132.5	140.9	155.3	165.3	183 5
	BF798	156.8	165.2	181.3	195.9	214.4
	BF803	142.1	152.7	163.1	170.3	188.4
	BF817	136.9	145.6	158.4	168.7	176.7
	BF833	146.7	151.0	164.1	174.9	187.6
	Mean ± S.D.	146.4 ± 9.06	155.1 ± 9.50	169.3 ± 10.56	181.0 ± 12.23	195.9 ± 14.37
2.5	BF776	138.5	149.5	164.9	173.8	185.0
	BF780	155.4	160.6	176.7	188.1	198.8
	BF785	142.1	152.7	167.3	180.4	188.8
	BF797	137.1	147.0	157.3	164.1	179.0
	BF801	150.7	158.6	175.1	180.4	185.4
	BF810	132.3	142.2	156.2	165.8	178.3
	BF814	156.9	164.9	179.1	187.5	201.9
	BF844	144.8	153.7	169.7	182.3	192.3
	BF845	148.0	152.3	171.5	187.8	198.7
	BF887	144.1	156.2	175.2	191.2	190.0
	Mean ± S.D.	145.0 ± 7.93	153.8 ± 6.68	169.3 ± 7.91	180.1 ± 9.47	189.8 ± 8.20
5.0	BF764	144.1	159.5	175.6	180.8	180.0
	BF770	148.0	159.6	174.7	173.2	123.7
	BF771	141.5	151.0	162.9	168.7	154.7
	BF786	153.2	158.0	164.5	170.4	155.2
	BF799	137.8	147.0	151.0	114.4[a]	-
	BF812	139.0	147.9	159.4	154.2	137.8
	BF825	133.1	139.3	153.8	154.7	140.2
	BF829	157.2	162.6	166.7	166.0	146.1
	BF831	152.3	164.8	184.6	181.6	168.7
	BF839	145.8	154.2	163.3	162.1	-
	Mean ± S.D.	145.2 ± 7.61	154.4 ± 8.01	165.6 ± 10.27	168.0 ± 9.93[b]	151.6 ± 17.52[b]
10.0	BF778	157.7	167.8	145.8	-	-
	BF782	150.2	161.1	126.9[c]	-	-
	BF789	144.0	159.9	133.5	-	-
	BF792	142.1	148.7	113.0	-	-
	BF804	135.6	138.5	129.2	-	-
	BF807	141.1	153.2	119.2	-	-
	BF820	148.9	157.5	121.3[c]	-	-
	BF826	146.8	153.8	121.7	-	-
	BF836	155.2	162.5	129.2[c]	-	-
	BF841	137.6	148.3	111.1[c]	-	-
	Mean ± S.D.	145.9 ± 7.23	155.1 ± 8.49	127.1 ± 11.71[b]		

a Found dead on Day 10; not included in mean ± S.D.
b Significantly different ($p < 0.05$) from the control group.
c Found dead on Day 7; not included in mean ± S.D.

TABLE I-4

INDIVIDUAL BODY WEIGHT GAINS (IN GRAMS) OF FEMALE SPRAGUE-DAWLEY RATS TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY

Dose (mg/kg)	Rat No.	Day of Study 0-3	3-7	7-10	10-15
0	BF769	8.2	14.3	13.0	17.3
	BF813	8.8	15.1	17.9	[illegible]

TABLE I-4

INDIVIDUAL BODY WEIGHT GAINS (IN GRAMS) OF FEMALE SPRAGUE-DAWLEY RATS TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY

Dose (mg/kg)	Rat No.	Day of Study 0-3	3-7	7-10	10-15
0	RF769	8.2	14.3	13.0	17.3
	RF813	8.8	15.1	17.9	12.9
	RF819	8.1	12.3	10.1	21.2
	RF828	5.1	17.8	8.9	8.4
	RF830	5.2	13.0	9.9	14.4
	RF832	7.1	19.2	7.4	14.8
	RF834	4.9	13.1	10.4	18.9
	RF835	6.4	14.9	14.1	14.6
	RF840	2.9	15.8	9.3	16.3
	RF843	4.4	17.7	13.3	9.4
	Mean ± S.D.	6.1 ± 1.92	15.3 ± 2.30	11.4 ± 3.11	14.8 ± 3.95
0.1	RF768	9.7	17.8	15.1	12.2
	RF796	10.8	20.5	14.5	23.2
	RF802	13.6	16.3	15.6	14.1
	RF818	8.3	11.9	13.3	12.8
	RF822	12.5	16.4	13.1	15.7
	RF823	10.8	13.5	15.5	13.5
	RF824	11.3	18.6	10.4	23.2
	RF827	2.9	15.4	14.1	9.6
	RF837	11.9	13.8	13.5	10.5
	RF838	7.0	16.3	7.9	19.9
	Mean ± S.D.	9.9 ± 3.13[b]	16.0 ± 2.56	13.3 ± 2.43	16.1 ± 6.21
1.0	RF767	8.8	17.8	11.1	17.4
	RF772	7.4	14.6	13.1	14.2
	RF763	7.1	16.7	15.5	14.4
	RF774	13.9	12.1	12.0	19.6
	RF783	8.9	14.0	12.5	7.9
	RF788	8.4	14.4	10.0	18.2
	RF798	8.4	16.1	14.6	18.5
	RF803	10.6	10.4	7.2	18.1
	RF817	8.7	12.8	10.3	8.0
	RF833	4.3	13.1	10.8	12.7
	Mean ± S.D.	8.6 ± 2.46	14.2 ± 2.24	11.7 ± 2.40	14.9 ± 4.28
2.5	RF776	11.0	15.4	8.9	11.2
	RF780	5.2	16.1	11.4	10.7
	RF785	10.6	14.6	13.1	8.4
	RF797	9.9	10.3	6.8	14.9
	RF801	7.9	16.5	5.3	5.0
	RF810	9.9	14.0	9.6	12.5
	RF814	8.0	14.2	8.4	16.1
	RF844	8.9	16.0	12.6	10.1
	RF845	4.3	19.2	16.3	10.1
	RF847	12.1	19.0	16.0	-1.2
	Mean ± S.D.	8.8 ± 2.50	15.5 ± 2.57	10.8 ± 3.70	9.7 ± 4.76
5.0	RF764	15.4	16.1	5.2	-0.8
	RF770	11.6	15.1	-1.5	-49.5
	RF771	9.5	11.9	5.8	-14.0
	RF786	4.8	6.5	5.9	-15.2
	RF799	9.2	4.0	-36.6[a]	-
	RF812	8.9	11.5	-5.2	-16.4
	RF825	6.2	14.5	0.9	-8.5
	RF829	5.4	4.1	-0.7	-19.9
	RF831	12.5	19.8	-3.0	-12.9
	RF839	8.4	9.1	-1.2	-
	Mean ± S.D.	9.2 ± 3.31	11.3 ± 5.31	0.7 ± 4.07[b]	-17.2 ± 14.29[b]
10.0	RF778	10.1	-22.0	-	-
	RF782	10.9	-34.2[c]	-	-
	RF789	15.9	-26.4	-	-
	RF792	6.6	-35.7	-	-
	RF804	2.9	-9.3	-	-
	RF807	12.1	-34.0	-	-
	RF820	8.6	-36.2[c]	-	-
	RF826	7.0	-32.1	-	-
	RF836	7.3	-33.3[c]	-	-
	RF841	10.7	-37.2[c]	-	-
	Mean ± S.D.	9.2 ± 3.57	-26.6 ± 9.88[b]		

a Found dead on Day 10; not included in mean ± S.D.
b Significantly different ($p < 0.05$) from the control group.
c Found dead on Day 7; not included in mean ± S.D.

TABLE I-5

FOOD CONSUMPTION (g/day) OF INDIVIDUAL MALE SPRAGUE-DAWLEY RATS TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY

Dose (mg/kg)	Rat No.	Day of Study 0-3	3-7	7-10	10-15
0	RF684	21.1	23.8	24.7	25.1
	RF685	20.1	20.9	21.2	21.6
	RF686	20.8	21.9	21.7	23.4
	RF697	20.8	21.0	21.7	21.3
	RF699	21.0	23.1	22.6	23.6
	RF714	22.5	22.3	22.5	24.5
	RF728	21.0	20.2	20.7	20.7
	RF734	24.3	24.5	23.8	26.0
	RF742	23.8	23.0	24.5	24.4
	RF745	24.0	23.5	23.8	24.6
	Mean ± S.D.	21.9 ± 1.56	22.4 ± 1.40	22.7 ± 1.41	23.4 ± 1.90
0.1	RF687	21.4	22.4	24.1	24.7
	RF691	24.1	24.8	25.0	26.1
	RF711	22.2	21.8	21.2	23.4
	RF712	23.0	23.0	22.9	23.0
	RF726	24.0	25.6	27.3	27.8
	RF727	24.2	25.0	25.8	26.1
	RF740	19.6	22.8	21.0	21.6
	RF746	23.7	22.8	23.0	23.9
	RF754	21.7	21.6	21.9	20.9
	RF756	21.5	22.4	22.2	23.8
	Mean ± S.D.	22.5 ± 1.52	23.2 ± 1.40	23.4 ± 2.07	24.1 ± 2.12
1.0	RF688	22.8	23.8	25.4	23.2
	RF690	21.2	21.5	23.8	23.0
	RF694	20.1	22.2	24.1	23.4
	RF700	21.4	21.3	10.5	10.[illegible]
	RF705	21.7	24.2	25.5	25.[illegible]
	RF708	22.0	23.4	25.0	25.7
	RF719	23.6	23.6	26.6	26.5
	RF741	23.7	25.3	27.2	26.3
	RF751	20.7	22.5	23.6	24.5
	RF758	18.5	19.0	20.6	20.8
	Mean ± S.D.	21.6 ± 1.59	22.7 ± 1.79	23.2 ± 4.83	22.9 ± 4.61
2.5	RF698	17.3	19.6	20.3	16.4
	RF707	23.5	25.5	26.2	22.3
	RF715	24.3	24.0	22.3	20.5
	RF723	22.8	25.8	24.7	21.7
	RF725	19.3	20.5	20.3	21.9
	RF738	21.3	22.8	21.7	18.7
	RF739	21.7	23.1	21.5	20.2
	RF750	19.7	20.6	19.9	17.1
	RF752	23.6	23.5	23.2	21.0
	RF759	21.8	22.5	24.4	23.2
	Mean ± S.D.	21.5 ± 2.21	22.8 ± 2.08	22.5 ± 2.08	20.3 ± 2.[illegible]5
5.0	RF692	21.2	19.8	12.8	-
	RF709	23.7	24.1	15.6	-
	RF710	20.1	20.8	13.7	-
	RF713	23.4	22.9	10.5	-
	RF722	21.9	21.2	13.6	-
	RF729	24.6	23.9	20.6	10.[illegible]
	RF731	18.5	19.7	12.6	-
	RF749	21.6	22.0	11.6	-
	RF753	21.7	21.4	12.1	-
	RF761	20.3	21.5	12.3	-
	Mean ± S.D.	21.7 ± 1.84	21.7 ± 1.52	13.5 ± 2.83[a]	
10.0	RF681	6.0	8.8	-	-
	RF682	19.9	-	-	-
	RF695	21.4	9.1[b]	-	-
	RF717	21.4	8.2	-	-
	RF718	23.6	13.8	-	-
	RF730	20.2	8.4[b]	-	-
	RF732	20.4	-	-	-
	RF743	18.0	8.6[b]	-	-
	RF748	22.4	6.2[b]	-	-
	RF760	21.9	7.9[b]	-	-
	Mean ± S.D.	19.5 ± 4.99	10.3 ± 3.07[a]		

a Significantly different ($p < 0.05$) from the control group.
b Found dead on Day 7; not included in mean ± S.D.

TABLE I-6

FOOD CONSUMPTION (g/day) OF INDIVIDUAL FEMALE SPRAGUE-DAWLEY RATS TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY

TABLE I-6

FOOD CONSUMPTION (g/day) OF INDIVIDUAL FEMALE SPRAGUE-DAWLEY RATS TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY

Dose (mg/kg)	Rat No.	Day of Study 0-3	3-7	7-10	10-15
0	RF769	17.9	18.7	20.8	18.3
	RF813	16.8	16.8	20.3	18.2
	RF819	16.9	16.6	16.4	17.9
	RF828	16.9	17.0	17.1	16.1
	RF830	16.1	16.4	16.5	15.8
	RF832	17.8	17.2	17.8	16.9
	RF834	15.8	17.4	16.8	17.0
	RF835	17.9	19.5	18.6	19.2
	RF840	14.7	15.9	15.4	16.5
	RF843	15.2	17.8	17.7	17.1
	Mean ± S.D.	16.6 ± 1.13	17.3 ± 1.09	17.7 ± 1.72	17.3 ± 1.08
0.1	RF768	17.5	18.0	18.4	17.4
	RF796	18.0	19.4	20.0	20.6
	RF802	17.4	17.6	16.7	17.0
	RF818	16.1	15.5	17.4	16.0
	RF822	19.6	18.6	18.0	18.5
	RF823	17.3	21.7	17.9	17.5
	RF824	19.0	18.4	18.8	19.8
	RF827	16.4	16.0	17.5	16.4
	RF837	17.1	17.8	17.9	16.6
	RF838	16.8	16.5	16.2	17.1
	Mean ± S.D.	17.5 ± 0.98	18.0 ± 1.79	17.9 ± 1.07	17.7 ± 1.49
1.0	RF767	15.2	17.7	18.4	18.7
	RF772	14.8	16.6	17.1	17.0
	RF763	16.4	20.3	21.1	20.2
	RF774	17.1	16.6	18.1	17.5
	RF783	15.8	16.0	16.3	15.8
	RF788	15.8	16.8	16.5	16.4
	RF798	17.0	17.8	18.0	19.4
	RF803	16.4	15.3	15.6	16.2
	RF817	16.5	15.8	16.4	15.5
	RF833	16.9	17.8	18.2	17.3
	Mean ± S.D.	16.2 ± 0.77	17.1 ± 1.43	17.6 ± 1.57	17.4 ± 1.57
2.5	RF776	18.1	18.4	15.2	17.4
	RF780	18.8	19.4	19.1	16.8
	RF785	17.4	18.0	18.9	15.6
	RF797	17.1	15.9	15.4	15.3
	RF801	16.5	18.0	16.9	16.3
	RF810	17.3	16.6	18.7	17.0
	RF814	18.7	19.0	18.7	18.3
	RF844	16.3	17.2	17.8	16.4
	RF845	16.5	21.3	19.8	18.0
	RF887	16.6	17.4	18.3	14.8
	Mean ± S.D.	17.3 ± 0.92	18.1 ± 1.54	17.9 ± 1.56	16.6 ± 1.14
5.0	RF764	17.6	18.5	15.8	12.5
	RF770	17.5	18.9	13.4	3.2
	RF771	17.8	17.6	14.7	9.1
	RF786	16.8	15.9	16.0	8.2
	RF799	15.7	14.9	4.0[a]	-
	RF812	16.7	16.4	11.8	7.6
	RF825	15.5	16.0	15.3	10.1
	RF829	16.5	16.2	12.8	6.8
	RF831	18.4	19.6	12.1	9.8
	RF839	17.1	16.9	10.1	-
	Mean ± S.D.	17.0 ± 0.91	17.1 ± 1.51	13.3 ± 1.83[b]	8.4 ± 2.74[b]
10.0	RF778	18.0	9.2[c]	-	-
	RF782	17.3	6.7[c]	-	-
	RF789	19.0	9.3	-	-
	RF792	15.4	5.1	-	-
	RF804	14.4	8.7	-	-
	RF807	18.0	4.1[c]	-	-
	RF820	17.4	2.8[c]	-	-
	RF826	16.5	6.6	-	-
	RF836	17.7	6.8[c]	-	-
	RF841	16.9	4.9[c]	-	-
	Mean ± S.D.	17.1 ± 1.35	7.2 ± 2.24[b]		

a Found dead on Day 10; not included in mean ± S.D.
b Significantly different ($p < 0.05$) from the control group.
c Found dead on Day 7; not included in mean ± S.D.

TABLE I-7

ABSOLUTE ORGAN WEIGHTS (IN GRAMS) OF MALE SPRAGUE-DAWLEY RATS TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY

TABLE I-7

ABSOLUTE ORGAN WEIGHTS (IN GRAMS) OF MALE SPRAGUE-DAWLEY RATS TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY

Dose (mg/kg)	Rat No.	Liver	Kidneys	Brain	Testes	Spleen	Heart	Adrenals
0	RF684	14.053	2.858	1.807	2.659	0.716	1.132	0.042
	RF685	14.467	3.267	1.856	2.739	0.522	1.009	0.041
	RF686	13.308	2.817	1.872	2.672	0.619	1.052	0.042
	RF697	12.450	2.735	1.840	2.772	0.547	0.960	0.036
	RF699	13.840	2.406	1.867	2.745	0.651	1.000	0.035
	RF714	12.729	2.687	2.037	2.845	0.664	0.983	0.047
	RF728	10.826	2.749	1.992	2.313	0.721	1.014	0.053
	RF734	12.363	2.761	1.905	2.628	0.643	1.085	0.047
	RF742	14.521	2.886	1.828	2.937	0.645	1.022	0.038
	RF745	14.081	2.725	1.919	2.841	0.712	1.029	0.045
Mean ± S.D.		13.26 ± 1.17	2.79 ± 0.21	1.89 ± 0.07	2.72 ± 0.17	0.65 ± 0.07	1.03 ± 0.05	0.043 ± 0.006
0.1	RF687	14.803	2.805	1.893	2.676	0.515	1.086	0.037
	RF693	14.632	3.126	1.964	2.926	0.708	0.974	0.046
	RF711	12.978	2.635	1.968	2.554	0.672	0.979	0.106
	RF712	13.123	2.608	1.954	2.728	0.548	0.941	0.046
	RF726	15.368	3.052	1.829	2.725	0.677	1.105	0.039
	RF727	11.501	2.758	2.011	2.577	0.495	1.165	0.042
	RF740	12.552	2.319	1.964	2.579	0.717	0.972	0.038
	RF746	12.365	2.994	2.039	3.053	0.554	0.987	0.040
	RF754	9.264	2.156	1.725	2.378	0.476	0.951	0.021
	RF756	12.496	2.831	1.902	2.536	0.602	1.094	0.043
Mean ± S.D.		12.91 ± 1.78	2.73 ± 0.31	1.92 ± 0.09	2.67 ± 0.20	0.60 ± 0.09	1.02 ± 0.08	0.046 ± 0.022
1.0	RF688	13.575	2.814	1.827	2.543	0.641	1.086	0.037
	RF690	13.660	2.978	1.918	2.660	0.627	1.010	0.101
	RF694	12.341	2.531	1.821	2.577	0.731	1.001	0.035
	RF700	7.142	2.039	1.814	2.217	0.363	0.721	0.047
	RF705	15.601	3.346	1.891	2.635	0.651	1.086	0.036
	RF708	12.348	3.217	1.921	2.585	0.637	1.017	0.033
	RF719	12.242	2.860	1.951	2.466	0.780	1.298	0.043
	RF741	12.739	2.904	1.906	2.854	0.810	1.170	0.049
	RF751	12.084	2.600	1.828	2.759	0.819	1.006	0.029
	RF758	10.259	2.389	1.849	2.607	0.563	0.873	0.042
Mean ± S.D.		12.30 ± 2.26	2.77 ± 0.39	1.87 ± 0.05	2.39 ± 0.16	0.66 ± 0.14	1.03 ± 0.16	0.045 ± 0.021
2.5	RF698	8.682	2.677	1.729	2.662	0.509	0.886	0.039
	RF707	10.435	2.930	1.831	2.572	0.716	0.956	0.048
	RF715	10.799	2.837	1.904	2.682	0.631	1.059	0.043
	RF723	11.901	3.310	2.110	3.362	0.812	1.126	0.041
	RF725	12.671	3.156	1.840	2.960	0.537	0.909	0.035
	RF738	13.441	3.439	1.998	2.749	0.671	1.001	0.036
	RF739	12.287	3.388	1.885	2.646	0.561	0.951	0.036
	RF750	8.763	2.483	1.859	2.637	0.601	0.826	0.034
	RF752	11.356	2.748	1.854	2.617	0.534	0.859	0.051
	RF759	13.282	2.949	1.927	2.786	0.621	1.088	0.026
Mean ± S.D.		11.36 ± 1.70[c]	2.99 ± 0.32	1.89 ± 0.10	2.77 ± 0.24	0.62 ± 0.09	0.97 ± 0.10	0.039 ± 0.007
5.0	RF692[a]	5.636	2.426	1.822	2.201	0.244	0.752	0.075
	RF709[a]	6.757	2.192	1.760	2.145	0.165	0.760	0.050
	RF710[a]	5.946	1.887	1.600	2.096	0.154	0.668	0.053[b]
	RF713[a]	8.026	2.530	1.831	2.335	0.248	1.008	0.032[b]
	RF722[a]	6.642	2.094	1.835	2.129	0.217	0.525	0.105
	RF729	8.454	2.901	1.903	2.708	0.348	0.897	0.053
	RF731[a]	6.152	1.731	1.686	1.813	0.157	0.533	0.052
	RF749[a]	6.446	2.060	1.752	2.159	0.175	0.900	0.063
	RF753[a]	6.259	2.212	1.695	2.379	0.151	0.888	0.064
	RF761[a]	6.231	1.902	1.788	1.939	0.225	0.907	0.089
Mean ± S.D.								
10.0	RF681[a]	6.302	2.100	1.750	1.769	0.217	0.963	0.042
	RF682[a]	7.033	2.131	1.739	2.061	0.265	0.891	0.062
	RF695[a]	7.101	1.972	1.662	1.814	0.236	0.915	0.042
	RF717[a]	7.443	2.917	1.844	1.894	0.211	0.748	0.060
	RF718[a]	8.008	2.809	1.783	2.171	0.302	0.902	0.064
	RF730[a]	6.364	1.975	1.862	2.281	0.217	0.619	0.064
	RF732[a]	6.928	2.425	1.894	2.238	0.232	0.822	0.058
	RF743[a]	6.407	2.161	1.563	2.016	0.195	0.715	0.035
	RF748[a]	7.004	2.392	1.583	1.876	0.252	0.819	0.056
	RF760[a]	7.276	2.414	1.882	1.925	0.274	0.886	0.063
Mean ± S.D.								

a Found dead; weights not included in mean ± S.D.
b One adrenal only.
c Significantly different ($p < 0.05$) from the control group.

TABLE I-8

RELATIVE ORGAN WEIGHTS (IN PERCENT TO BODY WEIGHT) OF MALE SPRAGUE-DAWLEY RATS TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY

Dose (mg/kg)	Rat No.	Liver	Kidneys	Brain	Testes	Spleen	Heart	Adrenal
0	BF684	4.7	1.0	0.6	1.0	0.2	0.4	0.01
	BF685	5.3	1.2	0.7	1.0	0.2	0.4	0.01
	BF686	4.6	1.0	0.6	0.9	0.2	0.4	0.01
	BF697	4.6	1.0	0.7	1.0	0.2	0.4	0.01
	BF699	4.6	0.8	0.6	0.9	0.2	0.3	0.01
	BF714	4.1	0.9	0.7	0.9	0.2	0.3	0.02
	BF728	4.0	1.0	0.7	0.9	0.2	0.4	0.02
	BF734	4.0	0.9	0.6	0.8	0.2	0.3	0.02
	BF742	4.8	1.0	0.6	1.0	0.2	0.3	0.01
	BF745	4.8	0.9	0.6	1.0	0.2	0.4	0.02
Mean ± S.D.		4.6 ± 0.41	1.0 ± 0.11	0.6 ± 0.05	0.9 ± 0.07	0.2 ± 0.03	0.4 ± 0.05	0.01 ± 0.005
0.1	BF687	4.8	0.9	0.6	0.9	0.2	0.4	0.01
	BF691	4.5	1.0	0.6	0.9	0.2	0.3	0.01
	BF711	4.6	0.9	0.7	0.9	0.2	0.3	0.04
	BF712	4.6	0.9	0.7	1.0	0.2	0.3	0.02
	BF725	4.7	0.6	0.6	0.8	0.2	0.3	0.01
	BF727	3.8	0.9	0.7	0.9	0.2	0.4	0.01
	BF740	4.6	0.8	0.7	1.0	0.3	0.4	0.01
	BF746	4.1	1.0	0.7	1.0	0.2	0.3	0.01
	BF754	3.7	0.9	0.7	1.0	0.2	0.4	0.01
	BF756	4.2	1.0	0.6	0.9	0.2	0.4	0.01
Mean ± S.D.		4.4 ± 0.39	0.9 ± 0.12	0.7 ± 0.05	0.9 ± 0.07	0.2 ± 0.03	0.4 ± 0.05	0.01 ± 0.010
1.0	BF688	4.7	1.0	0.6	0.9	0.2	0.4	0.01
	BF690	4.6	1.0	0.6	0.9	0.2	0.3	0.03
	BF694	4.3	0.9	0.6	0.9	0.3	0.3	0.01
	BF700	3.4	1.0	0.9	1.1	0.2	0.3	0.02
	BF705	5.0	1.1	0.6	0.8	0.2	0.3	0.01
	BF708	4.3	1.1	0.7	0.9	0.2	0.4	0.01
	BF719	3.9	0.9	0.6	0.8	0.2	0.4	0.01
	BF741	4.2	1.0	0.6	1.0	0.3	0.4	0.02
	BF751	4.5	0.9	0.6	1.0	0.3	0.3	0.01
	BF758	4.1	1.0	0.7	1.0	0.2	0.4	0.02
Mean ± S.D.		4.3 ± 0.45	1.0 ± 0.07	0.6 ± 0.10	0.9 ± 0.09	0.2 ± 0.05	0.4 ± 0.05	0.02 ± 0.007
2.5	BF698	3.6	1.1	0.7	1.1	0.2	0.4	0.02
	BF707	3.6	1.0	0.6	0.9	0.2	0.3	0.02
	BF715	3.7	1.0	0.6	0.9	0.2	0.4	0.01
	BF723	4.1	1.1	0.7	1.2	0.3	0.4	0.01
	BF725	4.5	1.1	0.6	1.1	0.2	0.3	0.01
	BF738	5.0	1.3	0.7	1.0	0.3	0.4	0.01
	BF739	4.5	1.2	0.7	1.0	0.2	0.3	0.01
	BF750	3.7	1.1	0.8	1.1	0.3	0.4	0.01
	BF752	4.3	1.0	0.7	1.0	0.2	0.3	0.02
	BF759	4.7	1.0	0.7	1.0	0.2	0.4	0.01
Mean ± S.D.		4.2 ± 0.51	1.1 ± 0.10	0.7 ± 0.06	1.0 ± 0.09	0.2 ± 0.05	0.4 ± 0.05	0.01 ± 0.005
5.0	BF692[a]	3.8	1.6	1.2	1.5	0.2	0.5	0.05
	BF709[a]	3.7	1.2	1.0	1.2	0.1	0.4	0.02
	BF710[a]	3.4	1.1	0.9	1.2	0.1	0.4	0.03
	BF713[a]	4.3	1.4	1.0	1.3	0.1	0.5	0.02[b]
	BF722[a]	4.1	1.3	1.1	1.3	0.1	0.3	0.06
	BF729	4.0	1.3	0.9	1.3	0.2	0.4	0.02
	BF731[a]	3.9	1.1	1.1	1.1	0.1	0.3	0.03
	BF749[a]	3.7	1.2	1.0	1.2	0.1	0.5	0.04
	BF753[a]	3.6	1.3	1.0	1.4	0.1	0.5	0.04
	BF761[a]	3.6	1.1	1.0	1.1	0.1	0.5	0.05
Mean ± S.D.								
10.0	BF681[a]	4.3	1.4	1.2	1.2	0.1	0.7	0.03
	BF682[a]	4.3	1.3	1.1	1.3	0.2	0.5	0.04
	BF695[a]	4.6	1.3	1.1	1.2	0.2	0.6	0.03
	BF717[a]	4.8	1.9	1.2	1.2	0.1	0.5	0.04
	BF718[a]	4.5	1.6	1.0	1.2	0.2	0.5	0.04
	BF730[a]	3.8	1.2	1.1	1.4	0.1	0.4	0.04
	BF732[a]	4.4	1.5	1.2	1.4	0.1	0.6	0.04
	BF743[a]	4.2	1.4	1.0	1.3	0.1	0.5	0.04
	BF748[a]	4.4	1.5	1.0	1.2	0.2	0.6	0.04
	BF760[a]	4.5	1.5	1.1	1.2	0.2	0.6	0.04
Mean ± S.D.								

a Found dead; weights not included in mean ± S.D.
b Based on one adrenal only.

TABLE I-9

ABSOLUTE ORGAN WEIGHTS (IN GRAMS) OF MALE SPRAGUE-DAWLEY RATS TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY

Dose

TABLE I-9

ABSOLUTE ORGAN WEIGHTS (IN GRAMS) OF FEMALE SPRAGUE-DAWLEY RATS TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY

Dose (mg/kg)	Rat No.	Liver	Kidneys	Brain	Ovaries	Spleen	Heart	Adrenals
0	RF769	9.051	1.839	1.851	0.069	0.417	0.735	0.049
	RF813	8.964	1.713	1.949	0.086	0.629	0.832	0.062
	RF819	9.286	1.754	1.603	0.099	0.393	0.697	0.037
	RF828	7.957	1.584	1.801	0.058[b]	0.372	0.650	0.046
	RF830	7.994	1.688	1.785	0.084	0.394	0.742	0.054
	RF832	8.538	1.946	1.829	0.102	0.608	0.723	0.061
	RF834	8.591	1.880	1.743	0.132	0.561	0.811	0.070
	RF835	9.153	2.117	1.704	0.091	0.464	0.859	0.052
	RF840	8.231	1.627	1.651	0.076	0.509	0.726	0.036
	RF843	8.061	1.711	1.807	0.077	0.366	0.721	0.051
Mean ± S.D.		8.58 ± 0.51	1.79 ± 0.16	1.77 ± 0.10	0.091 ± 0.019	0.45 ± 0.09	0.75 ± 0.06	0.052 ± 0.011
0.1	RF768	8.929	1.726	1.770	0.034[b]	0.496	0.764	0.043
	RF796	10.132	2.087	1.764	0.093	0.634	0.827	0.064
	RF802	9.665	1.867	1.773	0.066	0.563	0.785	0.052
	RF818	8.071	1.801	1.702	0.065	0.432	0.665	0.023[c]
	RF822	8.973	1.936	1.800	0.110	0.495	0.742	0.055
	RF823	7.882	1.821	1.813	0.111	0.521	0.797	0.053
	RF824	10.398	2.243	1.796	0.107	0.565	0.829	0.053
	RF827	8.258	1.658	1.722	0.053	0.451	0.694	0.059
	RF837	8.027	1.892	1.781	0.078	0.426	0.769	0.051
	RF838	8.400	1.900	2.562	0.057	0.442	0.670	0.059
Mean ± S.D.		8.87 ± 0.91	1.89 ± 0.17	1.85 ± 0.25	0.082 ± 0.023	0.50 ± 0.07	0.75 ± 0.06	0.054 ± 0.006
1.0	RF767	9.719	1.780	1.828	0.083	0.530	0.960	0.048
	RF772	7.540	1.789	1.843	0.078	0.450	0.700	0.048
	RF763	9.217	2.031	1.925	0.082	0.397	0.769	0.059
	RF774	10.624	1.771	1.822	0.093	0.562	0.838	0.052
	RF782	7.665	1.787	1.946	0.111	0.402	0.655	0.041
	RF788	7.928	1.677	1.701	0.098	0.423	0.646	0.033
	RF798	9.354	2.026	1.755	0.096	0.512	0.839	0.053
	RF803	8.184	1.732	1.806	0.059	0.429	0.680	0.070
	RF817	6.878	1.909	1.719	0.071	0.334	0.681	0.052
	RF833	7.893	1.766	1.724	0.104	0.488	0.754	0.049
Mean ± S.D.		8.50 ± 1.17	1.83 ± 0.12	1.81 ± 0.08	0.088 ± 0.016	0.45 ± 0.07	0.75 ± 0.10	0.051 ± 0.010
2.5	RF776	7.314	1.859	1.699	0.058	0.424	0.686	0.046
	RF780	8.994	2.172	1.760	0.082	0.364	0.725	0.046
	RF785	7.732	2.033	1.693	0.122	0.490	0.665	0.037[c]
	RF797	8.168	1.771	1.714	0.096	0.526	0.632	0.058
	RF801	8.017	2.033	0.781	0.055	0.387	0.701	0.041
	RF810	6.774	1.774	1.745	0.078	0.406	0.756	0.051
	RF814	8.015	2.303	1.606	0.065	0.415	0.708	0.046
	RF844	6.749	1.883	1.782	0.082	0.449	0.711	0.046
	RF845	8.633	1.907	1.688	0.126	0.539	0.711	0.060
	RF847	7.703	2.239	1.773	0.094	0.445	0.765	0.055
Mean ± S.D.		7.81 ± 0.73	2.00 ± 0.19[d]	1.62 ± 0.30	0.086 ± 0.024	0.44 ± 0.06	0.71 ± 0.04	0.050 ± 0.007
5.0	RF764	6.839	1.893	1.749	0.081	0.389	0.647	0.049
	RF770	5.182	2.191	1.697	0.067	0.149	0.595	0.049
	RF771	6.329	1.892	1.676	0.058	0.352	0.621	0.047
	RF786	5.558	2.165	1.793	0.076	0.319	0.577	0.053
	RF799[a]	4.666	1.488	1.619	0.080	0.139	0.497	0.095
	RF812	4.722	1.913	1.616	0.051	0.260	0.496	0.043
	RF825	6.376	1.990	1.764	0.053	0.344	0.371	0.060
	RF829	5.670	2.189	1.702	0.077	0.333	0.604	0.068
	RF831	5.674	2.050	1.809	0.056	0.450	0.695	0.064
	RF839[a]	4.922	2.039	1.670	0.068	0.158	0.331	0.067
Mean ± S.D.		5.79 ± 0.69[d]	2.04 ± 0.13[d]	1.73 ± 0.06	0.065 ± 0.012[d]	0.32 ± 0.09[d]	0.60 ± 0.06	0.054 ± 0.009
10.0	RF778[a]	5.551	2.052	1.675	0.059	0.236	0.521	0.030
	RF782[a]	6.150	1.903	1.720	0.070	0.181	0.599	0.088
	RF789[a]	5.576	1.979	1.678	0.087	0.250	0.606	0.063
	RF792[a]	5.320	1.769	1.709	0.044	0.172	0.579	0.045
	RF804[a]	4.585	1.766	1.571	0.047	0.175	0.475	0.087
	RF807[a]	5.225	1.769	1.438	0.075	0.152	0.738	0.066
	RF820[a]	6.179	1.859	1.748	0.079	0.187	0.464	0.078
	RF826[a]	5.715	1.825	1.392	0.105	0.230	0.606	0.082
	RF836[a]	6.304	1.765	1.764	0.046	0.186	0.677	0.087
	RF841[a]	4.622	1.475	1.618	0.077	0.121	0.475	0.072
Mean ± S.D.								

a Found dead; weights not included in mean ± S.D.
b One ovary only; not included in mean ± S.D.
c One adrenal only; not included in mean ± S.D.
d Significantly different ($p < 0.05$) from the control group.

TABLE I-10

RELATIVE ORGAN WEIGHTS (IN PERCENT TO BODY WEIGHT) OF FEMALE SPRAGUE-DAWLEY RATS TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY

TABLE I-10

RELATIVE ORGAN WEIGHTS (IN PERCENT TO BODY WEIGHT) OF FEMALE SPRAGUE-DA[illegible] RAT TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY

Dose Level (mg/kg)	Rat No.	Liver	Kidneys	Brain	Ovaries	Spleen	Heart	Adrenals
0	RF769	4.6	0.9	1.0	0.03	0.2	0.4	0.02
	RF813	4.7	0.9	1.0	0.04	0.3	0.4	0.03
	RF819	4.8	0.9	0.8	0.05[b]	0.2	0.4	0.02
	RF828	4.3	0.8	1.0	0.03	0.2	0.4	0.02
	RF830	4.2	0.9	0.9	0.04	0.2	0.4	0.03
	RF832	4.2	1.0	0.9	0.05	0.[illegible]	0.4	0.03
	RF834	4.6	1.0	0.9	0.07	0.[illegible]	0.4	0.04
	RF835	4.4	1.0	0.8	0.04	0.[illegible]	0.4	0.02
	RF840	4.6	0.9	0.9	0.04	0.3	0.4	0.02
	RF843	4.1	0.9	0.9	0.04	0.2	0.4	0.03
Mean ± S.D.		4.4 ± 0.24	0.9 ± 0.06	0.9 ± 0.07	0.04 ± 0.011	0.2 ± 0.05	0.4 ± 0.00	0.03 ± 0.007
0.1	RF768	4.5	0.9	0.9	0.02[b]	0.2	0.4	0.02
	RF796	4.7	1.0	0.8	0.04	0.3	0.4	0.03
	RF802	4.9	0.9	0.9	0.03	0.3	0.4	0.03
	RF818	4.4	1.0	0.9	0.04	0.2	0.4	0.01[c]
	RF822	4.4	0.9	0.9	0.05	0.2	0.4	0.03
	RF823	3.8	0.9	0.9	0.05	0.2	0.4	0.02
	RF824	4.6	1.0	0.8	0.05	0.2	0.4	0.02
	RF827	4.2	0.8	0.9	0.03	0.2	0.4	0.03
	RF837	4.3	1.0	1.0	0.04	0.2	0.4	0.03
	RF838	4.3	1.0	1.3	0.03	0.2	0.3	0.03
Mean ± S.D.		4.4 ± 0.30	0.9 ± 0.07	0.9 ± 0.14	0.04 ± 0.009	0.2 ± 0.04	0.4 ± 0.03	0.03 ± 0.005
1.0	RF767	4.6	0.8	0.9	0.04	0.3	0.4	0.02
	RF772	3.9	0.9	1.0	0.0[illegible]	0.3	0.5	0.02
	RF763	4.3	1.0	0.9	0.0[illegible]	0.2	0.3	0.02
	RF774	5.0	0.8	0.9	0.04	0.3	0.4	0.02
	RF783	4.2	1.0	1.1	0.06	0.2	0.4	0.02
	RF788	4.3	0.9	0.9	0.05	0.2	0.4	0.02
	RF798	4.4	0.9	0.8	0.04	0.2	0.4	0.02
	RF803	4.3	0.9	1.0	0.03	0.2	0.4	0.04
	RF817	3.9	1.1	1.0	0.04	0.2	0.4	0.03
	RF833	4.2	0.9	0.9	0.06	0.3	0.4	0.03
Mean ± S.D.		4.3 ± 0.32	0.9 ± 0.07	0.9 ± 0.08	0.04 ± 0.010	0.2 ± 0.05	0.4 ± 0.05	0.02 ± 0.007
2.5	RF776	4.0	1.0	0.9	0.03	0.2	0.4	0.02
	RF780	4.5	1.1	0.9	0.04	0.2	0.4	0.02
	RF785	4.1	1.1	0.9	0.06	0.2	0.4	0.02[c]
	RF797	4.6	1.0	1.0	0.05	0.3	0.4	0.03
	RF801	4.3	1.1	0.4	0.03	0.2	0.4	0.02
	RF810	3.8	1.0	1.0	0.04	0.2	0.4	0.03
	RF814	4.0	1.1	0.8	0.03	0.2	0.4	0.02
	RF844	3.5	0.9	0.9	0.04	0.2	0.4	0.02
	RF845	4.3	1.0	0.8	0.06	0.3	0.4	0.03
	RF887	4.0	1.2	0.9	0.05	0.2	0.4	0.03
Mean ± S.D.		4.1 ± 0.33	1.0 ± 0.08	0.8 ± 0.17	0.04 ± 0.012	0.2 ± 0.04	0.4 ± 0.00	0.02 ± 0.005
5.0	RF764	3.8	1.0	1.0	0.04	0.2	0.[illegible]	0.03
	RF770	4.2	1.8	1.4	0.05	0.1	0.[illegible]	0.04
	RF771	4.1	1.2	1.1	0.04	0.2	0.[illegible]	0.03
	RF786	3.6	1.4	1.2	0.05	0.2	0.4	0.03
	RF799[a]	4.1	1.3	1.4	0.07	0.1	0.6	0.08
	RF812	3.4	1.4	1.2	0.04	0.2	0.4	0.03
	RF825	4.4	1.4	1.2	0.04	0.2	0.4	0.04
	RF829	3.9	1.5	1.2	0.05	0.2	0.4	0.05
	RF831	3.4	1.2	1.1	0.03	0.3	0.4	0.04
	RF839[a]	4.0	1.6	1.4	0.06	0.1	0.4	0.07
Mean ± S.D.		3.8 ± 0.37[d]	1.4 ± 0.24[d]	1.2 ± 0.12[d]	0.04 ± 0.007	0.2 ± 0.05	0.4 ± 0.04	0.04 ± 0.007[d]
10.0	RF778[a]	4.7	1.7	1.4	0.05	0.2	0.4	0.08
	RF782[a]	4.8	1.5	1.4	0.06	0.1	0.5	0.07
	RF789[a]	4.3	1.5	1.1	0.07	0.2	0.5	0.05
	RF792[a]	5.0	1.7	1.6	0.04	0.2	0.5	0.04
	RF804[a]	4.4	1.7	1.5	0.04	0.2	0.5	0.08
	RF807[a]	4.5	1.5	1.2	0.06	0.1	0.6	0.06
	RF820[a]	5.1	1.5	1.4	0.06	0.2	0.4	0.06
	RF826[a]	4.7	1.5	1.1	0.09	0.2	0.5	0.07
	RF836[a]	4.9	1.4	1.4	0.04	0.1	0.5	0.07
	RF841[a]	4.2	1.3	1.5	0.07	0.1	0.4	0.06
Mean ± S.D.								

a Found dead; weights not included in mean ± S.D.
b Based on one ovary only; not included in mean ± S.D.
c Based on one adrenal only; not included in mean ± S.D.
d Significantly different ($p < 0.05$) from the control group.

TABLE I-11

INDIVIDUAL ORGANS AND TISSUES EXAMINED FOR HISTOPATHOLOGICAL CHANGES FROM

TABLE I-11

INDIVIDUAL ORGANS AND TISSUES EXAMINED FOR HISTOPATHOLOGICAL CHANGES FROM MALE SPRAGUE-DAWLEY RATS TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY

Dose (mg/kg)	Rat No.	Tissue	Diagnosis
0	BF699	Mandibular Lymph Node	Hyperplasia, Plasma Cell, Marked
0.1	BF727	Lungs	Alveolar Histiocytosis, Minimal Inflammation, Interstitial, Minimal (incomplete inflation)
		Kidneys	NSL (No Significant Lesion)
	BF746	Thymus	NSL
	BF756	Thymus	NSL
1.0	BF688	Kidneys	Congestion, Acute, Minimal
	BF719	Lungs	Inflammation, Interstitial, Minimal
2.5	BF723	Mandibular Lymph Node	Hyperplasia, Plasma Cell, Mild
	BF738	Kidneys	Congestion, Acute, Minimal
	BF739	Kidneys	NSL
5.0	BF713	Liver	Necrosis, Chronic, Mild Fibrosis, Mild Mineralization, Mild
	BF729	Lungs	Congestion, Acute, Moderate Edema, Alveolar, Mild
		Heart	Degeneration, Myocardium, Atrium, Minimal
		Kidneys	Inflammation, Interstitial, Medulla, Mild Congestion, Acute, Mild
		Liver	Congestion, Acute, Mild
	BF753	Lungs	NSL
10.0	BF682	Lungs	Congestion, Acute, Mild Inflammation, Interstitial, Minimal (incomplete inflation)
		Liver	Congestion, Acute, Mild
		Heart	NSL
		Kidneys	Necrosis, Acute, Tubules, Moderate (pars recta) Inflammation, Interstitial, Minimal, Medulla
		Adrenals	NSL
		Brain	NSL
	BF732	Lungs	Congestion, Acute, Mild Inflammation, Interstitial, Minimal (incomplete inflation)
		Heart	NSL
		Kidneys	Necrosis, Acute, Tubules, Moderate (pars recta) Congestion, Acute, Mild
		Adrenals	Congestion, Acute, Marked Hemorrhage, Acute, Minimal
		Liver	Congestion, Acute, Moderate
		Brain	NSL
	BF743	Bladder	Mucous Plug

TABLE I-12

INDIVIDUAL ORGANS AND TISSUES EXAMINED FOR HISTOPATHOLOGICAL CHANGES FROM FEMALE SPRAGUE-DAWLEY RATS TREATED WITH THALLIUM SULFATE IN THE RANGE-FINDING STUDY

Dose (mg/kg)	Rat No.	Tissue	Diagnosis
0.1	BF823	Thymus	Hemorrhage, Acute, Minimal
	BF824	Thymus	Hemorrhage, Acute, Minimal
1.0	BF774	Lungs	Edema, Perivascular, Moderate
			Hemorrhage, Acute, Minimal
	BF833	Lungs	Edema, Perivascular, Minimal
2.5	BF814	Lungs	NSL
	BF887	Skin	Dystrophy, Hair Follicle, Moderate
			Acanthosis, Epidermis, Minimal
5.0	BF770	Liver	Inflammation, Subacute, Multifocal, Minimal
			Congestion, Acute, Minimal
		Kidneys	Inflammation, Interstitial, Minimal
		Cecum	Inflammation, Necrotizing, Mild
		Brain	NSL
		Skin	Dystrophy, Hair Follicle, Mild
	BF786	Lungs	Edema, Perivascular, Moderate
	BF799	Cecum	Inflammation, Necrotizing, Marked
		Adrenals	Hemorrhage, Acute, Moderate
		Spleen	Depletion, Lymphoid, Marked
	BF812	Skin	Dystrophy, Hair Follicle, Moderate
			Acanthosis, Epidermis, Minimal
	BF829	Liver	Inflammation, Subacute, Multifocal, Mild
			Congestion, Acute, Minimal
		Skin	Dystrophy, Hair Follicle, Moderate
	BF831	Lungs	Congestion, Acute, Minimal
			Edema, Perivascular, Mild
		Thymus	NSL

APPENDIX II

STUDY PROTOCOL AND AMENDMENTS

Midwest Research Institute
425 Volker Boulevard
Kansas City, Missouri 64110

Project No. 8702(18)

Work Assignment No. 111148-008

Study Protocol

Range-Finding (14-Day) Toxicity of Thallium(I) Sulfate (CAS No. 7446-18-6) in Sprague-Dawley Rats

Prepared for

U.S. Environmental Protection Agency
Office of Solid Waste
401 M Street, S.W.
Washington, DC 20460

Through

Dynamac Corporation
The Dynamac Building
11140 Rockville Pike
Rockville, Maryland 20852

March 28, 1986

I. Introduction

EPA's Office of Solid Waste (OSW) is currently developing a framework for a regulatory program to restrict the continued land disposal of hazardous wastes at facilities regulated under Subtitle C of the Resource Conservation and Recovery Act of 1976, as amended (RCRA), by the Hazardous and Solid Waste Amendments of 1984. Under OSW's proposed framework, EPA will establish health-based thresholds for individual chemical constituents in leachates emanating from land disposal units (or their equivalents for release to air and surface water). The leachate thresholds will be established through a back calculation that starts from a point of potential exposure and estimates an acceptable leachate concentration at release from a land disposal unit using fate and transport models. The data provided from this study will be used to determine doses for the subchronic toxicity study which will assist in developing maximum acceptable concentrations for thallium(I) sulfate in leachates emanating from land disposal units.

A brief literature review on the mammalian toxicity of thallium is included in Appendix I.[1]

II. Objective

To obtain preliminary information on thallium(I) sulfate toxicity and to determine doses for the 90-day subchronic toxicity study.

III. Test Procedures

A. Animals

Species/Strain: Rats, Sprague-Dawley.

Number/Sex: One hundred twenty (120), equal number of males and females. Additional animals (40) will be purchased to ensure the availability of enough health animals for the study. Twenty rats (10 males and 10 females) will be kept for 14 days after study initiation. These animals will be used as an additional dose group if necessary. Disposition of unused animals will be documented.

Age: Approximately 6 weeks at initiation of dosing.

Source: Charles River Breeding Laboratories. Procurement records will be preserved.

Identification: Metal ear tags.

[1] B. L. Carson, H. V. Ellis III, and J. L. McCann, Toxicology and Biological Monitoring of Metals in Humans, Lewis Publishers, Inc. (1986).

Acclimation: About 2 weeks under test conditions. An attending veterinarian will examine and release the animals for the study. Documentation regarding the health examination and pertinent details of the quarantine period will be retained.

B.. Animal Care

General procedures for animal care and housing will be in accordance with DHEW Publication No. (NIH) 85-23, 1985, Guide for the Care and Use of Laboratory Animals, and MRI Manual for Animal Care. Cages, racks, bedding, and feeding containers will be changed in accordance with MRI standard operating procedures.

1. Rooms: Air conditioned rooms with 10 to 15 air changes/hr maintained at a temperature of 72 ± 3°F and a relative humidity of 50 ± 10%. The rooms will be maintained on a 12-hr light/dark cycle per day.

2. Caging: The rats will be housed individually in clear polycarbonate cages (19 x 10.5 x 8 in.).

3. Bedding: Sterilized Ab-Sorb-Dri® bedding will be used. The bedding will be changed twice per week.

4. Diet: Certified Purina Lab Mash No. 5002 will be administered ad libitum.

5. Water: Municipal tap water will be available ad libitum in water bottles. Records are obtained once a month from the Kansas City Water and Pollution Control Department and are maintained by the MRI Quality Assurance Unit. Copies of these records will be included in the final report.

C. Test Compound

1. Name: Thallium(I) sulfate (CAS No. 7446-18-6).

2. Source: Aldrich Chemical Company, Milwaukee, Wisconsin.

3. Identity analyses: Will be performed by elemental analysis for thallium, sulfur, hydrogen, and oxygen. Water analysis will also be performed. Analysis will be performed prior to the range-finding study.

4. Purity: Purity analyses will be performed by spark source mass spectrometry. This type of analysis is semiquantitative but has the advantage of detecting most common elements simultaneously. If contaminants are detected at levels greater than 100 ppm, the elements will be quantitated by inductively coupled argon plasma (ICAP) or atomic absorption (AA) analysis. The analysis will be performed prior to the range-finding study and repeated after the 90-day subchronic study.

5. Stability/storage: Stability determination on bulk chemical will not be performed. However, titration methods developed in this laboratory for dose solutions (see below) can be employed if necessary. The bulk chemical will be stored refrigerated (~ 4°C).

D. Dose Formulation

1. Preparation: Thallium(I) sulfate will be prepared as solutions in water, once per week or more often depending on results from stability studies.

2. Homogeneity: Will not be determined due to solubility in water of the test compound.

3. Analysis methods development: Dosage analysis will be performed using titration with potassium bromate.[2] The titration assay is specific for the thallium(I) ion and therefore is a stability indicating analysis.

The method will be validated by linearity studies at five concentrations (including the matrix blank) and precision studies by analysis of four replicates at a low and high concentration within the range of the linearity concentrations.

4. Stability: Formulated solutions will be analyzed after storage for 0, 7, 14, and 21 days at refrigerator (~ 4°C) and room temperature (~ 21°C).

5. Dose verification: Dose solutions will be analyzed in duplicate for each preparation. Analyses will be performed immediately after preparation and prior to administration to the animals.

E. Study Design

All animals selected for use in the study will be examined and determined to be in apparent good health, as evidenced by normal growth and absence of clinical signs during the quarantine period.

1. Randomization: Following the quarantine period, the rats will be assigned to treatment groups using a computer-based body weight stratification procedure. Body weights of rats selected for use in the study will not vary by more than ± 20% of the mean weight.

2. Experimental groups: The study will be performed with 120 rats divided into 6 groups, each containing 10 males and 10 females. One additional group (10 males and 10 females) will be randomly selected and kept nontreated for 14 days after study initiation. These animals will be used as an additional dose group if necessary. The compound will be administered by gavage daily for 14 days. Rats surviving the treatment will be sacrificed on study day 15.

[2] I. M. Kolthoff and P. J. Elving (Eds.), Treatise on Analytical Chemistry, Vol. 2, Part II, Interscience Publishers, New York, NY, 1962, pp. 64, 92.

TABLE 1

STUDY DESIGN

Group	Dose[a] (mg/kg)	Number Males	Number Females
High		10	10
Mid 1		10	10
Mid 2		10	10
Mid 3		10	10
Low		10	10
Vehicle control		10	10
		60	60

a To be determined.

3. Dose levels: Will be selected by the sponsor based on available literature information.

F. Animal Observations

1. Cage-side and clinical observations: Animals will be checked for viability twice daily (morning and afternoon). Detailed clinical observations (Table 2) will be performed before dosing and approximately 1 hr after dosing. Signs of toxicity will be recorded daily. Animal handling and positive identification are required during observations.

2. Weight gain: Body weights will be determined twice weekly. Weight gains will be computed.

4. Food consumption: Will be measured twice weekly.

G. Gross and Microscopic Examination

1. Necropsy: All animals dying spontaneously or killed in extremis and those killed at the scheduled necropsy will be subjected to detailed macroscopic examinations. Necropsies will be performed under the supervision of a pathologist.

2. Organ weights: The following organs will be removed, trimmed, and weighed immediately after dissection: liver, kidneys, spleen, heart, brain, adrenals, and gonads (testes or ovaries).

3. Histopathology:* Only tissues that show gross lesions will be examined microscopically. They will be preserved in 10% neutral buffered formalin, then sectioned, mounted, stained with hematoxylin and eosin (H&E), and examined. The same pathologist will examine all slides.

* Tissue processing and evaluation will be performed by Pathology Associates, Inc. (PAI), 10075 Tyler Place, Hyatt Park II, Ijamsville, Maryland.

TABLE 2

CLINICAL OBSERVATIONS

Behavioral	Gastrointestinal, Urinary
Adipsia	Anuria
Anorexia	Constipation
Ataxia	Diarrhea
Body position	Hematuria
Clonic convulsion	Polyuria
Gait	Salivation
Hyperactivity	
Lethargy	Skin
Moribundity	Alopecia
Paralysis	Cyanosis
Restlessness	Erythema
Respiration	Necrosis
Tonic convulsion	Coat condition
Tremor	
	Respiratory
Eyes	Apnea
Conjunctivitis	Cheyne-Stokes
Corneoiritis	Dyspneic
Exophthalmos	Epistaxis
Exudate	Polypnea
Lacrimation	Rales
Miosis	Rhinorrhea
Mydriasis	
Opacity	Miscellaneous
Palpebral closure	Edema
Photophobia	Hyperthermia
	Hypothermia
	Piloerection

H. Statistical Evaluation

The data obtained will be statistically evaluated by analysis of variance; mean differences will be assessed by appropriate intra-group comparisons. Nonparametric statistical methods may be substituted if heterogenicity of variance is found. The distribution properties of the data will be examined to ensure that the statistical methods used are appropriate. For evaluation of mean differences, a level of probability of $p < 0.05$ will be used.

Body weight gains, organ weights, organ/body weight ratios, and food consumption will be evaluated by analysis of variance or covariance as appropriate. If significant F-ratios are obtained, the Dunnett's t-test (or the Williams' test) will be used to determine the significance of the differences between all test groups and the control.

Frequency data such as mortality or gross lesions will be analyzed using the regression methods of Mantel and/or by an appropriate Chi square analysis.

IV. Reporting

1. Progress reports: Status reports summarizing the progress of the study will be provided at weekly intervals. The report will indicate the number of surviving animals in each group and other data as needed. In addition, the sponsor will be immediately informed of any remarkable treatment-related changes at any time during the study.

2. Final report: A draft final report will be submitted 2 weeks after study termination. The final report will be submitted 2 weeks later. This report will accurately and completely describe the study design, procedures and findings, analyses and summary of the data, and a statement of the conclusions derived from the analyses. The summary will highlight any deviations from control data which may be indicative of toxic effects.

The report will include the following:

Information on the test chemical: description, source, composition, purity, storage, etc.

Information on experimental animals: species, strain, sex, number, source, age, body weights, identification, and randomization.

Information on animal care: housing, caging, bedding, food, and water.

Information on dose preparation: dose levels, frequency of preparation, sampling, analyses, and storage.

A description of the methods used in the study.

The results of the study including a description of toxic symptoms, clinical signs, effects on body weight and food consumption, organ weights and organ/body weight ratios, and gross necropsy.

A description of all calculations performed on the data, analyses of the data, and a statement of the conclusions derived from the analysis.

The following information will be presented graphically and/or in tabulated form.

Body weight changes and weight gain
Food consumption
Mortality data
Organ weights and organ-to-body weight ratios
Toxicological signs
Gross pathology
Any histopathology

Data from individual animals (body weight, organ weights, clinical observations, etc.) will be incorporated in the appendix.

The report will also include the dates on which the study was initiated and completed and names and responsibilities of the personnel involved in the study. A statement prepared and signed by the quality assurance unit will be incorporated in the report. This statement will refer to where the raw data records, reports, samples, and shipments are stored.

V. Personnel Safety

The general safety policies of MRI will be followed. A chemical specific safety plan is attached to this protocol as Appendix II.

VI. Quality Assurance

These studies will be monitored by the MRI Quality Assurance Unit. All testing will be done in accordance with EPA Good Laboratory Practice standards (FIFRA or TSCA, November 29, 1983). QA aspects of the activities performed at PAI will be monitored internally by PAI Quality Assurance staff or externally by the MRI Quality Assurance manager.

After study completion, records will be stored in the MRI archives and retained for the period specified by the sponsor (January 8, 1988).

VII. Study Personnel

The studies will be conducted in the Pharmacology and Toxicology Section of MRI.

Task Manager/Toxicologist: Monaem El-hawari
Study Director/Toxicologist: Maxine Stoltz
Toxicologist/Pathologist: Debra Barrett
Veterinarian: Elizabeth Smith
Pathologist: Michael Stedham (PAI)
Chemists: Evelyn Murrill
Frank Pallas
Animal Care Supervisor: Edward Williams
Histology Supervisor: Fred Argilan (PAI)
Quality Assurance Manager: Eugene Podrebarac
Research Staff: Diane Czarnecki
Patricia Alm
Larry Litle
Leigh Laber
Lisa Brown
Tammy Brown
Ronnie Francis

VIII. Study Schedule

March 25, 1986:	Receive rats, quarantine
April 9, 1986:	Initiation of dosing
April 23, 1986:	Terminal sacrifice
May 7, 1986:	Interim report
May 21, 1986:	Final report

IX. Protocol Approvals

Study Director (MRI)	3-28-86 Date	Task Manager (MRI)	3/28/86 Date
Program Director (Dynamac)	4-29-86 Date	Bioassay Manager (Dynamac)	4-29-86 Date

ISSUED BY: Midwest Research Institute
425 Volker Boulevard
Kansas City, MO 64110

PROJECT NO.: 8702(18)
WORK ASSIGNMENT NO.: 111148-008
PROTOCOL: Range-Finding
DATE: April 8, 1986

PROTOCOL AMENDMENT NO. 1

TO: 8702(18) File, Range-Finding (14-Day) Toxicity of Thallium(I) Sulfate (CAS No. 7446-18-6) in Sprague-Dawley Rats.

SPONSOR: U.S. Environmental Protection Agency through Dynamac Corporation.

PART TO BE CHANGED/REVISED: (E.) Study Design, Dose Levels.

CHANGE/REVISION: The doses are 10, 5, 2.5, 1.0, 0.1, and 0 mg/kg.

REASON FOR CHANGE/REVISION: Doses were selected by the sponsor based on a pilot experiment performed at Midwest Research Institute.

APPROVED:

Study Director (MRI)	4-10-86 Date	Task Manager (MRI)	4/10/86 Date
Program Director (Dynamac)	4-23-86 Date	Bioassay Manager (Dynamac)	4-23-86 Date

ADDENDUM
to
FINAL REPORT

TOXICITY OF THALLIUM(I) SULFATE (CAS NO. 7446-18-6) IN SPRAGUE-DAWLEY RATS

VOLUME ONE: RANGE-FINDING (14-DAY) STUDY

Project No. 8702-L(18)

Work Assignment No. 111148-008

Study Initiation: April 8, 1986
Study Termination: April 23, 1986

By:

M. L. Stoltz, M. A. Stedham,* L. K. Brown,
L. Laber, and A. M. El-hawari

Midwest Research Institute
425 Volker Boulevard
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*Pathology Associates, Inc.

Prepared for

U.S. Environmental Protection Agency
Office of Solid Waste
401 M Street, S.W.
Washington, DC 20460

Through

Dynamac Corporation
The Dynamac Building
11140 Rockville Pike
Rockville, MD 20852

February 24, 1987

ADDENDUM
to
FINAL REPORT

TOXICITY OF THALLIUM(I) SULFATE
(CAS NO. 7446-18-6) IN SPRAGUE-DAWLEY RATS

VOLUME ONE: RANGE-FINDING (14-DAY) STUDY

1. Part to be revised: IV. Results, D. Body Weights and Body Weight Changes

"Weight loss, however, was demonstrated in males treated with the 5 mg/kg dose between Days 3 and 7 (Table 5). Significant weight losses were also apparent in males treated at the 2.5 mg/kg dose level between Days 10 and 15."

Revision: "Significant decreases in weight gain were also demonstrated in males treated with the 5 mg/kg dose between Days 3 and 7 and in males treated at the 2.5 mg/kg level between Days 10 and 15 (Table 5)."

Reason for revision: Animals did not lose weight during the periods indicated; they did, however, show decreased weight gain.

2. Part to be revised: V. Summary and Conclusions

"Significant body weight losses were observed in males and females treated at the 10 mg/kg level and in males treated at the 5 mg/kg level between days 3 and 7 of the study. Males treated at the 2.5 mg/kg level showed significant weight loss between days 10 and 15. In general, decreased food consumption paralleled the weight losses."

Revision: "Significant body weight losses were observed in males and females treated at the 10 mg/kg level. Males treated at the 5 mg/kg level showed decreased weight gain between days 3 and 7 of the study. In addition, males receiving the 2.5 mg/kg dose showed decreased weight gain between days 10 and 15. In general, decreased food consumption paralleled the lack of weight gain."

Reason for revision: Animals did not lose weight during the periods indicated; they did, however, show decreased weight gain.

3. Part to be revised: Table 9

Lesion	Dose (mg/kg) 0 M	0 F	0.1 M	0.1 F	1.0 M	1.0 F	2.5 M	2.5 F	5.0[a] M	5.0[a] F	10.0[b] M	10.0[b] F
Heart, Atria												
Enlarged and/or black									2		2	

Revision:

Lesion	Dose (mg/kg) 0 M	0 F	0.1 M	0.1 F	1.0 M	1.0 F	2.5 M	2.5 F	5.0[a] M	5.0[a] F	10.0[b] M	10.0[b] F
Heart, Atria												
Enlarged or filled with black blood									2[c]		2	

a Includes 11 early deaths.
b All early deaths.
c One heart not examined microscopically; black blood in atria due to the time period between death and necropsy.

Reason for revision: A discretionary decision was made by the pathologist that the dark blood was present only because the animal had been found dead.

4. Part to be revised: Table 9

Lesion	Dose (mg/kg) 0 M	0 F	0.1 M	0.1 F	1.0 M	1.0 F	2.5 M	2.5 F	5.0[a] M	5.0[a] F	10.0[b] M	10.0[b] F
Skin												
Alopecia							1	0	3			

Revision:

Lesion	Dose (mg/kg) 0 M	0 F	0.1 M	0.1 F	1.0 M	1.0 F	2.5 M	2.5 F	5.0[a] M	5.0[a] F	10.0[b] M	10.0[b] F
Skin												
Alopecia							1		3			

Reason for revision: The "0" entry was inconsistent with the table format.

Approved for:

MIDWEST RESEARCH INSTITUTE

Maureen A. Kelly February 24, 1987
Study Director/Date

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