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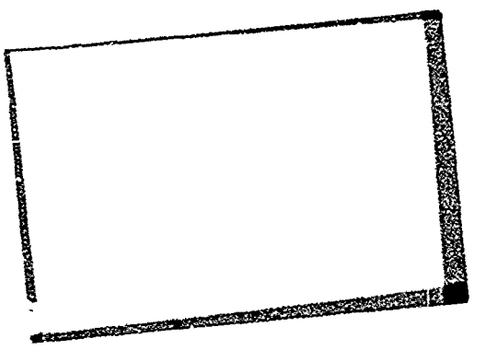
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(12)

(6) Mammalian Toxicological Evaluation of DIMP and DCPD (Phase 2).

(9) FINAL REPORT on phase 2

By

(10) E. Ross Hart, Ph.D.

(11) March 1980

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(12) 531

Supported by
U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Washington, D.C. 20314

(15) Contract No. DAMD 17-77-C-7003

Contracting Officer's Technical Representative: Dr. Jack C. Dacre
Environmental Protection Research Division
U.S. Army Medical Bioengineering Research and Development Laboratory
Fort Detrick, Frederick, Maryland 21701

Litton Bionetics, Inc.
5516 Nicholson Lane
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SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

| REPORT DOCUMENTATION PAGE | | READ INSTRUCTIONS BEFORE COMPLETING FORM |
|---|---|---|
| 1. REPORT NUMBER | 2. GOVT ACCESSION NO. | 3. RECIPIENT'S CATALOG NUMBER |
| 4. TITLE (and Subtitle)<br>Further Mammalian Toxicological Evaluation of DIMP and DCPD | | 5. TYPE OF REPORT & PERIOD COVERED<br>6. PERFORMING ORG. REPORT NUMBER |
| 7. AUTHOR(s)<br>E. Ross Hart, Ph.D. | | 8. CONTRACT OR GRANT NUMBER(s)<br>DAMD 17-77-C-7003 |
| 9. PERFORMING ORGANIZATION NAME AND ADDRESS<br>Litton Bionetics, Inc.<br>5516 Nicholson Lane<br>Kensington, MD 20795 | | 10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS |
| 11. CONTROLLING OFFICE NAME AND ADDRESS<br>U.S. Army Medical Research and Development Command<br>Washington, D.C. 20314 | | 12. REPORT DATE<br>March 1980<br>13. NUMBER OF PAGES<br>518 |
| 14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)<br>U. S. Army Medical Bioengineering Research and Development Command<br>Fort Detrick, Frederick, MD 21701 | | 15. SECURITY CLASS. (of this report)<br>Unclassified<br>15a. DECLASSIFICATION/DOWNGRADING SCHEDULE |

16. DISTRIBUTION STATEMENT (of this Report)
Approved for public release; distribution unlimited

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)
DIMP (DIISOPROPYLMETHYLPHOSPHONATE)
DCPD (DICYCLOPENTADIENE)
Teratology
Reproduction
Subchronic Toxicity

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Specially purified samples of DIMP proved non-mutagenic. About 90% of administered DIMP is recoverable from the urine of rats, mice or dogs and 95% of this is in the form of isopropyl-methyl-phosphonic acid (IMPA). No teratologic effects were produced by dietary levels of 100 to 3000 ppm given on days 6 through 15 of gestation. Dietary incorporation of DIMP at levels of 300 and 3000 ppm produced no dose-related reproductive response

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In the rat over three successive generations with two matings per generation. Nerve fiber degeneration (demyelination) in chickens treated once at 1500 mg/kg or twice at 1000 or 500 mg/kg. No toxic effects were seen over a 90-day period in beagles given dietary mixes containing 150, 1500 or 3000 ppm of DIMP.

Purified DCPD proved non-mutagenic. No teratologic effects were observed in rats given dietary levels of 80, 250 or 750 ppm on days 6 through 15 of gestation. No deleterious effects on reproductive processes were seen with two matings per generation. No important evidence of toxicity was seen in beagles given 100, 300 or 1000 ppm in their diet over a 90 day period.

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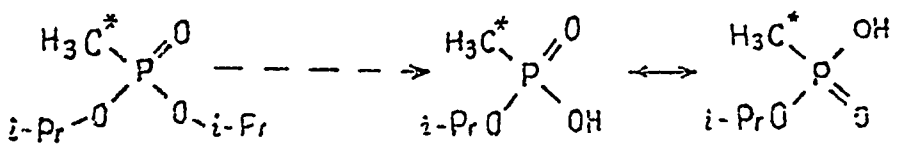
## EXECUTIVE SUMMARY

### DIMP

The test compound, DIMP USAMBRDL EPRD-1, did not demonstrate mutagenic activity in any of the assays conducted in this evaluation and was considered not mutagenic under these test conditions.

The test compound, DIMP Lot AF-74, did not demonstrate mutagenic activity in any of the assays conducted in this evaluation and was considered not mutagenic under these test conditions.

Greater than 90% of the radioactivity of administered labelled diisopropyl methyl phosphonate (DIMP) to rats, mice and dogs was recovered in the urine. In all three species about 95% of recovered radioactivity comes from a single highly polar component. This component is identified as isopropyl-methyl-phosphonic acid (IMPA). The identification is based on comparing the metabolite with authentic IMPA by three different chromatographic techniques; namely, thin layer chromatography, ion chromatography and gas liquid chromatography coupled with mass spectrometry.



The test material was administered in the diet at doses of 100, 300 and 3000 ppm to pregnant female rats on days 6 through 15 of gestation. There were no changes in the dams or among the fetuses that indicated an adverse compound-related effect.

Dietary incorporation of DIMP at levels of 300 and 3000 ppm produced no dose-related reproductive response in the rat for three successive generations with two matings per generation. The first mating of the third generation resulted in significant pup losses from Day 4 to Day 21 for the treatment groups. This decrease was not evidenced for the second mating. Food consumption and body weight data for the parent (F0), second generation (F1b) and third generation (F2b) rats, indicated statistical equivalence with the controls for all treatment levels except the high dose F2b female group. Litter and necropsy observations for the first breeding of the three generations were unremarkable and free of any dose-dependent relationship.

Treatment of atropinized White Leghorn hens with DIMP once at 1500 mg/kg or twice at 1000 or 500 mg/kg did not produce evidence of nerve fiber degeneration after 21 days (animals treated once) or 46 days (animals treated twice) when the sciatic nerve was examined microscopically. Evidence of unsteady gait was easily distinguished clinically from signs exhibited by the positive control animals and was judged to be unrelated to nerve fiber degeneration.

The positive control animals, treated with TOCP once at 500 mg/kg, developed classical progressive clinical signs of nerve fiber degeneration beginning 12 to 14 days after treatment. Most of the animals showed microscopic evidence of nerve fiber degeneration.

Beagle dogs, four per sex per group, were given diisopropylmethylphosphate (DIMP) in the diet for 90 days. Dietary concentrations were 150, 1500 and 3000 ppm, and a control group was maintained in parallel. Initially and at 4, 8 and 13 weeks hemograms and clinical chemistry values were obtained on all dogs. The dogs were examined daily as to general condition, and weekly body weights and food consumption data were obtained. An ophthalmologic examination was conducted initially and at 13 weeks. At termination each dog was grossly necropsied and approximately 27 tissues were preserved. Eight organs were weighed. Tissues from the control and high-level groups were examined histologically. The dogs continued in good general health throughout the study. No clear or meaningful changes were seen in the data collected that could be ascribed to the ingestion of DIMP by these dogs, and it is concluded that this compound produced no toxic effects at a dietary concentration of 3000 ppm or below, over the 90-day period of study.

DCPD

The test compound, DCPD Lot No. 040667, did not demonstrate mutagenic activity in any of the assays conducted in this evaluation and was considered not mutagenic under these test conditions.

The test compound, DCPD W-761226, did not demonstrate mutagenic activity in any of the assays conducted in this evaluation and was considered not mutagenic under these test conditions.

With the concurrence of the Project Officer, emphasis was placed on DIMP rather than DCPD with the result that no additional significant information was developed regarding DCPD. Previous findings are summarized below:

DCPD was absorbed after oral administration to mice, rats, and dogs. Peak plasma levels occurred in 2 hours in mice and dogs, and in 6 hours in rats. DCPD was widely distributed in all three species at 1 to 2 hours with the highest levels in urinary bladder, gall bladder and body fat in mice, in gall bladder and bile in dogs, and in body fat, adrenals and urinary bladder in rats. Excretion appeared to be primarily via the urine in all three species. About 85% of the administered radioactivity was accounted for in urine and feces within 24 hours. Urine from mice and dogs showed two radioactive components while rat urine also contained a third. All of these seemed to differ from DCPD on TLC, but none has yet been identified.

The test material was administered in the diet at doses of 80, 250 and 750 ppm to pregnant female rats on Days 6 through 15 of gestation. There were no changes in the dams or among the fetuses that indicated an adverse compound-related effect.

Two groups of 10 male and 20 female albino rats each (F0 generation) were given dicyclopentadiene (DCPD) in the diet at 80 or 750 ppm, with a similar group maintained as controls. The rats in each group were mated twice to produce the F1a and F1b litters.

The same number of F1b pups per sex per group were likewise mated to produce F2a and F2b pups, and the F2b animals were maintained to produce F3a and F3b litters. Analyses of the diet mixes indicated 87 and 92% of the desired concentrations were achieved, on the average, for the low- and high-dose levels, respectively.

For each generation in each group there were determined fertility indices, live-to-total pup ratios, mean litter sizes, pup survival indices and mean body weights at Day 4 post partum and at weaning. Gross necropsy observations were made of representative pups of all Fa litters, of the F3b litters, and of the parent rats. Body weights and food consumption were determined for parent rats at various intervals, also.

It is concluded no deleterious effects on reproductive processes or general condition of the rats were produced by DCPD in this study. Likewise, no evidence of dose-related teratologic effect was seen.

The test material, Dicyclopentadiene, was administered by incorporation into the diet at concentrations of 100, 300, and 1000 ppm to Beagle dogs for 13 weeks. The animals were observed daily for general condition and behavior. Clinical pathological evaluations, including analysis of the clinical chemical constituents of serum, urine and hemograms, were performed at approximately monthly intervals. Tissues from the control and high dose dogs were compared histopathologically for differences. Based on the results obtained using these criteria it was concluded that treatment produced no significant toxicity with the possible exception of minor indications of intestinal distress expressed as vomiting and soft stools among dogs of the treated groups, especially the highest dose (1000 ppm).

# FOREWORD

This report includes the results of microbial mutagenesis and demylination studies authorized under a predecessor contract (DAMD 17-75-C-5068).

In conducting the research described in this report, the investigator(s) adhered to the "Guide for Laboratory Animal Facilities and Care", as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences-National Research Council.

The method of euthanasia consisted of overdosage with carbon dioxide by inhalation in the case of group sacrifices or overdosage of pentobarbital sodium intraperitoneally or intravenously when one or a few individuals were sacrificed at a given time.

PART I - SECTION A

INTRODUCTION AND MATERIAL

DIMP

## 1. INTRODUCTION

In a continuation of an evaluation of the mammalian toxicity of DIMP, this compound has been studied by subchronic (90 day) administration to dogs, for reproductive and teratologic effects in rats, for neurotoxicity in chickens, for mutagenic effects in certain tester strains of salmonella and additional aspects of its metabolic fate have been investigated in mice, rats and dogs.

Earlier parts of the evaluation were reported in November 1976 under Contract No. DAMD 17-75-C-5068.

## 2. MATERIAL

DIMP (Diisopropylmethylphosphonate) was obtained as a custom synthesis from Richmond Organics, 7342 Forest Hill Avenue, Richmond, Virginia 23225. Three separate orders were placed and three shipments were received and designated as follows:

| Receipt Date | Quantity | LBI No. |
|---|---|---|
| 8/5/75 | 500 g | 755A |
| 12/15/75 | 500 g | 776A |
| 2/16/76 | 500 g | 781A |

DIMP was analyzed using an OV-17/Reoplex 400 column as described in the procedure for analysis of DIMP in water samples used by Shell Chemical Company and the Colorado Department of Health. DIMP had a retention time of 6.2 minutes. Two impurities were observed, one at 5.2 minutes and the other at 11.8 minutes. Content was calculated on a total peak area basis.

| | | Impurity | |
|---|---|---|---|
| LBI No. | DIMP | #1 | #2 |
| 755A | 95.2% | 3.1% | 1.7% |
| 776A | 89.6% | 5.6% | 4.8% |
| 781A | 88.0% | 6.7% | 5.3% |

Because of poor water solubility, solutions were prepared for administration to animals by dissolving DIMP in polyethylene glycol 400 (PEG 400) "Carbowax" obtained from Fisher Scientific Company.

On January 8, 1977 an additional supply of DIMP was received from USAMBRDL. The bulk sample used for mammalian tests was provided by Chemical Systems Laboratory, Aberdeen Proving Ground, Maryland, and purified by distillation through a 12 foot packed column under reduced pressure. The purity was estimated by gas chromatography to be approximately 96%, with impurities consisting most probably of triisopropyl phosphite and all five compounds obtainable from DIMP by interchange of isopropyl and methyl groups. A small sample of high purity (>99.9%) was prepared by reaction of methylphosphonodichloridate with isopropyl alcohol in basic medium for use in mutagenesis tests.

PART I - SECTION B

MICROBIAL MUTAGENESIS

DIMP

LBI PROJECT NO. 10734-01

## SUMMARY

The test compound, DIMP USAMBRDL EPRD-1, did not demonstrate mutagenic activity in any of the assays conducted in this evaluation and was considered not mutagenic under these test conditions.

The test compound, DIMP Lot AF-74, did not demonstrate mutagenic activity in any of the assays conducted in this evaluation and was considered not mutagenic under these test conditions.

## 1. OBJECTIVE

The objective of this study was to evaluate the test compound for genetic activity in microbial assays with and without the addition of mammalian metabolic activation preparations.

## 2. MATERIALS

### A. Test Compound

1. Date Received: December 14, 1976

2. Description: Colorless liquid labelled USAMBRDL EPRD-1

### B. Indicator Microorganisms

*Salmonella typhimurium*, strains: TA-1535, TA-98, TA-1537, TA-100, TA-1538

*Saccharomyces cerevisiae*, strain: D4

### C. Activation System (Ames et al., Mutation Research 31:347, 1975)

1. Reaction Mixture

| Component | Final Concentration/ml |
|---|---|
| TPN | 4 µmoles |
| Glucose-6-phosphate | 5 µmoles |
| Sodium phosphate (diabasic) | 100 µmoles |
| $MgCl_2$ | 8 µmoles |
| KCl | 33 µmoles |
| Homogenate fraction equivalent to 25 mg of wet tissue | 0.1-0.15 ml 9,000 x g supernatant of rat liver |

2. MATERIALS (Continued)

2. S-9 Homogenate

A 9,000 x g supernatant was prepared from Sprague-Dawley adult male rat liver induced by Aroclor 1254 five days prior to kill.

D. Positive Control Chemicals

Table 1 below lists the chemicals used for positive controls in the nonactivation and activation assays.

TABLE 1

| ASSAY | CHEMICAL[a] | SOLVENT | PROBABLE MUTAGENIC SPECIFICITY |
|---|---|---|---|
| Nonactivation | Methylnitrosoguanidine (MNNG) | Water or Saline | BPS[b] |
| | 2-Nitrofluorene (NF) | Dimethylsulfoxide[c] | FS[b] |
| | Quinacrine mustard (QM) | Water or saline | FS[b] |
| Activation | 2-Anthramine (ANTH) | Dimethylsulfoxide[c] | BPS[b] |
| | 2-Acetylaminofluorene (AAF) | Dimethylsulfoxide[c] | FS[b] |
| | 8-Aminoquinoline (AMQ) | Dimethylsulfoxide[c] | FS[b] |

[a]Concentrations given in Results Section

[b]BPS = Base-pair substitution

FS = Frameshift

[c]Previously shown to be nonmutagenic

E. Solvent

Either deionized water or dimethylsulfoxide (DMSO) was used to prepare stock solutions of solid materials. All dilutions of test materials were made in either deionized water or DMSO. The solvent employed and its concentration are recorded in the Results Section.

## 3. EXPERIMENTAL DESIGN

### A. Plate Test (Overlay Method*)

Approximately $10^8$ cells from an overnight culture of each indicator strain were added to separate test tubes containing 2.0 ml of molten agar supplemented with biotin and a trace of histidine. For non-activation tests, at least four dose levels of the test compound were added to the contents of the appropriate tubes and poured over the surfaces of selective agar plates. In activation tests, a minimum of four different concentrations of the test chemical were added to the appropriate tubes with cells. Just prior to pouring, an aliquot of reaction mixture (0.5 ml containing the 9,000 x g liver homogenate) was added to each of the activation overlay tubes, which were then mixed, and the contents poured over the surface of a minimal agar plate and allowed to solidify. The plates were incubated for 48 hours at 37C, and scored for the number of colonies growing on each plate. The concentrations of all chemicals are given in the Results Section. Positive and solvent controls using both directly active positive chemicals and those that require metabolic activation were run with each assay.

### B. Recording and Presenting Data

The numbers of colonies on each plate were counted and recorded on printed forms. These raw data were analyzed in a computer program and reported on a printout. The results are presented as revertants per plate for each indicator strain employed in the assay. The positive and the solvent controls are provided as reference points. Other relevant data are provided on the computer printout.

*Certain classes of chemicals known to be mutagens and carcinogens do not produce detectable responses using the standard Ames overlay method. Some dialkyl nitrosamines and certain substituted hydrazines are mutagenic in suspension assays, but not in the plate assay. Chemicals of these classes should be screened in a suspension assay.

# TABLE I-B-1

4. SUMMARY OF PLATE TEST RESULTS — LITTON BIONETICS, INC.

A. NAME OR CODE DESIGNATION OF THE TEST COMPOUND: DIMP
B. SOLVENT: DMSO
C. TEST DATE: JAN. 3, 1977
NOTE: CONCENTRATIONS ARE GIVEN IN MICROLITERS (UL) OR MICROGRAMS (UG) PER PLATE.

| TEST | SPECIES | TISSUE | REVERTANTS PER PLATE* TA-1535 1 | TA-1535 2 | TA-1537 1 | TA-1537 2 | TA-1538 1 | TA-1538 2 | TA-98 1 | TA-98 2 | TA-100 1 | TA-100 2 | D4* 1 | D4* 2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NONACTIVATION | | | | | | | | | | | | | | |
| SOLVENT CONTROL | --- | --- | 12 | | 20 | | 18 | | 37 | | 191 | | 37 | |
| POSITIVE CONTROL** | --- | --- | >1000 | | 789 | | >1000 | | >1000 | | >1000 | | >1000 | |
| TEST COMPOUND | | | | | | | | | | | | | | |
| 0.00100 UL | --- | --- | 21 | | 18 | | 26 | | 35 | | 188 | | 16 | |
| 0.01000 UL | --- | --- | 23 | | 14 | | 28 | | 37 | | 205 | | 19 | |
| 0.10000 UL | --- | --- | 21 | | 13 | | 28 | | 27 | | 163 | | 20 | |
| 1.00000 UL | --- | --- | 14 | | 11 | | 29 | | 32 | | 207 | | 13 | |
| 5.00000 UL | --- | --- | 15 | | 10 | | 33 | | 28 | | 185 | | 15 | |
| ACTIVATION | | | | | | | | | | | | | | |
| SOLVENT CONTROL | RAT | LIVER | 20 | | 23 | | 25 | | 35 | | 196 | | 125 | |
| POSITIVE CONTROL*** | RAT | LIVER | >1000 | | 891 | | >1000 | | >1000 | | >1000 | | 255 | |
| TEST COMPOUND | | | | | | | | | | | | | | |
| 0.00100 UL | RAT | LIVER | 12 | | 18 | | 13 | | 27 | | 202 | | 54 | |
| 0.01000 UL | RAT | LIVER | 24 | | 16 | | 24 | | 37 | | 235 | | 93 | |
| 0.10000 UL | RAT | LIVER | 19 | | 20 | | 28 | | 43 | | 241 | | 139 | |
| 1.00000 UL | RAT | LIVER | 9 | | 19 | | 25 | | 34 | | 233 | | 140 | |
| 5.00000 UL | RAT | LIVER | 13 | | 22 | | 29 | | 33 | | 223 | | 139 | |

* IBY. CONVERTANTS PER PLATE

** TA-1535 MNNG 10 UG/PLATE
TA-1537 QM 10 UG/PLATE
TA-1538 NF 100 UG/PLATE
TA-98 NF 100 UG/PLATE
TA-100 MNNG 10 UG/PLATE
D4 MNNG 10 UG/PLATE
SOLVENT DMSO 2.5 %/PLATE

*** TA-1535 ANTH 100 UG/PLATE
TA-1537 AMQ 100 UG/PLATE
TA-1538 AAF 100 UG/PLATE
TA-98 AAF 100 UG/PLATE
TA-100 ANTH 100 UG/PLATE
D4 DHNA 100 MICROMOLES/PLATE
SOLVENT DMSO 2.5 %/PLATE

5. INTERPRETATION OF RESULTS AND CONCLUSIONS

The test compound was examined for mutagenic activity in a series of *in vitro* microbial assays employing *Salmonella* and *Saccharomyces* indicator organisms. The compound was tested directly and in the presence of liver microsomal enzyme preparations from Aroclor-induced rats. The following results were obtained:

A. Toxicity

The compound was tested over a series of concentrations such that there was either quantitative or qualitative evidence of some chemically induced physiological effects at the high dose level. The low dose in all cases was below a concentration that demonstrated any toxic effect. The dose range employed for the evaluation of this compound was from 0.001 µl to 5 µl per plate.

B. Nonactivation Test Results

The results of the tests conducted on the compound in the absence of a metabolic systerm were all negative.

C. Activation Test Results

The results of the tests conducted on the compound in the presence of the rat liver activation system were all negative.

D. Conclusions

The test compound, DIMP USAMBRDL EPRD-1, did not demonstrate mutagenic activity in any of the assays conducted in this evaluation and was considered not mutagenic under these test conditions.

Submitted by:

David J. Brusick, Ph.D. — 1/26/77
Director — Date
Department of Genetics

Reviewed by:

Robert J. Weir, Ph.D. — 1/27/77
Vice President — Date

## 6. EXPLANATION OF EVALUATION PROCEDURES FOR PLATE ASSAYS

Plate test data consist of direct revertant colony counts obtained from a set of selective agar plates seeded with populations of mutant cells suspended in a semisolid overlay. Because the test chemical and the cells are incubated in the overlay for 2 to 3 days, and a few cell divisions occur during the incubation period, the test is semi-quantitative in nature. Although these features of the assay reduce the quantitation of results, they provide certain advantages not contained in a quantitative suspension test:

- The small number of cell divisions permits potential mutagens to act on replicating DNA, which is often more sensitive than nonreplicating DNA.
- The combined incubation of the compound and the cells in the overlay permits constant exposure of the indicator cells for 2 to 3 days.

### A. Surviving Populations

Plate test procedures do not permit exact quantitation of the number of cells surviving chemical treatment. At low concentrations of the test chemical, the surviving population on the treatment plates is essentially the same as that on the negative control plate. At high concentrations, the surviving population is usually reduced by some fraction. Our protocol normally employs several doses ranging over two or three log concentrations, the highest of these doses being selected to show slight toxicity as determined by subjective criteria.

### B. Dose Response Phenomena

The demonstration of dose-related increases in mutant counts is an important criterion in establishing mutagenicity. A factor that might modify dose-response results for a mutagen would be the selection of doses that are too low (usually mutagenicity and toxicity are related). If the highest dose is far lower than a toxic concentration, no increases may be observed over the dose range selected. Conversely, if the lowest dose employed is highly cytotoxic, the test chemical may kill any mutants that are induced, and the compound will not appear to be mutagenic.

6. EXPLANATION OF EVALUATION PROCEDURES FOR PLATE ASSAYS (Continued)

C. Control Tests

Positive and negative control assays are conducted with each experiment and consist of direct-acting mutagens for nonactivation assays and mutagens that require metabolic biotransformation in activation assays. Negative controls consist of the test compound solvent in the overlay agar together with the other essential components. The negative control plate for each strain gives a reference point to which the test data are compared. The positive control assay is conducted to demonstrate that the test systems are functional with known mutagens.

D. Evaluation Criteria for Ames Assay

Because the procedures used to evaluate the mutagenicity of the test chemical are semiquantitative, the criteria used to determine positive effects are inherently subjective and are based primarily on a historical data base. Most data sets are evaluated using the following criteria:

1. Strains TA-1535, TA-1537, and TA-1538

If the solvent control value is within the normal range, a chemical that produces a positive dose response over three concentrations with the lowest increase equal to twice the solvent control value is considered to be mutagenic.

2. Strains TA-98, TA-100, and D4

If the solvent control value is within the normal range, a chemical that produces a positive dose response over three concentrations with the highest increase equal to twice the solvent control value for TA-100 and two to three times the solvent control value for strains TA-98 and D4 is considered to be mutagenic. For these strains, the dose response increase should start at approximately the solvent control value.

3. Pattern

Because TA-1535 and TA-100 were both derived from the same parental strain (G-46) and because TA-1538 and TA-98 were both derived from the same parental strain (D3052), there is a built-in redundancy in the microbial assay. In general the two strains of a set respond to the same mutagen and such a pattern is sought. It is also anticipated that if a

6. EVALUATION OF EVALUATION PROCEDURES FOR PLATE ASSAYS (Continued)

D. Evaluation Criteria for Ames Assay

3. Pattern

given strain, e.g. TA-1537, responds to a mutagen in nonactivation tests it will generally do so in activation tests. (The converse of this relationship is not expected.) While similar response patterns are not required for all mutagens, they can be used to enhance the reliability of an evaluation decision.

4. Reproducibility

If a chemical produces a response in a single test that cannot be reproduced in one or more additional runs, the initial positive test data loses significance.

The preceding criteria are not absolute and other extenuating factors may enter into a final evaluation decision. However, these criteria are applied to the majority of situations and are presented to aid those individuals not familiar with this procedure. As the data base is increased, the criteria for evaluation can be more firmly established.

E. Relationship Between Mutagenicity and Carcinogenicity

It must be emphasized that the Ames Salmonella/microsome test is not a definitive test for chemical carcinogens. It is recognized, however, that correlative and functional relationships have been demonstrated between these two end points. The results of comparative tests on 300 chemicals by McCann et al. (Proc. Nat. Acad. Sci. USA, 72:5135-5139, 1975) show an extremely good correlation between results of microbial mutagenesis tests and in vivo rodent carcinogenesis assays.

All evaluation and interpretation of the data presented in this report are based only on the demonstration of or lack of mutagenic activity.

## STANDARD OPERATING PROCEDURES

To ensure an accurate and reliable mutagenicity testing program, LBI instituted the following procedures:

- The test compound was registered in a bound log book recording the date of receipt, complete client identification, physical description and LBI code number.

- Complete records of weights and dilutions associated with the testing of the submitted material were entered into a bound notebook.

- Raw data information was recorded on special printed forms that were dated and initialed by the individual performing the data collection at the time the observations were made. These forms were filed as permanent records.

- All animal tissue S-9 preparations used in the activation tests were taken from dated and pretested frozen lots identified by a unique number. The S-9 preparations were monitored for uniformity and the information recorded.

1. OBJECTIVE

The objective of this study was to evaluate the test compound for genetic activity in microbial assays with and without the addition of mammalian metabolic activation preparations.

2. MATERIALS

A. Test Compound

1. Date Received: December 20, 1976

2. Description: Colorless liquid labelled Lot AF-74

B. Indicator Microorganisms

Salmonella typhimurium, strains: TA-1535 TA-98
TA-1537 TA-100
TA-1538

Saccharomyces cerevisiae, strain: D4

C. Activation System (Ames et al., Mutation Research 31:347, 1975)

1. Reaction Mixture

| Component | Final Concentration/ml |
|---|---|
| TPN | 4 µmoles |
| Glucose-6-phosphate | 5 µmoles |
| Sodium phosphate (diabasic) | 100 µmoles |
| $MgCl_2$ | 8 µmoles |
| KCl | 33 µmoles |
| Homogenate fraction equivalent to 25 mg of wet tissue | 0.1-0.15 ml 9,000 x g supernatant of rat liver |

2. S-9 Homogenate

A 9,000 x g supernatant was prepared from Spraque-Dawley adult male rat liver induced by Aroclor 1254 five days prior to kill.

2. MATERIALS (Continued)

D. Positive Control Chemicals

Table 1 below lists the chemicals used for positive controls in the nonactivation and activation assays.

TABLE 1

| ASSAY | CHEMICAL[a] | SOLVENT | PROBABLE MUTAGENIC SPECIFICITY |
|---|---|---|---|
| Nonactivation | Methylnitrosoguanidine (MNNG) | Water or Saline | BPS[b] |
| | 2-Nitrofluorene (NF) | Dimethylsulfoxide[c] | FS[b] |
| | Quinacrine mustard (QM) | Water or saline | FS[b] |
| Activation | 2-Anthramine (ANTH) | Dimethylsulfoxide[c] | BPS[b] |
| | 2-Acetylaminofluorene (AAF) | Dimethylsulfoxide[c] | FS[b] |
| | 8-Aminoquinoline (AMQ) | Dimethylsulfoxide[c] | FS[b] |

[a]Concentrations given in Results Section

[b]BPS = Base-pair substitution

FS = Frameshift

[c]Previously shown to be nonmutagenic

E. Solvent

Either deionized water or dimethylsulfoxide (DMSO) was used to prepare stock solutions of solid materials. All dilutions of test materials were made in either deionized water or DMSO. The solvent employed and its concentration are recorded in the Results Section.

## 3. EXPERIMENTAL DESIGN

### A. Plate Test (Overlay Method*)

Approximately $10^8$ cells from an overnight culture of each indicator strain were added to separate test tubes containing 2.0 ml of molten agar supplemented with biotin and a trace of histidine. For non-activation tests, at least four dose levels of the test compound were added to the contents of the appropriate tubes and poured over the surfaces of selective agar plates. In activation tests, a minimum of four different concentrations of the test chemical were added to the appropriate tubes with cells. Just prior to pouring, an aliquot of reaction mixture (0.5 ml containing the 9,000 x g liver homogenate) was added to each of the activation overlay tubes, which were then mixed, and the contents poured over the surface of a minimal agar plate and allowed to solidify. The plates were incubated for 48 hours at 37C, and scored for the number of colonies growing on each plate. The concentrations of all chemicals are given in the Results Section. Positive and solvent controls using both directly active positive chemicals and those that require metabolic activation were run with each assay.

### B. Recording and Presenting Data

The numbers of colonies on each plate were counted and recorded on printed forms. These raw data were analyzed in a computer program and reported on a printout. The results are presented as revertants per plate for each indicator strain employed in the assay. The positive and the solvent controls are provided as reference points. Other relevant data are provided on the computer printout.

*Certain classes of chemicals known to be mutagens and carcinogens do not produce detectable responses using the standard Ames overlay method. Some dialkyl nitrosamines and certain substituted hydrazines are mutagenic in suspension assays, but not in the plate assay. Chemicals of these classes should be screened in a suspension assay.

# TABLE I-B-2

4. SUMMARY OF PLATE TEST RESULTS — LITTON BIONETICS, INC.

A. NAME OR CODE DESIGNATION OF THE TEST COMPOUND: DIMP LOT AF-74
B. SOLVENT: DMSO
C. TEST DATE: JAN. 3, 1977
NOTE: CONCENTRATIONS ARE GIVEN IN MICROLITERS (UL) OR MICROGRAMS (UG) PER PLATE.

| TEST | SPECIES | TISSUE | REVERTANTS PER PLATE | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | TA-1535 | | TA-1537 | | TA-1538 | | TA-98 | | TA-100 | | D4* | |
| | | | 1 | 2 | 1 | 2 | 1 | 2 | 1 | 2 | 1 | 2 | 1 | 2 |
| **SPONTANEOUS** | | | | | | | | | | | | | | |
| SOLVENT CONTROL | --- | --- | 12 | | 24 | | 20 | | 22 | | 112 | | 24 | |
| POSITIVE CONTROL** | --- | --- | >1000 | | 363 | | >1000 | | >1000 | | >1000 | | 790 | |
| TEST COMPOUND | | | | | | | | | | | | | | |
| 0.00100 UL | --- | --- | 24 | | 34 | | 15 | | 25 | | 125 | | 12 | |
| 0.01000 UL | --- | --- | 35 | | 32 | | 20 | | 34 | | 107 | | 23 | |
| 0.10000 UL | --- | --- | 31 | | 26 | | 16 | | 26 | | 101 | | 22 | |
| 1.00000 UL | --- | --- | 25 | | 27 | | 19 | | 29 | | 80 | | 27 | |
| 5.00000 UL | --- | --- | 27 | | 24 | | 24 | | 31 | | 50 | | 3 | |
| **ACTIVATION** | | | | | | | | | | | | | | |
| SOLVENT CONTROL | RAT | LIVER | 20 | | 33 | | 27 | | 37 | | 108 | | 125 | |
| POSITIVE CONTROL*** | RAT | LIVER | >1000 | | 285 | | >1000 | | >1000 | | >1000 | | 255 | |
| TEST COMPOUND | | | | | | | | | | | | | | |
| 0.00100 UL | RAT | LIVER | 23 | | 41 | | 9 | | 38 | | 114 | | 68 | |
| 0.01000 UL | RAT | LIVER | 9 | | 23 | | 12 | | 41 | | 75 | | 117 | |
| 0.10000 UL | RAT | LIVER | 10 | | 20 | | 16 | | 21 | | 140 | | 125 | |
| 1.00000 UL | RAT | LIVER | 6 | | 43 | | 12 | | 36 | | 153 | | 118 | |
| 5.00000 UL | RAT | LIVER | 25 | | 22 | | 8 | | 38 | | 116 | | 113 | |

* IBX, CONVERTANTS PER PLATE

** TA-1535 MNNG 10 UG/PLATE
TA-1537 9A 10 UG/PLATE
TA-1538 NF 100 UG/PLATE
TA-98 NF 100 UG/PLATE
TA-100 MNNG 10 UG/PLATE
D4 MNNG 10 UG/PLATE
SOLVENT DMSO 2.5 %/PLATE

*** TA-1535 ANTH 100 UG/PLATE
TA-1537 AMQ 100 UG/PLATE
TA-1538 AAF 100 UG/PLATE
TA-98 AAF 100 UG/PLATE
TA-100 ANTH 100 UG/PLATE
D4 DHNA 100 MICROMOLES/PLATE
SOLVENT DMSO 2.5 %/PLATE

## 5. INTERPRETATION OF RESULTS AND CONCLUSIONS

The test compound was examined for mutagenic activity in a series of *in vitro* microbial assays employing *Salmonella* and *Saccharomyces* indicator organisms. The compound was tested directly and in the presence of liver microsomal enzyme preparations from Aroclor-induced rats. The following results were obtained:

### A. Toxicity

The compound was tested over a series of concentrations such that there was either quantitative or qualitative evidence of some chemically induced physiological effects at the high dose level. The low dose in all cases was below a concentration that demonstrated any toxic effect. The dose range employed for the evaluation of this compound was from 0.001 µl to 5 µl per plate.

### B. Nonactivation Test Results

The results of the test conducted on the compound in the absence of a metabolic system were all negative.

### C. Activation Test Results

The results of the tests conducted on the compound in the presence of the rat liver activation system were all negative.

### D. Conclusions

The test compound, DIMP Lot AF-74, did not demonstrate mutagenic activity in any of the assays conducted in this evaluation and was considered not mutagenic under these test conditions.

Submitted by:

David J. Brusick, Ph.D.
Director
Department of Genetics

1/27/77
Date

Reviewed by:

Robert J. Weir, Ph.D.
Vice President

1/27/77
Date

## 6. EXPLANATION OF EVALUATION PROCEDURES FOR PLATE ASSAYS

Plate test data consist of direct revertant colony counts obtained from a set of selective agar plates seeded with populations of mutant cells suspended in a semisolid overlay. Because the test chemical and the cells are incubated in the overlay for 2 to 3 days, and a few cell divisions occur during the incubation period, the test is semi-quantitative in nature. Although these features of the assay reduce the quantitation of results, they provide certain advantages not contained in a quantitative suspension test:

- The small number of cell divisions permits potential mutagens to act on replicating DNA, which is often more sensitive than nonreplicating DNA.
- The combined incubation of the compound and the cells in the overlay permits constant exposure of the indicator cells for 2 to 3 days.

### A. Surviving Populations

Plate test procedures do not permit exact quantitation of the number of cells surviving chemical treatment. At low concentrations of the test chemical, the surviving population on the treatment plates is essentially the same as that on the negative control plate. At high concentrations, the surviving population is usually reduced by some fraction. Our protocol normally employs several doses ranging over two or three log concentrations, the highest of these doses being selected to show slight toxicity as determined by subjective criteria.

### B. Dose Response Phenomena

The demonstration of dose-related increases in mutant counts is an important criterion in establishing mutagenicity. A factor that might modify dose-response results for a mutagen would be the selection of doses that are too low (usually mutagenicity and toxicity are related). If the highest dose is far lower than a toxic concentration, no increases may be observed over the dose range selected. Conversely, if the lowest dose employed is highly cytotoxic, the test chemical may kill any mutants that are induced, and the compound will not appear to be mutagenic.

6. EXPLANATION OF EVALUATION PROCEDURES FOR PLATE ASSAYS (Continued)

C. Control Tests

Positive and negative control assays are conducted with each experiment and consist of direct-acting mutagens for nonactivation assays and mutagens that require metabolic biotransformation in activation assays. Negative controls consist of the test compound solvent in the overlay agar together with the other essential components. The negative control plate for each strain gives a reference point to which the test data are compared. The positive control assay is conducted to demonstrate that the test systems are functional with known mutagens.

D. Evaluation Criteria for Ames Assay

Because the procedures used to evaluate the mutagenicity of the test chemical are semiquantitative, the criteria used to determine positive effects are inherently subjective and are based primarily on a historical data base. Most data sets are evaluated using the following criteria:

1. Strains TA-1535, TA-1537, and TA-1538

If the solvent control value is within the normal range, a chemical that produces a positive dose response over three concentrations with the lowest increase equal to twice the solvent control value is considered to be mutagenic.

2. Strains TA-98, TA-100, and D4

If the solvent control value is within the normal range, a chemical that produces a positive dose response over three concentrations with the highest increase equal to twice the solvent control value for TA-100 and two to three times the solvent control value for strains TA-98 and D4 is considered to be mutagenic. For these strains, the dose response increase should start at approximately the solvent control value.

3. Pattern

Because TA-1535 and TA-100 were both derived from the same parental strain (G-46) and because TA-1538 and TA-98 were both derived from the same parental strain (D3052), there is a built-in redundancy in the microbial assay. In general the two strains of a set respond to the same mutagen and such a pattern is sought. It is also anticipated that if a

6. EVALUATION OF EVALUATION PROCEDURES FOR PLATE ASSAYS (Continued)

D. Evaluation Criteria for Ames Assay

3. Pattern

given strain, e.g. TA-1537, responds to a mutagen in nonactivation tests it will generally do so in activation tests. (The converse of this relationship is not expected.) While similar response patterns are not required for all mutagens, they can be used to enhance the reliability of an evaluation decision.

4. Reproducibility

If a chemical produces a response in a single test that cannot be reproduced in one or more additional runs, the initial positive test data loses significance.

The preceding criteria are not absolute and other extenuating factors may enter into a final evaluation decision. However, these criteria are applied to the majority of situations and are presented to aid those individuals not familiar with this procedure. As the data base is increased, the criteria for evaluation can be more firmly established.

E. Relationship Between Mutagenicity and Carcinogenicity

It must be emphasized that the Ames Salmonella/microsome test is not a definitive test for chemical carcinogens. It is recognized, however, that correlative and functional relationships have been demonstrated between these two end points. The results of comparative tests on 300 chemicals by McCann et al. (Proc. Nat. Acad. Sci. USA, 72:5135-5139, 1975) show an extremely good correlation between results of microbial mutagenesis tests and in vivo rodent carcinogenesis assays.

All evaluation and interpretation of the data presented in this report are based only on the demonstration of or lack of mutagenic activity.

## STANDARD OPERATING PROCEDURES

To ensure an accurate and reliable mutagenicity testing program, LBI instituted the following procedures:

- The test compound was registered in a bound log book recording the date of receipt, complete client identification, physical description and LBI code number.

- Complete records of weights and dilutions associated with the testing of the submitted material were entered into a bound notebook.

- Raw data information was recorded on special printed forms that were dated and initialed by the individual performing the data collection at the time the observations were made. These forms were filed as permanent records.

- All animal tissue S-9 preparations used in the activation tests were taken from dated and pretested frozen lots identified by a unique number. The S-9 preparations were monitored for uniformity and the information recorded.

PART I - SECTION C

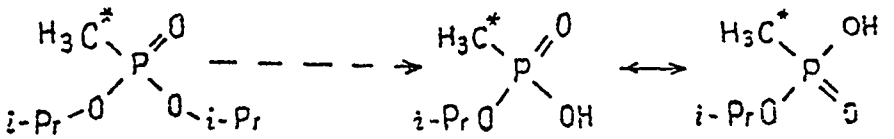
PHARMACOKINETICS AND METABOLISM

DIMP

LBI PROJECT NO. 10734-02

## SUMMARY

Greater than 90% of the radioactivity of administered labelled diisopropyl methyl phosphonate (DIMP) to rats, mice and dogs was recovered in the urine. In all three species about 95% of recovered radioactivity comes from a single highly polar component. This component is identified as isopropyl-methyl-phosphonic acid (IMPA). The identification is based on comparing the metabolite with authentic IMPA by three different chromatographic techniques; namely, thin layer chromatography, ion chromatography and gas liquid chromatography coupled with mass spectrometry.



1. Objective:

The purpose of this study was to isolate and identify the major metabolite of diisopropyl-methyl (-*$CH_3$) phosphonate ($^{14}$C-DIMP) in the urine of rats, mice and dogs, following a single oral dose.

2. Material:

DIMP (Lot No. 922-057), labelled in the methyl position with $^{14}$C, was synthesized by New England Nuclear Corporation, Boston Massachusetts. The specific activity was 3.07 μCi/mM and the purity was greater than 99% as indicated by gas and thin-layer chromatography.

IMPA was supplied by Dr. Leon Schiff of DRDAR, Edgewood, Aberdeen Proving Grounds, Maryland. The compound was analyzed for purity by thin-layer chromatography using three different solvent systems. The results showed purity > 97%.

The urine collected in the first phase of the study (1976) was used here for investigating the metabolites. The urine was stored frozen at -20°C. The urine was rechecked chromatographically and no significant changes in the initial pattern were found, indicating that no appreciable change has occurred over the storage period.

Rat and mouse 0-24 hours urine was pooled and used in this phase. Dog 0-24 hours urine from 2 different animals was used interchangeably.

All solvents used were analytical grade reagents. TLC plates precoated with silica gel G, as well as cellulose, were obtained from Brinkman Instrument Inc, Westbury, New Jersey.

3. Experimental Design:

A. Extraction of radioactivity from urine:

(1) Extraction of DIMP from urine:

Two to five ml of 0-24 hour urine of all three species, as well as control urine spiked with $^{14}$C-DIMP, were extracted with three equal volumes of chloroform.

(ii) Extraction of DIMP metabolites from urine:

In another experiment, urine from the three species was acidified with conc HCl (2 to 3 drops per ml) and extracted with 3 equal volumes of water saturated 1 Butanol.

(iii) Percentage distribution of radioactivity between two phases:

In both cases, after separating the two phases by centrifugation, 50 µl aliquots of each phase were placed in a scintillation vial with 20 ml of Hydromix (liquid scintillation cocktail for aqueous samples, Yorktown Research, New Jersey) and counted. The percentage distribution of radioactivity between the two phases was then calculated.

B. Thin Layer Chromatography:

Ten to thirty microliter samples containing 3000 to 5000 cpm were spotted on TLC silica gel G as well as cellulose plates. Several solvent systems were used for developing the TLC plates. The radioactive spots on the TLC plates (5 x 20 cm) were localized by scanning with a radiochromatogram scanner, (Model 7201, Packard Instrument Co.) at appropriate settings for time constant (10 seconds), linear range (300 cpm) and chart speed (1.0 cm/min). Radioactivity present in each peak area was quantitated by a disc integrator. Further localization was made by placing the plates on Kodak XR-1 x-ray film in an 8" x 10" cassette for 1 to 2 weeks. The films were developed and copies of the positive spots were made. In order to quantitate activity, the spots were scraped directly into scintillation vials containing 15-20 ml of scintillation fluid. The samples were counted and the radioactivity was calculated as percent in each zone.

C. Enzyme Hydrolysis:

To one ml of urine from each of the three species, 1 ml of 0.1M acetate buffer (pH 5.0) was added, as well as 0.1 ml of glusulase containing 176,133 units/ml β glucuronidase and 42,048 units sulphatase (Lot No. KN409A, Endo Laboratories, Garden City, New York). The mixtures were incubated for 24 hours at 37°C in a shaking water bath.

The hydrolyzed urine was then subjected to thin layer chromatography as described above. The chromatographic pattern was compared to non-hydrolyzed samples of the same urine.

D. Isolation & Purification:

One ml of 0-24 hour rat DIMP urine, as well as control rat urine, were each spread across a 20 x 20 cm, 2 mm thick silica gel plate, one inch from the base.

The plate was developed in 1-Butanol:Water:Acetic acid (5:4:1). (The solvents were thoroughly mixed in a separatory funnel, the phases were allowed to separate and the aqueous layer was discarded.)

The radioactivity was first visualized by radio-autography using Kodak XR-1 X-ray film. The radioactive zone was then localized and scraped off from the plate into a 50 ml centrifuge tube and extracted with 3 x 15 ml of methanol. All the methanol extracts were combined and centrifuged at 9000 rpm and filtered through a 0.45 micron millipore filter. The methanol was then taken to dryness at 40°C under a stream of nitrogen. An equivalent zone from the plate with the control urine was scraped, extracted, filtered and taken to dryness.

E. Preparing the methyl derivative of the major metabolite.

Approximately 2 millimoles (250 mg) of MNNG (N-methyl-N'-nitro-N-nitroso guanidine) were placed in the inside tube of the diazomethane generator (Aldrich) with half a milliliter of water to dissipate any heat generated. Ether (≈3 ml) was placed in the outside tube and the two parts were assembled with a butyl-O-ring and held with a pinch-type clamp. The lower part was immersed in an ice bath and about 0.6 ml of 5 N NaOH was injected dropwise through the silicone rubber septum by a syringe. The diazomethane thus formed was collected into the ether layer.

Two ml of diazomethane in ether prepared as above were added to each of three separate vials, one containing 2 microliters of neat IMPA, the second had the fractionated metabolite as described in section 'D', and the third had the fractionated control (section 'D').

The vials were capped and allowed to stand overnight. The ether was then removed under a stream of nitrogen and all 3 vials were reconstituted in 1.0 ml of methanol.

Gas Chromatography/Mass Spectrometry:

A Finnigan GC/MS model 4000 equipped with 6110 data system was used to acquire both EI & CI spectra for the methyl derivatives of IMPA, the urinary major metabolite and urine control. These were prepared as described in section E (Experimental Design).

A 6' x 2 mm I.D. glass column packed with 10% FFAP on 80/100 Chromosorb W AW was used. The other GLC conditions were set as follows: flow rate was held at 20 ml/min of He, the injector temperature was set at 170°C, the separator at 200°C and the transfer line at 210°C. The column temperature was held at 100°C for 2 minutes, then temperature programmed to 170°C at 5°C/min.

The mass spectometer was tuned and calibrated with FC-43. The following conditions were used: electron energy - 70 ev, emission current - 250 mA, E.M. voltage - -1700 v, ion source temperature = 200°C in EI mode and 150°C at isobutane CI mode. Under computer control, the mass spectometer was scanned repetitively from m/e 40 to 200 in EI mode and m/e 60 - 250 in CI mode at a rate of 2 sec/scan.

After the sample was injected to the gas chromatograph, the solvent was diverted for 110 sec. and the data acquisition was started at 120 sec.

Ion Chromatography

For the analysis of the major metabolite by ion chromatography, it was necessary to prepare a sample of non-radioactive metabolite. A rat weighing 225g was dosed with 1 ml of non-radiolabeled DIMP in PEG 400 (48.8 mg/ml). The rat was maintained in a Roth metabolism chamber with food and water ad lib. for a 24-hr period. A total of 5 ml of urine was collected.

A 0.25 ml aliquot (1.7 mg IMPA) of the urine was streaked across a TLC plate 1 inch from the bottom edge. On each end of the plate a marker (aliquot of a 24-hr urine specimen from a rat administered $^{14}$C-DIMP) was also spotted. The TLC parameters were:

Plate: 200 micron silica gel 60 F-254, 20 x 20 cm.

Solvent system: n-propanol/benzene/diethyl ether/ethanol/ 2N $NH_4OH$ (30/10/20/20/20)

Development: 107 mm from origin.

The two ends (sides - edges) of the plate containing the radioactive marker were removed with a glass cutter and scanned in a Packard Model 7201 Radiochromatogram Scanner. The Rf of the radiolabeled metabolite was determined to be 0.38.

The TLC plate was reassembled and the area at Rf 0.38 corresponding to the non-radiolabeled metabolite was scraped off. One-half of the material, containing approximately 850 µg of suspected IMPA, was eluted by shaking with three 5.0 ml portions of deionized distilled water. The material was centrifuged after each shaking and the supernatents further clarified by passing through a 0.45 micron Millipore filter.

A control urine sample (0-24 hour rat urine) was processed similarly and the area corresponding to Rf of the metabolite was scraped and treated in the same way.

A third sample was scraped from a silica gel plate developed in the same solvent system but with nothing applied on it.

RESULTS AND DISCUSSION:

A. Extraction:

Table I summarizes the results of chloroform extraction experiment.

Table I

Percent $^{14}C$ Radioactivity Extracted into Chloroform From 0-24 Hour Mouse, Rat, and Dog Urine After Administration of a Single Oral Dose of 225 mg/kg of DIMP-$^{14}C$

| Sample | % $^{14}C$ Extracted In Chloroform | % $^{14}C$ Remaining In Urine | Total % $^{14}C$ Recovered |
|---|---|---|---|
| Chloroform Extract Control Urine Spiked With DIMP-$^{14}C$ | 98.37 | 1.63 | 100.00 |
| Chloroform Extract 0-24 Hour Mouse Urine | 3.23 | 95.97 | 99.20 |
| Chloroform Extract 0-24 Hour Rat Urine | 2.80 | 96.30 | 99.10 |
| Chloroform Extract 0-24 Hour Dog Urine | 1.10 | 99.00 | 101.10 |

As shown in Table I, over 98% of the radioactive DIMP was extracted to the chloroform layer. However, the low percentage of radioactivity present in the chloroform extract of the 0-24 hr urine from each of the three species indicates that most of the DIMP was metabolized to more polar compound(s) and remained in the aqueous phase.

The results of the water saturated butanol extract (Table II) shows a marked similarity across the three species. It also reflects the highly polar nature of the metabolite.

Table II

| Sample | %$^{14}$C Extracted in water sat. 1-butanol | %$^{14}$C Remaining in urine |
|---|---|---|
| Dog (0-24 hour urine) | 88.7 | 11.3 |
| Mouse (0-24 hour urine) | 82.8 | 17.2 |
| Rat (0-24 hour urine) | 87.1 | 12.9 |

B. Fractionation of Radioactive components by TLC.

Distribution of Radioactivity:

Urine from rat, mouse and dog containing approximately 5000 cpm were each spotted on a 5 x 20 cm silica gel plate (0.25 mm thick). The plates were then developed in n-butanol: $H_2O$:acetic acid. Table III summarizes the findings of these experiments.

Table III

THIN LAYER ANALYSIS OF 24-HOUR URINE SAMPLES FROM RAT, MOUSE AND DOG DOSED WITH $^{14}$C-DIMP

| Species | Metabolite A (IMPA) Rf | % | Metabolite B Rf | % | Metabolite C Rf | % | Metabolite D Rf | % |
|---|---|---|---|---|---|---|---|---|
| Rat | 0.12 | 93.2 | 0.31 | 2.7 | 0.56 | 2.6 | 0.65 | 1.5 |
| Mouse | 0.17 | 95.6 | 0.36 | 3.5 | ND | ND | 0.72 | 0.9 |
| Dog | 0.15 | 99.6 | 0.31 | 0.4 | ND | ND | ND | ND |

System: Silica Gel: n-butanol/water/acetic acid (50/40/10)

In this system, $^{14}$C-DIMP had an Rf of 0.60.

Again the results here stress the similarity across the species at least as far as the major metabolite is concerned.

Relation of major metabolite to IMPA

Further thin layer work was done using different solvent systems and different stationary phases. Urine from species containing approximately 5000 cpm were spotted on both 5 x 20 cm (cellulose and silica gel) plates at the origin, one inch from the base. Five µl of 5% IMPA aqueous solution were spotted alongside the urine. The plates were then developed by two different solvent systems. The metabolite was localized by radioscanning. IMPA was localized by iodine vapor.

Table IV

| | Dog | | Mouse | | Rat | |
|---|---|---|---|---|---|---|
| TLC System | $^{14}C(R_f)$ | IMPA($R_f$) | $^{14}C(R_f)$ | IMPA($R_f$) | $^{14}C(R_f)$ | IMPA($R_f$) |
| Cellulose plate Solvent system A | 0.42 | 0.45 | 0.40 | 0.42 | 0.42 | 0.47 |
| Silica gel plate Solvent system B | 0.29 | 0.32 | 0.30 | 0.34 | 0.33 | 0.34 |

Solvent system A: n-butanol: n-propanol: 1N $NH_4OH$ (3:1:1)
Solvent system B: benzene: 1-propanol: ethanol: ether: 2N $NH_4OH$ (1:3:2:2:2)

Here again the $R_f$ values show the species similarity and that the metabolite is identifiable as IMPA.

c. Enzyme hydrolysis:

An experiment was set up as described in Section C to determine if the metabolites were conjugated to glucuronic acid. The urine, before and after incubation was spotted on silica gel G and developed in n-butanol: $H_2O$: acetic acid (5:4:1). No difference in the pattern of radioactivity distribution was found. Extraction with $CHCl_3$ before and after enzyme incubation showed no appreciable difference in percent distribution of radioactivity.

This is taken as good evidence that glucuronic acid and sulphate conjugation do not take place in DIMP metabolism.

d. Ion Chromatography:

The samples prepared as described above (experimental design Section E) were sent to Dr. Leon J. Schiff of DRDAR-CLB-CA, Bldg. 3220, Edgewood Area, Aberdeen Proving Ground, Md. 21010, for ion chromatographic analysis.

The ion chromatograms obtained are shown in figures 1 thru 4. Fig. 1 is the ion chromatogram of 5.0 ppm IMPA standard in 0.005M sodium borate buffer; fig. 2 is that of control urine silica gel extract; fig. 3 is blank silica gel extract and fig. 4 is the ion chromatogram of DIMP 0-24 hrs urine metabolite, silica gel TLC extract.

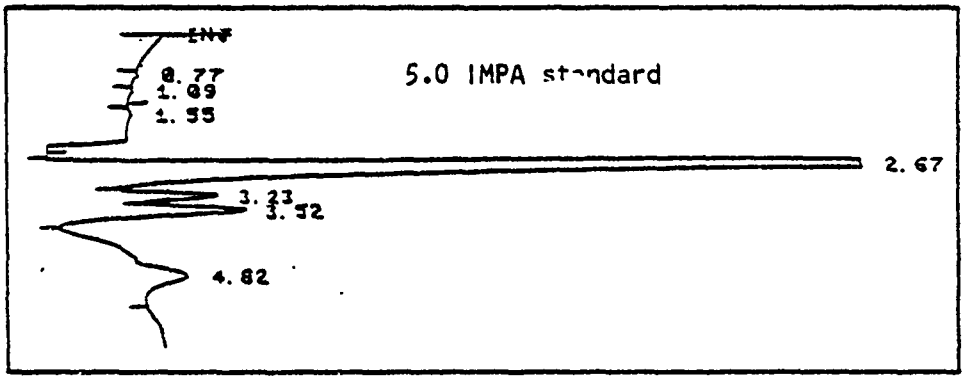



Figure 1

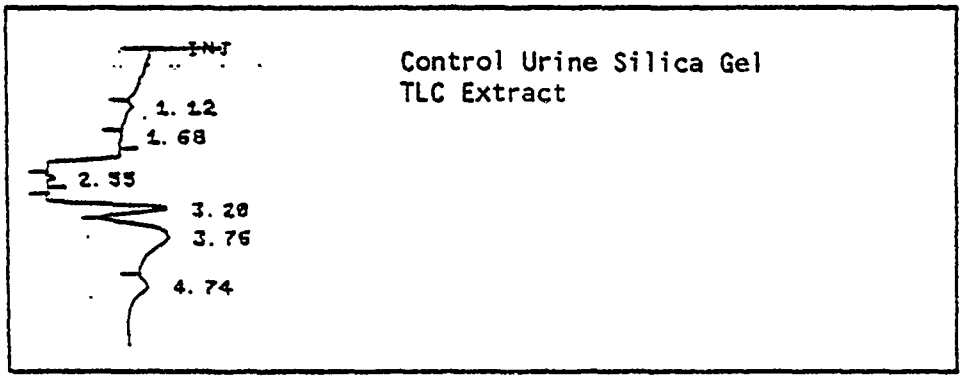



Figure 2

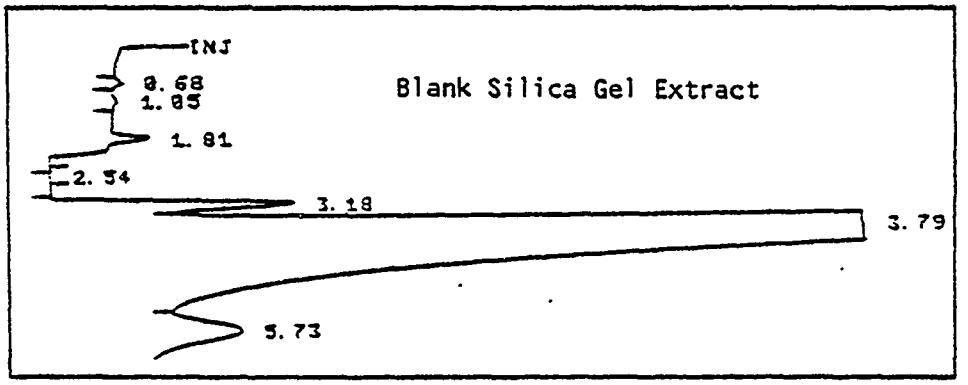



Figure 3

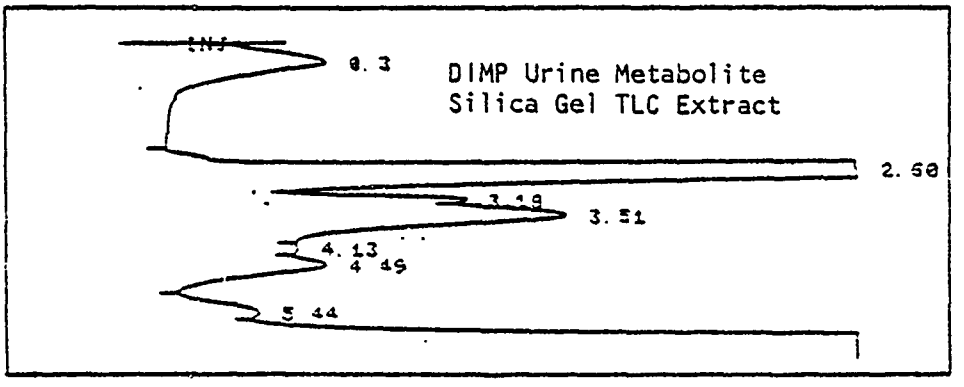
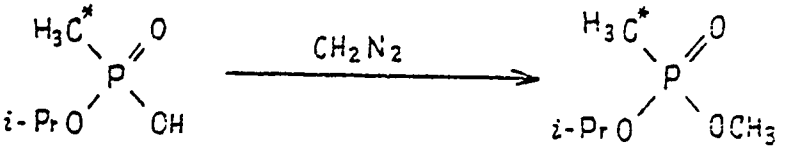



Figure 4

It is evident that only the DIMP metabolite sample showed a peak which matched the retention time of IMPA standard at 2.6-2.8 min region. This provides more evidence that the major metabolite isolated from rat urine is IMPA.

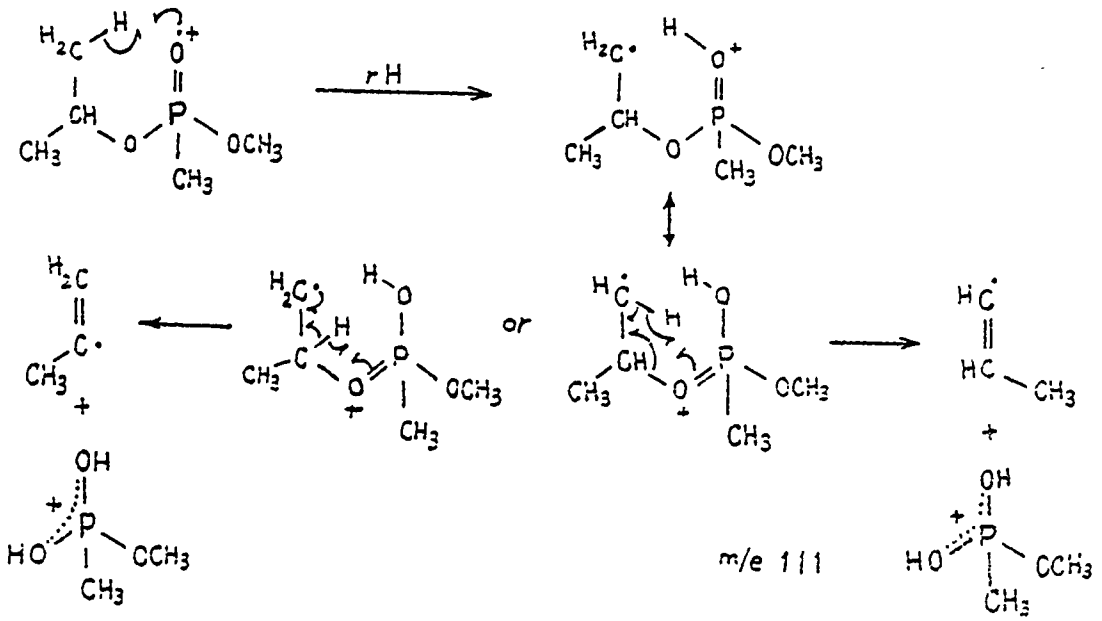
e. Gas Chromatography/Mass Spectrometry Identification of Major Metabolite

Attempts had been made to analyze intact IMPA gas chromatographically without any success. This may be due to its high polarity and low volatility which were overcome by forming a methyl derivative with diazomethane.




IMPA standard, fractionated rat urine extract and fractionated urine control extract were methylated under the same conditions as described in Section D. All of them were submitted to both EI and isobutane CI GC/MS.

Under electron impact conditions, comparison of the total ion current (TIC) trace obtained from the methylated major metabolite isolated from rat urine (Fig. 5) with IMPA methyl ester (Fig. 6) and with methylated urine control (Fig. 7) clearly indicated that the peak with a retention time of 8.3 min (scan no. 197) from the methylated major metabolite was isopropyl methyl methyl phosphonate (IMMPA). The same peak was absent in the control urine. The EI mass spectrum (Fig. 8) taken at that peak was in good agreement with that of the IMMPA standard (Fig. 9). Although the molecular ion (m/e 152) intensity in both cases was quite low, the same fragmentation pattern and other characteristic ions confirmed the identity of the major methylated metabolite as IMPA methyl ester. The ions at m/e 137 and m/e 93 correspond to $(M - CH_3)^+$ and $M\text{-}OCH(CH_3)_2^+$ respectively. The second strongest ions at m/e 111 may arise from double hydrogen rearrangement ("McLafferty + 1" rearrangement):



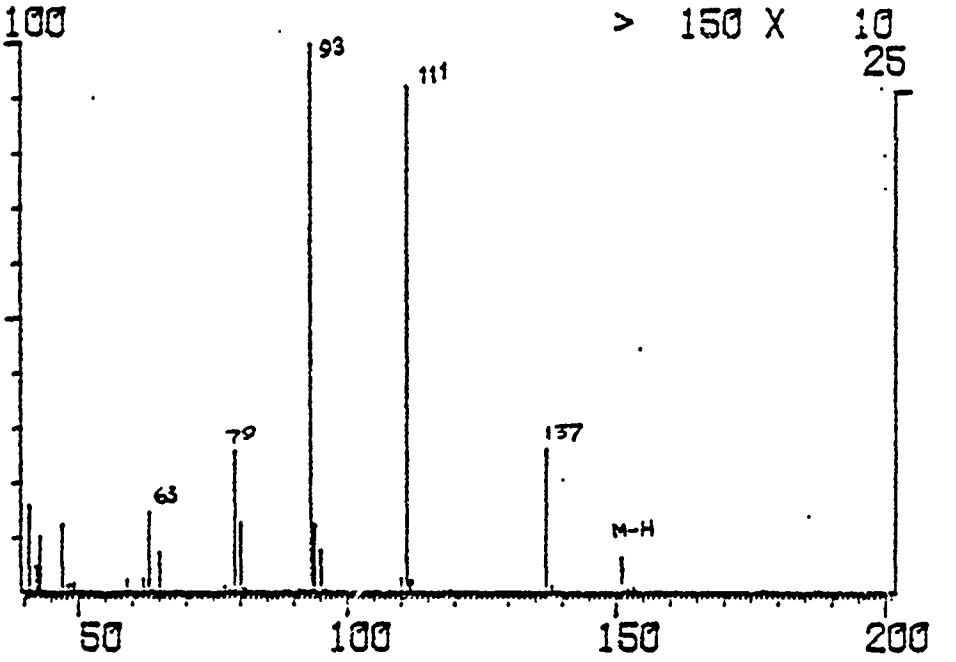



Figure 8

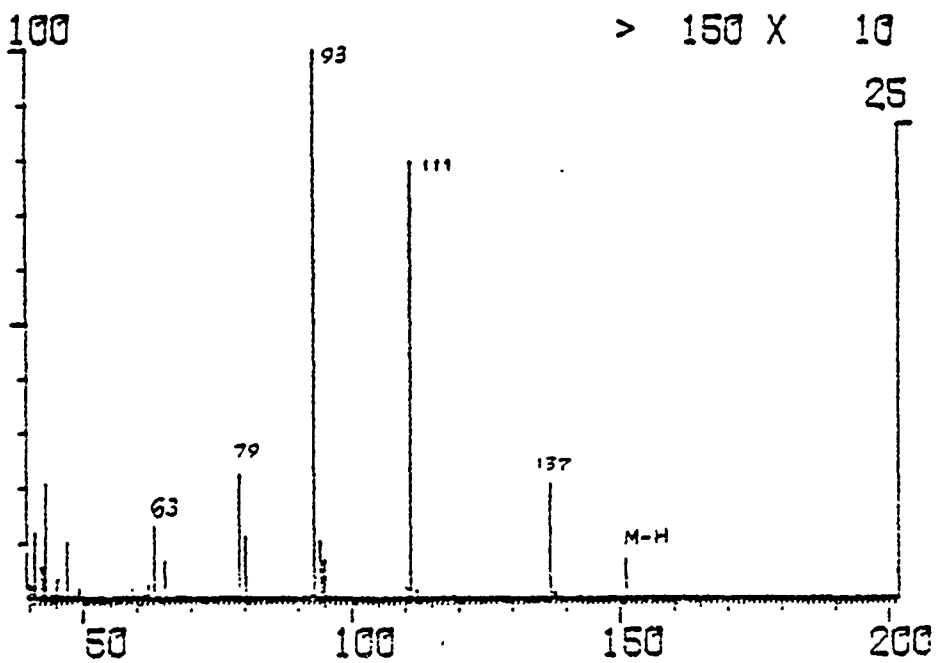



Figure 9

409905: 5 UL METABOLITE EXTRACT DERIVATIZED
EI GC/MS

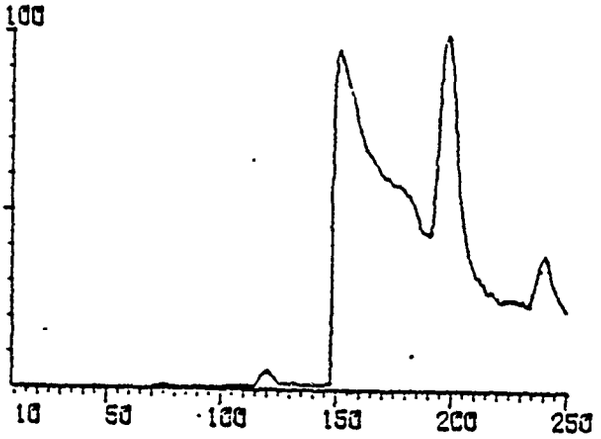



Fig. 5

409904:IMPA METHYL ESTER: STD.; EI GC/MS

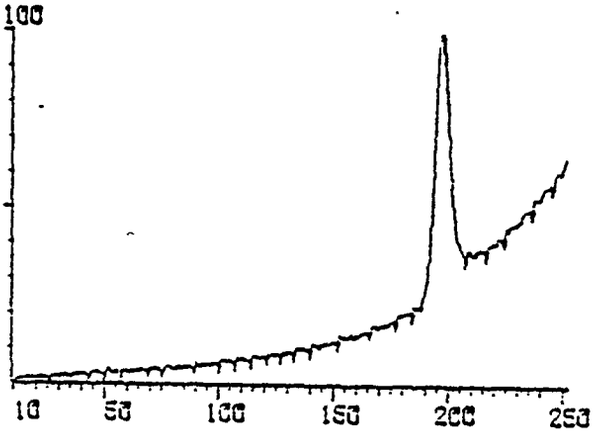



Fig. 6

409906: 5 UL DERIVATIZED CONTROL URINE
EI GC/ MS

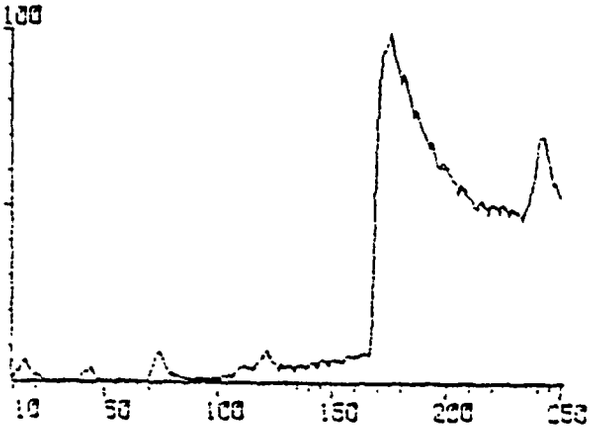



Fig. 7

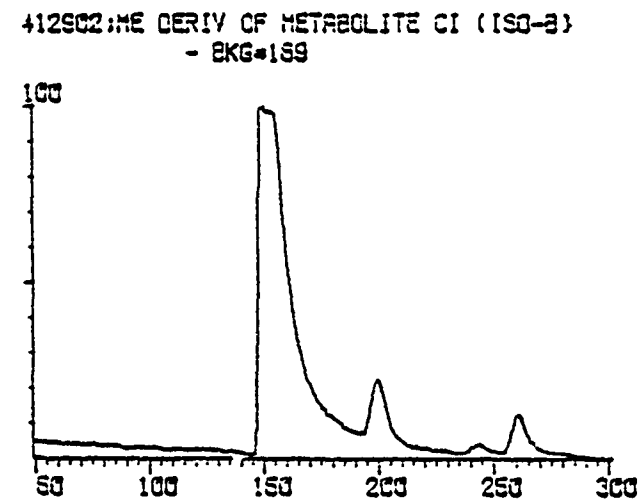



Fig. 10

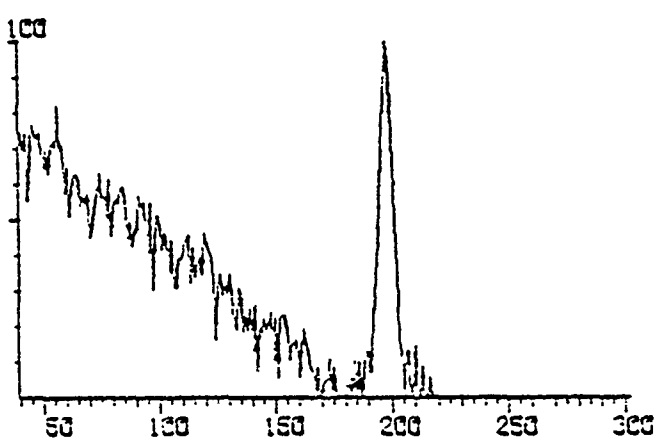



Fig. 11

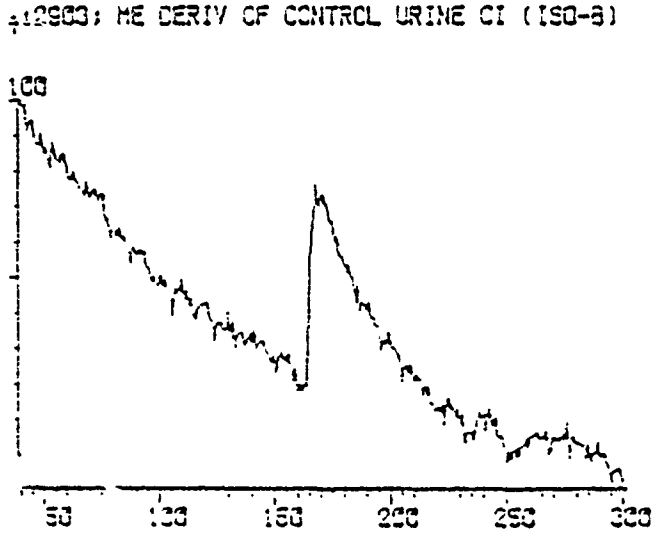



Fig. 12

412901; CI (ISO-B) ME DERIV OF IMPA -+ 2NG
# 197 - BKG#189

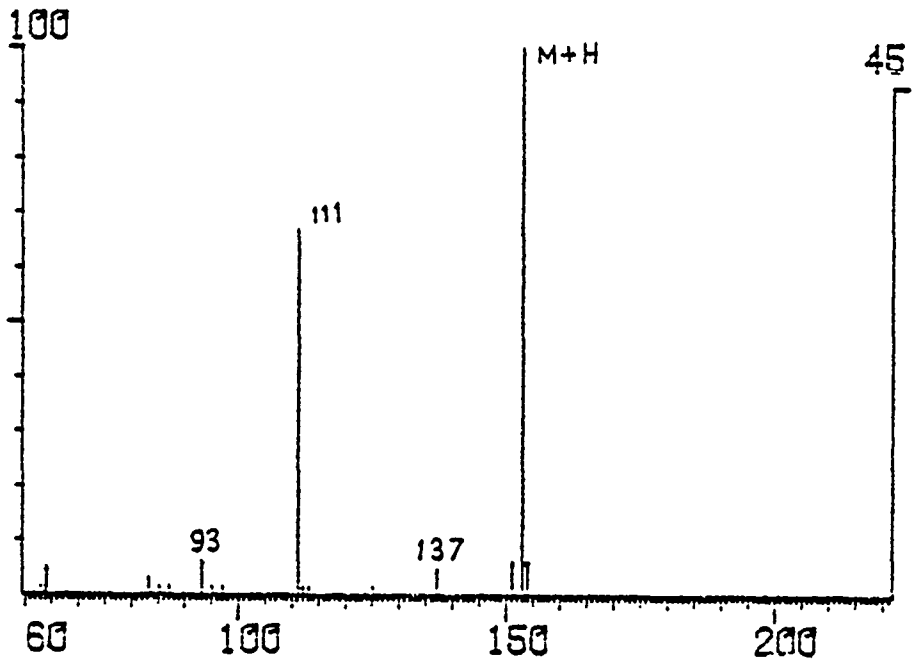



Figure 13

412902;ME DERIV OF METABOLITE CI (1 [illegible]
# 199 - BKG#189

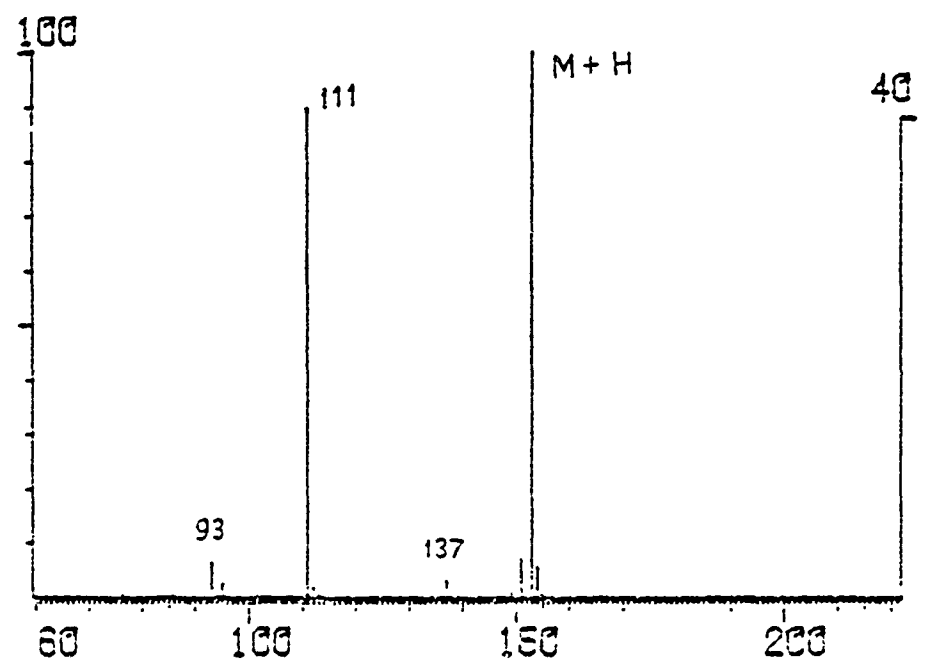
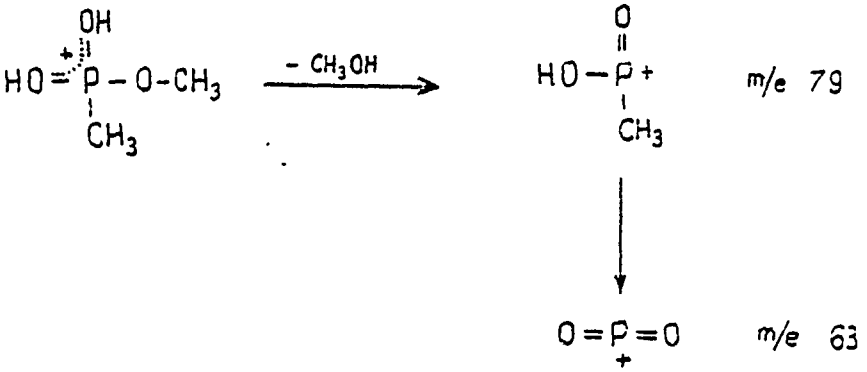



Figure 14

The ions at m/e 79 may be attributed up to a loss of $CH_3OH$ from the m/e 111 ions:



Further evidence for the identity of the major metabolite as IMPA was provided by isobutane CI GC/MS. The super-imposition of the retention time of the peak from the methylated major metabolite (Fig. 10) with that from the IMMPA (Fig. 11) was in excellent agreement with the EI GC/MS data. Once again, that peak was totally absent in the control urine (Fig. 12). CI mass spectrum from the methylated major metabolite (Fig. 13) and that from IMPA methyl ester (Fig. 14) were almost identical. The quasimolecular ion m/e 153, $(M + H)^+$, in both spectra unambiguously confirmed it was IMPA methyl ester.

The ions at m/e 137 $(M + H = CH_4)^+$ and m/e 111 share the same structure as the corresponding ions formed i t' E1 mode.

## 5. Conclusion

Based on the $R_f$ value on two different TLC plates and three different developing solvent systems, ion chromatograms, GLC retention time as well as El and isobutane Cl mass spectra, it is evident that the major metabolite isolated from the urine of rats dosed with DIMP can be identified as IMPA (isopropyl methyl phosphonic acid).

PART I - SECTION D

TERATOLOGY IN RATS

DIMP

LBI PROJECT NO. 10734-04

## SUMMARY

The test material was administered in the diet at doses of 100, 300 and 3000 ppm to pregnant female rats on days 6 through 15 of gestation. There were no changes in the dams or among the fetuses that indicated an adverse compound-related effect.

## 1. OBJECTIVE

The objective of this study was to investigate the effect of the test material on fetuses during the period of organogenesis when administered to the pregnant rat.

## 2. MATERIAL

Refer to Part I - Section A.

## 3. EXPERIMENTAL DESIGN

Female rats [CRL:COBS CD (SD) BR] were obtained from Charles River Breeding Laboratories, Inc., Portage, Michigan, and acclimated to laboratory conditions for one week. At that time, each female was paired with a sexually mature male of the same strain from the same supplier. The females were examined daily for the presence of a copulatory plug. The presence of such a plug was taken as evidence of mating and designated as day 0 of gestation. The female rats were 11 weeks of age at the time of the first dose (March 3, 1977). Mated female rats were assigned sequentially to treatment groups and identified by cage cards as indicated on the following page.

3. EXPERIMENTAL DESIGN (Continued)

| Group No. | Female Rat Numbers | Dose in Diet (ppm) |
|---|---|---|
| 1 | 4720 - 4739 | 0 (Control) |
| 2 | 4740 - 4759 | 100 |
| 3 | 4760 - 4779 | 300 |
| 4 | 4780 - 4799 | 3000 |

These doses were approved by Dr. E. Ross Hart of Litton Bionetics, Inc., based on previous studies.

The female rats were individually housed in wire cages in a temperature-controlled animal room with artificial illumination automatically controlled to provide a 12-hour light cycle. No other species were housed in the animal room during the course of the study. No other chemicals were under concurrent investigation in the animal room. The appropriate diets and fresh water were provided ad libitum. The test material was incorporated into the basal diet (Purina Laboratory Chow Meal) on gestation days 6 through 15 so as to provide the dose levels indicated previously. The test material (1, 3 or 30 g) was suspended in 100 ml of polyethylene glycol 400 and blended with 10 kg of the basal diet in a twin shell blender for 15 minutes. The control diet contained 100 ml of PEG 400 per 10 kg of meal.

The mated female rats were weighed on days 0, 6, 16 and 20 of gestation. Food consumption was measured during the periods 0-6, 6-16 and 16-20 days of gestation. The female rats were observed daily for changes in general appearance, behavior and condition.

On day 20 of gestation, the adult female rats were anesthetized with chloroform and the visceral and thoracic organs examined. The uterus was removed and opened. The number of implantation sites and their placement in the uterine horns, live and dead fetuses, and resorption sites were recorded. The fetuses were removed, examined externally for abnormalities, weighed and the crown to rump length was measured.

One third of the fetuses of each litter were fixed in Bouin's fluid. These were later examined for changes in the soft tissues of the head, thoracic and visceral organs. The remaining fetuses of each litter were examined for skeletal abnormalities following staining with Alizarin Red S.

The uterus and ovaries from the adult females were preserved in 10% formalin for possible future examination.

## 4. RESULTS

No deaths occurred among the adult female rats. Except for female rat number 4735 (control), these animals were normal in appearance throughout the study. Rat number 4735 delivered a litter of pups on her calculated day 19 of gestation. Because the pups appeared to be full term, the assignment of day 0 of gestation was judged to be erroneous, possibly due to the retention of the copulatory plug by the female. Although the data on this litter was included in Table 2 of the Appendix, it was not used in the calculations or summary.

Mean body weight and food consumption, as shown in the Appendix on Table 1, indicated no marked difference between treated and control pregnant rats ($p < 0.05$ Dunnett's t-test, Americal Statistical Assn., 50: 1096-1121, 1955).

Based on the observations of the uterine contents obtained on day 20 of gestation, the test material did not produce any effect. These data have been summarized in Table A and the details have been tabulated in Table 2 included in the Appendix. Although a 2 x 2 contingency with Yate's correction (Hollander and Wolfe) analysis of the total number of implantation sites in both the right and left horns in the 300 ppm dose level shows a significant decrease from the control group, a Wilcoxon Rank Sum analysis (Snedecor and Cochran Statistical Methods, Iowa State Press, Ames, Iowa, pp. 215-223, 1974) did not indicate a significant difference ($p < 0.05$) and this effect was judged to be a statistical artifact. Examination of the internal organs of the females revealed no abnormalities except for an ovarian cyst in female rat number 4774 (300 ppm). This change was not judged to be related to treatment.

Examination of the offspring at delivery revealed subcutaneous hematomas on two fetuses of the control group (4729 and 4738) and on one fetus of the 3000 ppm dose group (4797). In addition, two fetuses of female number 4769 (300 ppm) were dead, although, apparently at a normal stage of development on day 20 of gestation; and one fetus of female rat number 4740 (100 ppm) had a short lower jaw. This last abnormality was also observed at examination of cleared specimens as a malformation of the maxilla and mandible.

TABLE I-D-3

LITTON BIONETICS, INC.
PROJECT NO. 9004

TABLE A

SUMMARY OF REPRODUCTION PERFORMANCE

| | DOSE (ppm) | | | |
|---|---|---|---|---|
| | 0 | 100 | 300 | 3000 |
| Pregnancy Ratio (Pregnant/Bred) | 14/20 | 14/20 | 11/20 | 15/20 |
| Implantation Sites (Left Horn/Right Horn) | 86/67 | 78/90 | 50[b]/68[b] | 91/91 |
| Resorptions/Live Fetuses | 13/140 | 16/152 | 7/110 | 9/173 |
| Average Fetal Weight (G)[a] | 3.7 | 3.9 | 3.8 | 3.9 |
| Average Fetal Length (cm)[a] | 3.1 | 3.1 | 3.1 | 3.1 |
| Mean Live Litter Size (pups) | 11 | 11 | 10 | 12 |

[a]Based on average of litter means

[b]$p < 0.05$ 2 x 2 contingency table with Yate's correction; not significant $p > 0.05$ Wilcoxon Rank Sum (LSA)

4. RESULTS (Continued)

Examination of the Bouin's fixed specimens revealed one fetus of female rat number 4732 (control) with posterior displacement of the left kidney. There were no other changes observed. The sex and number of fetuses examined for soft tissue changes were as follows:

| Treatment | Males | Females |
|---|---|---|
| 0 (Control) | 26 | 27 |
| 100 | 21 | 29 |
| 300 | 17 | 20 |
| 3000 | 30 | 28 |

The results of the skeletal examination of the cleared and stained fetuses have been detailed in Appendix Table 3. Most of the changes noted, while not strictly normal, are frequently observed in 21 day old rat fetuses of this strain and source in our laboratory.

Those findings not commonly encountered have been so indicated in Table 3. The results have been summarized below:

| Dose | Number Examined | Number Normal | Number with Common Skeletal Variations | Number with Unusual Changes |
|---|---|---|---|---|
| Control | 100 | 73 | 27 | 0 |
| 100 ppm | 102 | 69 | 33 | 2 |
| 300 ppm | 75 | 58 | 15 | 4 |
| 3000 ppm | 114 | 67 | 45* | 3 |

* ($p < 0.05$ 2 x 2 contingency table)

There was a slight increase in the ratio of abnormal/normal fetuses at the high level as compared to the control. However, analysis of these data using Wilcoxon Rank Sum analysis which employs the litter as the basic unit for comparison, did not indicate a statistically significant effect. Furthermore, the nature of the changes observed did not suggest a specific area of involvement. Therefore, the changes observed were not judged to indicate a drug-induced teratogenic effect at this dose.

5. CONCLUSION

Administration of the test material to female rats by incorporation into the diet at 100, 300 and 3000 ppm produced no effect on the pregnant dams. There was no evidence of compound-induced terata, variation in sex ratio, embryo toxicity or inhibition of fetal growth and development.

Submitted By:

Robert P Beliles 8/18/79

Robert P. Beliles, Ph.D.
Director
Department of Toxicology

Animal Resources Supervisor:

Desmond E. Davis
Certified Laboratory Animal
Technologist

Susan L. Makris

Susan L. Makris, B.S.
Toxicology Technician

Reviewed By:

7/30/79

Robert J. Weir, Ph.D.
Vice President

TABLE I-D-4

LITTON BIONETICS, INC.
PROJECT NO. 9004

TABLE 1

BODY WEIGHT AND FOOD CONSUMPTION OF PREGNANT RATS

| DOSE (ppm) | | MEAN BODY WEIGHTS IN GRAMS[a] | | | | MEAN DAILY FOOD CONSUMPTION IN GRAMS[a] | | |
|---|---|---|---|---|---|---|---|---|
| | | DAY 0 | DAY 6 | DAY 16 | DAY 20 | DAY 0-6 | DAY 6-16 | DAY 16-20 |
| 0 (Control) | Mean | 214 | 240 | 281 | 337 | 20 | 18 | 25 |
| | SD | 17 | 19 | 22 | 28 | 7 | 1 | 5 |
| | SE | 4.6 | 5.4 | 6.1 | 7.7 | 2.2 | 0.6 | 1.3 |
| | n | 13 | 13 | 13 | 13 | 10 | 5 | 13 |
| 100 | Mean | 219 | 245 | 299 | 346 | 22 | 20 | 23 |
| | SD | 17 | 16 | 27 | 40 | 9 | 2 | 4 |
| | SE | 4.5 | 4.2 | 7.3 | 10.6 | 2.3 | 0.5 | 1.0 |
| | n | 14 | 14 | 14 | 14 | 13 | 11 | 14 |

[a]Calculations do not include non-pregnant females

LITTON BIONETICS, INC.
PROJECT NO. 9004

TABLE 1 (Continued)

BODY WEIGHT AND FOOD CONSUMPTION OF PREGNANT RATS

| DOSE (ppm) | | MEAN BODY WEIGHTS IN GRAMS[a] | | | | MEAN DAILY FOOD CONSUMPTION IN GRAMS[a] | | |
|---|---|---|---|---|---|---|---|---|
| | | DAY 0 | DAY 6 | DAY 16 | DAY 20 | DAY 0-6 | DAY 6-16 | DAY 16-20 |
| 300 | Mean | 217 | 242 | 286 | 341 | 18 | 19 | 25 |
| | SD | 19 | 19 | 25 | 34 | 2 | 3 | 4 |
| | SE | 5.6 | 5.8 | 7.5 | 10.1 | 0.7 | 1.0 | 1.1 |
| | n | 11 | 11 | 11 | 11 | 11 | 7 | 11 |
| 3000 | Mean | 217 | 247 | 295 | 346 | 19 | 21 | 26 |
| | SD | 15 | 13 | 19 | 29 | 1 | 2 | 3 |
| | SE | 3.9 | 3.5 | 4.8 | 7.5 | 0.3 | 0.8 | 0.7 |
| | n | 15 | 15 | 15 | 15 | 15 | 8 | 15 |

[a]Calculations do not include non-pregnant females

TABLE I-D-5

LITTON BIONETICS, INC.
PROJECT NO. 9004

TABLE 2

OBSERVATIONS AT CAESAREAN SECTION

DOSE - Control (0 ppm)

| FEMALE NUMBER | IMPLANTATION SITES | | RESORPTION SITES | DEAD FETUSES | VIABLE FETUSES | | |
|---|---|---|---|---|---|---|---|
| | LEFT HORN | RIGHT HORN | | | NUMBER | MEAN WEIGHT (gram) | MEAN LENGTH (cm) |
| 4720 | 0 | 0 | 0 | 0 | 0 | --- | --- |
| 4721 | 0 | 0 | 0 | 0 | 0 | --- | --- |
| 4722 | 3 | 5 | 2 | 0 | 6 | 3.7 | 3.0 |
| 4723 | 4 | 5 | 3 | 0 | 6 | 3.9 | 3.2 |
| 4724 | 0 | 0 | 0 | 0 | 0 | --- | --- |
| 4725 | 8 | 6 | 1 | 0 | 13 | 3.7 | 3.0 |
| 4726 | 5 | 7 | 0 | 0 | 12 | 4.0 | 3.0 |
| 4727 | 3 | 2 | 1 | 0 | 4 | 3.5 | 2.9 |
| 4728 | 9 | 6 | 2 | 0 | 13 | 3.6 | 3.2 |
| 4729 | 10 | 7 | 0 | 0 | 17 | 3.6 | 3.1 |
| 4730 | 7 | 5 | 1 | 0 | 11 | 3.5 | 3.1 |
| 4731 | 0 | 0 | 0 | 0 | 0 | --- | --- |
| 4732 | 10 | 6 | 1 | 0 | 15 | 3.6 | 3.1 |
| 4733 | 0 | 0 | 0 | 0 | 0 | --- | --- |
| 4734 | 0 | 0 | 0 | 0 | 0 | --- | --- |
| 4735+ | 9 | 5 | 1 | 0 | 13 | 5.9 | 3.4 |
| 4736 | 8 | 6 | 0 | 0 | 14 | 3.7 | 3.1 |
| 4737 | 11 | 4 | 1 | 0 | 14 | 3.7 | 2.9 |
| 4738 | 8 | 6 | 1 | 0 | 13 | 3.6 | 3.2 |
| 4739 | 0 | 2 | 0 | 0 | 2 | 4.5 | 3.3 |
| Total | 86 | 67 | 13 | 0 | 140 | | |
| Mean* | | | | | 11 | 3.7 | 3.1 |
| SD | | | | | 5 | 0.3 | 0.1 |
| SE | | | | | 1.3 | 0.07 | 0.04 |
| n | | | | | 13 | 13 | 13 |

*Mean, SD and SE do not include non-pregnant females
+Delivered prior to sacrifice (day 19), not included in Mean, SE and SE

LITTON BIONETICS, INC.
PROJECT NO. 9004

TABLE 2 (Continued)

OBSERVATIONS AT CAESAREAN SECTION

DOSE - 100 ppm

| FEMALE NUMBER | IMPLANTATION SITES | | RESORPTION SITES | DEAD FETUSES | VIABLE FETUSES | | |
|---|---|---|---|---|---|---|---|
| | LEFT HORN | RIGHT HORN | | | NUMBER | MEAN WEIGHT (gram) | MEAN LENGTH (cm) |
| 4740 | 2 | 0 | 1 | 0 | 1 | 3.4 | 3.0 |
| 4741 | 0 | 0 | 0 | 0 | 0 | --- | --- |
| 4742 | 0 | 0 | 0 | 0 | 0 | --- | --- |
| 4743 | 0 | 0 | 0 | 0 | 0 | --- | --- |
| 4744 | 12 | 2 | 0 | 0 | 14 | 3.9 | 3.2 |
| 4745 | 0 | 0 | 0 | 0 | 0 | --- | --- |
| 4746 | 0 | 0 | 0 | 0 | 0 | --- | --- |
| 4747 | 4 | 11 | 0 | 0 | 15 | 3.3 | 2.9 |
| 4748 | 1 | 0 | 0 | 0 | 1 | 4.2 | 3.5 |
| 4749 | 2 | 10 | 0 | 0 | 12 | 3.4 | 3.0 |
| 4750 | 7 | 9 | 1 | 0 | 15 | 3.6 | 3.2 |
| 4751 | 9 | 5 | 1 | 0 | 13 | 3.5 | 3.1 |
| 4752 | 5 | 6 | 7 | 0 | 4 | 3.7 | 3.2 |
| 4753 | 0 | 7 | 1 | 0 | 6 | 4.1 | 3.1 |
| 4754 | 8 | 7 | 2 | 0 | 13 | 4.3 | 3.1 |
| 4755 | 0 | 0 | 0 | 0 | 0 | --- | --- |
| 4756 | 5 | 9 | 0 | 0 | 14 | 3.6 | 3.1 |
| 4757 | 9 | 6 | 1 | 0 | 14 | 4.1 | 2.9 |
| 4758 | 6 | 8 | 1 | 0 | 13 | 3.7 | 3.2 |
| 4759 | 8 | 10 | 1 | 0 | 17 | 5.4 | 3.4 |
| Total | 78 | 90 | 16 | 0 | 152 | | |
| Mean* | | | | | 11 | 3.9 | 3.1 |
| SD | | | | | 5 | 0.5 | 0.2 |
| SE | | | | | 1.4 | 0.15 | 0.05 |
| n | | | | | 14 | 14 | 14 |

*Mean, SD and SE do not include non-pregnant females

LITTON BIONETICS, INC.
PROJECT NO. 9004

TABLE 2 (Continued)

OBSERVATIONS AT CAESAREAN SECTION

DOSE - 300 ppm

| FEMALE NUMBER | IMPLANTATION SITES | | RESORPTION SITES | DEAD FETUSES | VIABLE FETUSES | | |
|---|---|---|---|---|---|---|---|
| | LEFT HORN | RIGHT HORN | | | NUMBER | MEAN WEIGHT (gram) | MEAN LENGTH (cm) |
| 4760 | 0 | 0 | 0 | 0 | 0 | --- | --- |
| 4761 | 0 | 0 | 0 | 0 | 0 | --- | --- |
| 4762 | 0 | 0 | 0 | 0 | 0 | --- | --- |
| 4763 | 2 | 5 | 0 | 0 | 7 | 4.0 | 2.9 |
| 4764 | 6 | 8 | 1 | 0 | 13 | 3.1 | 2.9 |
| 4765 | 4 | 0 | 0 | 0 | 5 | 3.8 | 3.0 |
| 4766 | 6 | 6 | 0 | 0 | 12 | 3.4 | 2.9 |
| 4767 | 1 | 6 | 0 | 0 | 7 | 3.4 | 3.0 |
| 4768 | 0 | 0 | 0 | 0 | 0 | --- | --- |
| 4769 | 1 | 10 | 1 | 2 | 8 | 3.6 | 3.1 |
| 4770 | 0 | 0 | 0 | 0 | 0 | --- | --- |
| 4771 | 0 | 0 | 0 | 0 | 0 | --- | --- |
| 4772 | 0 | 0 | 0 | 0 | 0 | --- | --- |
| 4773 | 4 | 9 | 3 | 0 | 10 | 4.6 | 3.2 |
| 4774 | 0 | 0 | 0 | 0 | 0 | --- | --- |
| 4775 | 11 | 5 | 1 | 0 | 15 | 3.3 | 3.1 |
| 4776 | 3 | 3 | 0 | 0 | 6 | 4.4 | 3.2 |
| 4777 | 4 | 8 | 1 | 0 | 11 | 5.0 | 3.3 |
| 4778 | 0 | 0 | 0 | 0 | 0 | --- | --- |
| 4779 | 8 | 8 | 0 | 0 | 16 | 3.6 | 3.0 |
| Total | 50 | 68 | 7 | 2 | 110 | | |
| Mean* | | | | | 10 | 3.8 | 3.1 |
| SD | | | | | 4 | 0.6 | 0.1 |
| SE | | | | | 1.1 | 0.18 | 0.04 |
| n | | | | | 11 | 11 | 11 |

*Mean, SD and SE do not include non-pregnant females

LITTON BIONETICS, INC.
PROJECT NO. 9004

TABLE 2 (Continued)

OBSERVATIONS AT CAESAREAN SECTION

DOSE - 3000 ppm

| FEMALE NUMBER | IMPLANTATION SITES | | RESORPTION SITES | DEAD FETUSES | VIABLE FETUSES | | |
|---|---|---|---|---|---|---|---|
| | LEFT HORN | RIGHT HORN | | | NUMBER | MEAN WEIGHT (gram) | MEAN LENGTH (cm) |
| 4780 | 1 | 2 | 0 | 0 | 3 | 4.2 | 3.3 |
| 4781 | 0 | 0 | 0 | 0 | 0 | --- | --- |
| 4782 | 8 | 6 | 0 | 0 | 14 | 4.0 | 3.1 |
| 4783 | 0 | 0 | 0 | 0 | 0 | --- | --- |
| 4784 | 4 | 11 | 0 | 0 | 15 | 3.5 | 3.0 |
| 4785 | 6 | 6 | 1 | 0 | 11 | 4.1 | 3.1 |
| 4786 | 2 | 0 | 0 | 0 | 2 | 4.5 | 3.3 |
| 4787 | 8 | 5 | 2 | 0 | 11 | 3.7 | 3.2 |
| 4788 | 8 | 6 | 0 | 0 | 14 | 3.8 | 3.2 |
| 4789 | 0 | 0 | 0 | 0 | 0 | --- | --- |
| 4790 | 8 | 5 | 1 | 0 | 12 | 3.7 | 3.1 |
| 4791 | 0 | 0 | 0 | 0 | 0 | --- | --- |
| 4792 | 0 | 7 | 0 | 0 | 7 | 4.3 | 3.2 |
| 4793 | 8 | 5 | 0 | 0 | 13 | 3.8 | 2.9 |
| 4794 | 7 | 5 | 0 | 0 | 12 | 4.3 | 3.1 |
| 4795 | 0 | 0 | 0 | 0 | 0 | --- | --- |
| 4796 | 11 | 5 | 1 | 0 | 15 | 3.8 | 3.1 |
| 4797 | 9 | 9 | 2 | 0 | 16 | 3.5 | 3.1 |
| 4798 | 6 | 10 | 1 | 0 | 15 | 3.7 | 3.1 |
| 4799 | 5 | 9 | 1 | 0 | 13 | 3.4 | 3.0 |
| Total | 91 | 91 | 9 | 0 | 173 | | |
| Mean* | | | | | 12 | 3.9 | 3.1 |
| SD | | | | | 4 | 0.3 | 0.1 |
| SE | | | | | 1.1 | 0.09 | 0.03 |
| n | | | | | 15 | 15 | 15 |

*Mean, SD and SE do not include non-pregnant females

LITTON BIONETICS, INC.
PROJECT NO. 9004

TABLE 3

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE - CONTROL

| FEMALE NUMBER | NUMBER OF FETUSES EXAMINED | OBSERVATIONS |
|---|---|---|
| 4722 | 4 | 4 No visible skeletal abnormalities. |
| 4723 | 4 | 3 No visible skeletal abnormalities.<br>1 Unilateral rib 14. |
| 4725 | 9 | 7 No visible skeletal abnormalities.<br>1 Reduced ossification of interparietal bone.<br>1 Reduced ossification of interparietal bone, reduced ossification of supraoccipital bone, reduced ossification of hyoid bone. |
| 4726 | 8 | 6 No visible skeletal abnormalities.<br>1 Reduced ossification of interparietal bone, reduced ossification of hyoid bone.<br>1 Bilateral rib 14. |
| 4727 | 2 | 1 No visible skeletal abnormalities.<br>1 Non-fused thoracic vertebral centra. |
| 4728 | 8 | 7 No visible skeletal abnormalities.<br>1 Unilateral rib 14. |
| 4729 | 11 | 6 No visible skeletal abnormalities.<br>1 Reduced ossification of interparietal bone, reduced ossification of supraoccipital bone, hyoid not ossified, reduced ossification of parietal bone.<br>1 Reduced ossification of interparietal bone.<br>2 Reduced ossification of interparietal bone, reduced ossification of supraoccipital bone, hyoid not ossified.<br>1 Reduced ossification of interparietal bone, reduced ossification of supraoccipital bone, reduced ossification of hyoid bone. |

TABLE I-D-6 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 9004

TABLE 3 (Continued)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE- CONTROL

| FEMALE NUMBER | NUMBER OF FETUSES EXAMINED | OBSERVATIONS |
|---|---|---|
| 4730 | 7 | 5 No visible skeletal abnormalities.<br>1 Hyoid not ossified.<br>1 Unilateral rib 14. |
| 4732 | 10 | 6 No visible skeletal abnormalities.<br>1 Hyoid not ossified, reduced ossification of interparietal bone, reduced ossification of supraoccipital bone.<br>1 Reduced ossification of interparietal bone.<br>1 Reduced ossification of hyoid bone.<br>1 Reduced ossification of interparietal bone, reduced ossification of hyoid bone, unilateral rib 14. |
| 4735 | 9 | 8 No visible skeletal abnormalities.<br>1 Bilateral rib 14. |
| 4736 | 9 | 9 No visible skeletal abnormalities. |
| 4737 | 9 | 7 No visible skeletal abnormalities.<br>2 Reduced ossification of right rib 13. |
| 4738 | 9 | 4 No visible skeletal abnormalities.<br>1 Reduced ossification of interparietal bone, reduced ossification of hyoid bone.<br>1 Hyoid not ossified.<br>1 Non-fused thoracic vertebral centra.<br>1 Reduced ossification of interparietal bone, reduced ossification of supraoccipital bone.<br>1 Reduced ossification of interparietal bone, reduced ossification of supraoccipital bone, reduced ossification of hyoid bone. |
| 4739 | 1 | 1 Reduced ossification of left rib 13. |

LITTON BIONETICS, INC.
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TABLE 3 (Continued)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE- 100 ppm

| FEMALE NUMBER | NUMBER OF FETUSES EXAMINED | OBSERVATIONS |
|---|---|---|
| 4740 | 1 | *1 Maxilla malformed, mandible malformed, unilateral rib 14. |
| 4744 | 9 | 2 No visible skeletal abnormalities.<br>3 Bilateral rib 14.<br>1 Unilateral rib 14.<br>2 Reduced ossification of interparietal bone, reduced ossification of hyoid bone.<br>1 Reduced ossification of hyoid bone. |
| 4747 | 10 | 9 No visible skeletal abnormalities.<br>1 Bilateral rib 14. |
| 4748 | 1 | 1 No visible skeletal abnormalities. |
| 4749 | 8 | 6 No visible skeletal abnormalities.<br>1 Unilateral rib 14.<br>1 Bilateral rib 14. |
| 4750 | 10 | 4 No visible skeletal abnormalities.<br>1 Hyoid not ossified.<br>2 Reduced ossification of interparietal bone, reduced ossification of hyoid bone.<br>1 Reduced ossification of supraoccipital bone, reduced ossification of hyoid bone.<br>1 Reduced ossification of interparietal bone, reduced ossification of supraoccipital bone, reduced ossification of hyoid bone.<br>*1 Reduced ossification of supraoccipital bone, reduced ossification of sternebrae, reduced ossification of pubes. |
| 4751 | 8 | 7 No visible skeletal abnormalities.<br>1 Bilateral rib 14. |
| 4752 | 3 | 2 No visible skeletal abnormalities.<br>1 Unilateral rib 14. |
| 4753 | 4 | 4 No visible skeletal abnormalities. |

*Not commonly encountered.

LITTON BIONETICS, INC.
PROJECT NO. 9004

TABLE 3 (Continued)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE - 100 ppm

| FEMALE NUMBER | NUMBER OF FETUSES EXAMINED | OBSERVATIONS |
|---|---|---|
| 4754 | 8 | 7 No visible skeletal abnormalities.<br>1 Bilateral rib 14. |
| 4756 | 11 | 8 No visible skeletal abnormalities.<br>2 Unilateral rib 14.<br>1 Reduced ossification of hyoid bone. |
| 4757 | 9 | 4 No visible skeletal abnormalities.<br>1 Unilateral rib 14.<br>1 Reduced ossification of hyoid bone, unilateral rib 14.<br>1 Reduced ossification of interparietal bone, reduced ossification of supraoccipital bone, reduced ossification of hyoid bone.<br>1 Hyoid not ossified.<br>1 Reduced ossification of hyoid bone. |
| 4758 | 9 | 5 No visible skeletal abnormalities.<br>1 Hyoid not ossified.<br>1 Hyoid not ossified, unilateral rib 14.<br>1 Reduced ossification of hyoid bone.<br>1 Hyoid not ossified, reduced ossification of supraoccipital bone. |
| 4759 | 11 | 10 No visible skeletal abnormalities.<br>1 Unilateral rib 14. |

LITTON BIONETICS, INC.
PROJECT NO. 9004

TABLE 3 (Continued)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE - 300 ppm

| FEMALE NUMBER | NUMBER OF FETUSES EXAMINED | OBSERVATIONS |
|---|---|---|
| 4763 | 4 | 3 No visible skeletal abnormalities.<br>1 Reduced ossification of interparietal bone. |
| 4764 | 9 | 6 No visible skeletal abnormalities.<br>2 Non-fused thoracic vertebral centra.<br>*1 Reduced ossification of interparietal bone, hyoid not ossified, reduced ossification of sacral vertebral arches, reduced ossification of sternebrae, wavy ribs (right side), distal phalanges of hind extremities not ossified. |
| 4765 | 3 | 1 Non-fused thoracic vertebral centra.<br>1 Reduced ossification of interparietal bone, reduced ossification of supraoccipital bone, reduced ossification of hyoid bone.<br>*1 Reduced ossification of hyoid bone, reduced ossification of right ischium. |
| 4766 | 8 | 7 No visible skeletal abnormalities.<br>1 Reduced ossification of hyoid bone. |
| 4767 | 5 | 2 No visible skeletal abnormalities.<br>1 Reduced ossification of interparietal bone.<br>*1 Reduced ossification of interparietal bone, reduced ossification of supraoccipital bone, reduced ossification of parietal bone, unilateral rib 14, reduced ossification of hyoid bone.<br>*1 Reduced ossification of interparietal bone, reduced ossification of supraoccipital bone, reduced ossification of parietal bone, hyoid not ossified, reduced ossification of right ribs, wavy ribs (right side). |
| 4769 | 6 | 6 No visible skeletal abnormalities. |
| 4773 | 7 | 7 No visible skeletal abnormalities. |
| 4775 | 4 | 3 No visible skeletal abnormalities.<br>1 Reduced ossification of hyoid bone. |
| 4776 | 10 | 9 No visible skeletal abnormalities.<br>1 Bilateral rib 14. |

*Not commonly encountered.

TABLE I-D-6 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 9004

TABLE 3 (Continued)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE - 300 ppm

| FEMALE NUMBER | NUMBER OF FETUSES EXAMINED | OBSERVATIONS |
|---|---|---|
| 4777 | 8 | 7 No visible skeletal abnormalities.<br>1 Unilateral rib 14. |
| 4779 | 11 | 8 No visible skeletal abnormalities.<br>2 Bilateral rib 14.<br>1 Unilateral rib 14. |

LITTON BIONETICS, INC.
PROJECT NO. 9004

TABLE 3 (Continued)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE- 3000 ppm

| FEMALE NUMBER | NUMBER OF FETUSES EXAMINED | OBSERVATIONS |
|---|---|---|
| 4780 | 2 | 2 No visible skeletal abnormalities. |
| 4782 | 10 | 5 No visible skeletal abnormalities.<br>1 Reduced ossification of hyoid bone.<br>1 Non-fused thoracic vertebral centra.<br>1 Reduced ossification of interparietal bone, reduced ossification of supraoccipital bone, reduced ossification of hyoid bone, reduced ossification of right rib 10.<br>1 Reduced ossification of supraoccipital bone, reduced ossification of hyoid bone.<br>*1 Reduced ossification of supraoccipital bone, reduced ossification of hyoid bone, reduced ossification of parietalbone, reduced ossification of interparietal bone. |
| 4784 | 10 | 5 No visible skeletal abnormalities.<br>4 Unilateral rib 14.<br>1 Bilateral rib 14. |
| 4785 | 7 | 3 No visible skeletal abnormalities.<br>1 Reduced ossification of interparietal bone, unilateral rib 14.<br>1 Reduced ossification of interparietal bone, reduced ossification of hyoid bone, non-fused thoracic vertebral centra.<br>1 Unilateral rib 14.<br>1 Reduced ossification of interparietal bone. |
| 4786 | 1 | 1 Bilateral rib 14. |
| 4787 | 7 | 6 No visible skeletal abnormalities.<br>1 Unilateral rib 14. |
| 4788 | 9 | 6 No visible skeletal abnormalities.<br>2 Reduced ossification of hyoid bone.<br>1 Reduced ossification of hyoid bone, bilateral rib 14. |

*Not commonly encountered.

TABLE I-D-6 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 9004

TABLE 3 (Continued)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE - 3000 ppm

| FEMALE NUMBER | NUMBER OF FETUSES EXAMINED | OBSERVATIONS |
|---|---|---|
| 4790 | 8 | 1 No visible skeletal abnormalities.<br>1 Reduced ossification of supraoccipital bone, reduced ossification of hyoid bone.<br>1 Reduced ossification of hyoid bone.<br>1 Reduced ossification of hyoid bone, unilateral rib 14.<br>1 Reduced ossification of supraoccipital bone, hyoid not ossified, unilateral rib 14.<br>1 Reduced ossification of interparietal bone.<br>*1 Reduced ossification of interparietal bone, reduced ossification of supraoccipital bone, reduced ossification of hyoid bone, reduced ossification of parietal bone, reduced ossification of maxilla, reduced ossification of sacral vertebral arches.<br>1 Reduced ossification of hyoid bone, bilateral rib 14. |
| 4792 | 4 | 3 No visible skeletal abnormalities.<br>1 Reduced ossification of interparietal bone. |
| 4793 | 9 | 5 No visible skeletal abnormalities.<br>1 Unilateral rib 14.<br>1 Bilateral rib 14.<br>1 Reduced ossification of interparietal bone, reduced ossification of supraoccipital bone.<br>1 Reduced ossification of interparietal bone, reduced ossification of supraoccipital bone, reduced ossification of hyoid bone. |
| 4794 | 8 | 8 No visible skeletal abnormalities. |
| 4796 | 10 | 6 No visible skeletal abnormalities.<br>2 Reduced ossification of hyoid bone.<br>1 Reduced ossification of interparietal bone.<br>1 Reduced ossification of interparietal bone, reduced ossification of hyoid bone. |

*Not commonly encountered

LITTON BIONETICS, INC.
PROJECT NO. 9004

TABLE 3 (Continued)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE - 3000 ppm

| FEMALE NUMBER | NUMBER OF FETUSES EXAMINED | OBSERVATIONS |
|---|---|---|
| 4797 | 10 | 3 No visible skeletal abnormalities.<br>2 Reduced ossification of interparietal bone, reduced ossification of hyoid bone.<br>2 Hyoid not ossified.<br>1 Reduced ossification of hyoid bone.<br>1 Reduced ossification of supraoccipital bone, reduced ossification of hyoid bone.<br>1 Reduced ossification of hyoid bone, unilateral rib 14. |
| 4798 | 10 | 5 No visible skeletal abnormalities.<br>1 Hyoid not ossified.<br>2 Reduced ossification of hyoid bone.<br>1 Reduced ossification of interparietal bone.<br>*1 Reduced ossification of interparietal bone, reduced ossification of supraoccipital bone, reduced ossification of hyoid bone, reduced ossification of parietal bone. |
| 4799 | 9 | 9 No visible skeletal abnormalities. |

*Not commonly encountered.

PART I - SECTION E

THREE-GENERATION REPRODUCTION IN RATS

DIMP

LBI PROJECT NO. 10734-06

## SUMMARY

Dietary incorporation of DIMP at levels of 300 and 3000 ppm produced no dose-related reproductive response in the rat for three successive generations with two matings per generation. The first mating of the third generation resulted in significant pup losses from Day 4 to Day 21 for the treatment groups. This decrease was not evidenced for the second mating. Food consumption and body weight data for the parent (F0), second generation (F1b) and third generation (F2b) rats, indicated statistical equivalence with the controls for all treatment levels except the high dose F2b female group. Litter and necropsy observations for the first breeding of the three generations were unremarkable and free of any dose-dependent relationship.

## 1. OBJECTIVE

The objective of this study was to evaluate the effects of dietary incorporation of DIMP in the rat on several indicators of the reproductive process for three successive generations with two breedings per generation.

## 2. MATERIAL

Refer to Part I - Section A.

## 3. EXPERIMENTAL DESIGN

### A. First Generation (F0 Parents, F1a and F1b Offspring)

One hundred and twenty weanling rats [CRL:COBS CD (SD) BR] were obtained from Charles River Breeding Laboratories, Inc., Portage, Michigan on March 30, 1977, at the Falls Church facility of the Department of Toxicology. Thirty male and sixty female rats were selected as the F0 parents and assigned by randomization into the following three groups.

| Group Number | Animal Numbers | | Dose (ppm) |
|---|---|---|---|
| | Males | Females | |
| 1 | 5020-5029 | 5030-5049 | 0 |
| 2 | 5050-5059 | 5060-5079 | 300 |
| 3 | 5080-5089 | 5090-5109 | 3000 |

The remaining rats were sacrificed and discarded. The F0 parents were ear tagged and individually housed in hanging shoebox cages with AB-SORB-DRI bedding. The rats were maintained in a temperature-controlled animal room with artificial

3. EXPERIMENTAL DESIGN (Continued)

A. First Generation (FO Parents, Fla and Flb Offspring - Continued)

illumination automatically controlled to provide a 12-hour light cycle. The FO parents were fed Purina Laboratory Chow for one week and observed for any gross effects prior to initiation of the test diets. The test diet and acidified water (pH 2.5) were provided ad libitum. The time framework for this study has been presented in Text Table A.

Ten kg of the test diet for each dose level were prepared weekly by adding the requisite amount of DIMP for a given dose level to 300 ml of a PEG 400 vehicle and mixing the vehicle and basal diet in a twin-shell blender for 20 minutes. Control diet was prepared with the suspension vehicle in a similar fashion. Appendix B lists the concentration data as a function of the study week and also describes the analytical procedure for quantitating the DIMP level. Stability tests for the low and high level feed mixtures from the fifteenth study week were performed for samples stored in open and closed containers. The results (Table 1 of Appendix B) were indicative of considerable sample volatility from open containers. The mean sample concentrations and associated standard errors for the 300 and 3000 ppm feed mixtures were 251 ± 5 ppm and 2667 ± 36 ppm, respectively, for the time course of this study.

During the twelfth study week, the FO parents were placed in breeding cages, one male and two females, for a two-week mating period. The males and females were then returned to their individual cages where the females were allowed to litter and nurse their pups. One-third of the Fla pups were subjected to a cursory necropsy after weaning. One week after lactation of the Fla pups, the FO females were remated in a similar manner with a different male. During Day 4 of lactation the Fla and Flb litters were reduced for subsequent viability and weight measurements at Days 9 and 21. One week after lactation of the Flb pups all FO parents were killed and necropsied.

The data and observations listed below were recorded for the parents and their offspring.

FO Parents

Body weights and food consumption (averaged over seven days) at study Weeks 4, 9, 11 and 20.
Daily observations for mortality.
Weekly appearance observations.
Anatomic observations at necropsy.

TABLE I-E-7

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE A

TIME FRAMEWORK FOR STUDY

| STUDY WEEK NO(S). | PHASE |
|---|---|
| 1 | Fo parents begin DIMP dietary input |
| 12, 13, 14 | F1a mating period (Fo parents) |
| 16, 17 | Lactation Day 0 for F1a pups |
| 19, 20 | F1a pup necropsy |
| 21, 22, 23 | F1b mating period (Fo parents) |
| 24, 25, 26 | Lactation Day 0 for F1b pups |
| 27, 28, 29 | Fo parents necropsied |
| 40, 41, 42 | F2a mating period (F1b parents) |
| 43, 44, 45 | Lactation Day 0 for F2a pups |
| 47, 48 | F2a pup necropsy |
| 49, 50, 51 | F2b mating period (F1b parents) |
| 53, 54 | Lactation Day 0 for F2b pups |
| 56, 57, 58 | F1b parents necropsied |
| 70, 71, 72 | F3a mating period (F2b parents) |
| 73, 74 | Lactation Day 0 for F3a pups |
| 77, 78 | F3a pup necropsy |
| 78, 79, 80 | F3b mating period (F2b parents) |
| 81, 82, 83 | Lactaton Day 0 for F3b pups |
| 85, 86 | F3b pup necropsy |
| 87 | F2b parents necropsied |

3. EXPERIMENTAL DESIGN (Continued)

A. First Generation (F0 Parents, F1a and F1b Offspring - Continued)

F1a and F1b Pups

Number of live and dead pups at birth, sex and body weights.
Number and sex of surviving pups at lactation Day 4.
Number, sex and body weights for reduced litter pups surviving at Day 21.
Daily mortality and appearance observations.
Anatomic observations at necropsy of one-third of F1a litters.

B. Second Generation (F1b Parents, F2a and F2b Offspring)

After weaning, 10 male and 20 female F1b pups were selected from each dose and control group, and identified by ear tag as listed below. The rats were individually housed for the second generation breedings.

| Group Number | Animal Numbers | | Dose (ppm) |
|---|---|---|---|
| | Males | Females | |
| 1 | 5446-5455 | 5456-5475 | 0 |
| 2 | 5476-5485 | 5486-5505 | 300 |
| 3 | 5506-5515 | 5516-5535 | 3000 |

The same schedule for mating, littering and observations, as previously described for the first generation rats, was followed for the second generation rats.

C. Third Generation (F2b Parents, F3a and F3b Offspring)

After weaning, 10 male and 20 female F2b pups were selected from each dose and control group, and ear tagged as listed below. They were individually housed for the third generation breedings.

| Group Number | Animal Numbers[a] | | Dose (ppm) |
|---|---|---|---|
| | Males | Females | |
| 1 | 1397-1406 | 1407-1426 | 0 |
| 2 | 1427-1436 | 1437-1456 | 300 |
| 3 | 1457-1466 | 1467-1487 | 3000 |

[a]"A" series animal number ear tags.

The same schedule for mating, littering and observations, as previously described for the first generation rats, was followed for the third generation rats. In addition, one-third of the F3b litters were killed and necropsied at weaning.

3. EXPERIMENTAL DESIGN (Continued)

C. Third Generation (F2b Parents, F3a and F3b Offspring - Continued)

The newborn viability ratios (live pups/total pups), pup viability ratios (pups at Day 4/pups at Day 0), lactation indices (pups at Day 21/pups at Day 4) and gestation indices (females littering/pregnant) for the treatment groups were statistically compared with the controls using 2x2 contingency tables with Chi-squared corrected for continuity. Dunnett's t-test for analysis for statistical differences was used to compare control and treatment means for the parent body weights, parent food consumption and pup weights. A p value of 0.05 was used to determine statistical significance.

4. RESULTS

A. First Generation (F0 Parents, F1a and F1b Offspring)

The detailed litter data, parent body weights, parent food consumption data, litter and parent observations, and necropsy data for parents and pups have been incorporated in Appendix A for this and succeeding generations. Litter summaries have been presented as text tables.

One female rat in the high dose group (No. 5109) died during the sixth week of the study. No visible abnormalities were noted and the death was judged not to be related to treatment. One male control rat (No. 5027) failed to successfully mate for two breedings. Necropsy data for this rat failed to show any evidence of sexual or reproductive dysfunction.

During the second week of study female control rat (No. 5030) developed ocular changes in the right eye which persisted until necropsy. A consultant ophthalmologist examined the animal and he indicated the presence of a unilateral cataract. His report has been appended.

The litter summaries for the first and second matings, Text Tables B and C, respectively, with detailed listing in appended Tables 1 and 4, showed a slight weight reduction of approximately 12% for the F1b control pups, both males and females at Day 21, versus the F1b pups. All other indices of reproductive performance presented in the summary tables exhibited statistical equivalence between control and treatment levels for both male and female groups. The pup viability counts for Days 4 and 21 were greater than 96% in all instances. Pup viability counts are usually calculated from the differential totals at Days 4 and 21 because of pup cannibalization by the dam. For this reason, the litter observation tables, appended Tables 2 and 5 do not correspond with the viability counts presented in the summaries.

The parent body weights and daily food consumption means, appended in Table 6, for the treatment groups were statistically equivalent to the controls for both male and female groups at all measurement levels.

TABLE I-E-8

LITTON BIONETICS
PROJECT NO. 10734-06

TABLE B

SUMMARY OF FIRST GENERATION - FIRST MATING (F1a)

| | DOSE (PPM) 0 | | 300 | | 3000 | |
|---|---|---|---|---|---|---|
| | RATIO | PERCENT | RATIO | PERCENT | RATIO | PERCENT |
| **Indices** | | | | | | |
| Male virility (males producing litter/mated) | 9/10 | 90 | 10/10 | 100 | 10/10 | 100 |
| Female fertility (females producing litter/mated) | 17/20 | 85 | 17/20 | 85 | 16/19 | 84 |
| Gestation (females live litter/pregnant) | 17/17 | 100 | 17/17 | 100 | 16/16 | 100 |
| Newborn viability (live pups/total pups) | 227/227 | 100 | 231/237 | 97 | 206/208 | 99 |
| Pup viability (pups Day 4/pups Day 0) | 226/227 | 100 | 226/231 | 98 | 206/206 | 100 |
| Lactation (pups Day 21/pups Day 4)[a] | 133/134 | 99 | 134/135 | 99 | 128/128 | 100 |
| **Pup weight in grams (Mean ± S.D.)** | | | | | | |
| Day 0 males | 7±1.2 | | 6±0.6 | | 7±0.7 | |
| Day 0 females | 6±0.9 | | 6±0.0 | | 7±0.6 | |
| Day 21 males | 53±6.9 | | 50±4.7 | | 53±5.8 | |
| Day 21 females | 49±4.7 | | 48±4.7 | | 51±5.6 | |
| Sex ratio offspring (M/F) Day 0 | 104/123 | | 107/124 | | 100/106 | |
| Live pups per litter (Mean ± S.D.) | 13±2.6 | | 14±2.7 | | 13±1.8 | |

[a]After litters were reduced at Day 4.

TABLE I-E-9

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE C

SUMMARY OF FIRST GENERATION - SECOND MATING (F1b)

| | DOSE (PPM) 0 | | 300 | | 3000 | |
|---|---|---|---|---|---|---|
| | RATIO | PERCENT | RATIO | PERCENT | RATIO | PERCENT |
| **Indices** | | | | | | |
| Male virility (males producing litter/mated) | 9/10 | 90 | 10/10 | 100 | 10/10 | 100 |
| Female fertility (females producing litter/mated) | 16/18 | 89 | 18/20 | 90 | 17/19 | 89 |
| Gestation (females live litter/pregnant) | 16/16 | 100 | 18/18 | 100 | 17/17 | 100 |
| Newborn viability (live pups/total pups) | 204/206 | 99 | 243/246 | 99 | 209/216 | 97 |
| Pup viability (pups Day 4/pups Day 0) | 195/204 | 96 | 239/243 | 98 | 208/209 | 100 |
| Lactation (pups Day 21/pups Day 4)[a] | 118/120 | 98 | 144/144 | 100 | 130/132 | 98 |
| **Pup weight in grams (Mean ± S.D.)** | | | | | | |
| Day 0 males | 7±0.7 | | 7±0.6 | | 7±0.6 | |
| Day 0 females | 6±0.6 | | 7±0.7 | | 7±0.7 | |
| Day 21 males | 46±7.0 | | 49±5.7 | | 53±8.2 | |
| Day 21 females | 43±7.8 | | 48±5.7 | | 50±7.8 | |
| Sex ratio offspring (M/F) Day 0 | 96/108 | | 107/136 | | 108/101 | |
| Live pups per litter (Mean ± S.D.) | 14±1.8 | | 14±2.2 | | 12±3.0 | |

[a]After litters were reduced at Day 4.

4. RESULTS (Continued)

A. First Generation (FO Parents, Fla and Flb Offspring - Continued)

Parent observations have been appended in Table 7. A slight incidence of alopecia was observed throughout the study. The alopecia frequently disappeared with time.

Pup necropsy observations for one-third of the Fla control and treatment groups have been presented in Appendix Table 3. No gross abnormalities were recorded for the 17 litters that were examined.

Adult necropsy findings have been noted in Appendix Table 8. The major finding was the high incidence of kidney mottling. The number of occurrences was equally distributed across the control and treatment groups.

B. Second Generation (Flb Parent, F2a and F2b Offspring)

It was discovered that litter mates had inadvertently been paired for the F2a and F3b matings, appended Tables 9 and 20. Text Table D lists the brother-sister pairs and whether the matings were successful. The pairings were judged not to compromise the integrity of the study because the majority of the occurrences were in the F2a mating, whose litters were not subsequently bred, and because the majority of these matings (85%) successfully littered. It was interesting to note that 16 control pups from the litter-mate pairings died between Days 0 and 4. Inclusion of this number in the pup viabilities (Text Table E, Day 4/Day 0) raised this ratio to 91%. This percentage, however, was still significantly depressed, using the Chi-square statistic, from the treatment ratios. No Flb parents died on the study.

For the first mating, female parent No. 5527 (3000 ppm) produced stillborn Siamese twins which were joined at the ventral thoracic region. One twin was well developed anatomically, but the second twin lacked a discernible head. The remaining observations for the F2a and F2b litters, detailed on Appendix Tables 10 and 13, were not indicative of any compound-related effects and appeared unremarkable.

Within the 300 ppm group, male rat Nos. 5476 and 5477 failed to successfully mate for the first breeding. Male parent No. 5507 (3000 ppm) also failed to successfully mate. This was reflected in the newborn pup counts (Text Table E) which were decreased from the controls by 20%. The number of live pups per litter was equivalent.

TABLE I-E-10

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE D

LITTER MATE PAIRINGS

F2a MATING

| 0 PPM | | | 300 PPM | | | 3000 PPM | | |
|---|---|---|---|---|---|---|---|---|
| MALE NUMBER | FEMALE NUMBER | LITTER PRODUCED | MALE NUMBER | FEMALE NUMBER | LITTER PRODUCED | MALE NUMBER | FEMALE NUMBER | LITTER PRODUCED |
| 5447 | 5458 | Yes | 5477 | 5488 | No | 5507 | 5518 | No |
| 5448 | 5460 | Yes | 5478 | 5490 | Yes | 5508 | 5520 | Yes |
| 5449 | 5462 | Yes | 5479 | 5492 | Yes | 5509 | 5522 | Yes |
| 5450 | 5464 | Yes | 5480 | 5494 | Yes | 5510 | 5524 | Yes |
| 5451 | 5466 | Yes | 5481 | 5496 | Yes | 5511 | 5526 | Yes |
| 5452 | 5468 | No | 5482 | 5498 | Yes | 5512 | 5528 | Yes |
| 5452 | 5469 | Yes | 5483 | 5500 | Yes | 5512 | 5529 | No |
| 5453 | 5470 | Yes | 5484 | 5502 | Yes | 5513 | 5530 | Yes |
| 5453 | 5471 | No | 5484 | 5503 | Yes | 5513 | 5531 | Yes |
| 5454 | 5472 | Yes | | | | 5514 | 5532 | Yes |
| 5454 | 5473 | Yes | | | | 5514 | 5533 | Yes |

F3b MATING

| | | | | | |
|---|---|---|---|---|---|
| 1430 | 1444 | Yes | 1465 | 1485 | Yes |
| 1431 | 1445 | Yes | | | |

TABLE I-E-11

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE E

SUMMARY OF SECOND GENERATION - FIRST MATING (F2a)

| | DOSE (PPM) | | | | | |
|---|---|---|---|---|---|---|
| | 0 | | 300 | | 3000 | |
| | RATIO | PERCENT | RATIO | PERCENT | RATIO | PERCENT |
| **Indices** | | | | | | |
| Male virility (males producing litter/mated) | 10/10 | 100 | 8/10 | 80 | 9/10 | 90 |
| Female fertility (females producing litter/mated) | 18/20 | 90 | 15/16 | 94 | 16/18 | 89 |
| Gestation (females live litter/pregnant) | 18/18 | 100 | 15/15 | 100 | 16/16 | 100 |
| Newborn viability (live pups/total pups) | 223/233 | 96 | 173/178 | 97 | 184/189 | 97 |
| Pup viability (pups Day 4/pups Day 0) | 186/223 | 83 | 167/173 | 97 | 175/184 | 95 |
| Lactation (pups Day 21/pups Day 4)[a] | 112/121 | 93 | 109/118 | 92 | 124/125 | 99 |
| **Pup weight in grams (Mean ± S.D.)** | | | | | | |
| Day 0 males | 6±0.9 | | 6±1.2 | | 7±0.7 | |
| Day 0 females | 6±1.1 | | 6±1.0 | | 7±0.9 | |
| Day 21 males | 39±7.5 | | 43±8.1 | | 39±4.1 | |
| Day 21 females | 38±7.7 | | 39±8.1 | | 38±3.8 | |
| Sex ratio offspring (M/F) Day 0 | 106/117 | | 82/91 | | 79/105 | |
| Live pups per litter (Mean ± S.D.) | 12±2.6 | | 12±2.4 | | 12±2.0 | |

[a]After litters were reduced at Day 4.

4. RESULTS (Continued)

B. Second Generation (F1b Parents, F2a and F2b Offspring - Continued)

The F2b mating (Text Table F and Appendix Table 12) produced a greater number of pregnant dams which was reflected in the larger total pup counts for the 300 and 3000 ppm levels. Concurrently, there was a slight, but insignificant, increase in the average litter size. Average pup weights at Day 21 for the F2b males and females were 9 and 19% greater than those from the F2a mating. Pup viabilities for both matings ranged from 92 to 99%.

Body weight and food consumption data have been tabulated in Appendix Table 14. Analysis of the data showed that the only statistical difference from the controls occurred at Week 4 for the high dose male parents. This significance disappeared by Week 9.

Clinical signs have been appended in Table 15. Localized hair loss (female No. 5489) and ulceration of the right ear with subsequent loss of this ear (female No. 5524) were the only observable clinical signs recorded for the F1b parents.

Pup necropsy observations for the F2a litters have been appended in Table 11. No significant observations were noted.

There were several instances of ovarian, uterine and Fallopian tube cysts observed at necropsy for the F1b dams. These findings have been detailed in Appendix Table 16. These findings were not considered to be treatment related since the number of occurrences was distributed equally between treatment and control groups.

C. Third Generation (F2b Parents, F3a and F3b Offspring)

No F2b parents died during the study. The third generation matings resulted in newborn viabilities of 98 to 100% and equivalent average litter size for all groups. These findings have been summarized in Text Tables G and H and appended in Tables 17 and 20. Many pup losses were noted for the 3000 ppm F2b group from Day 0 to Day 4, significantly reducing this viability ratio from the control (Appendix Table 2[illegible]. Lactation viabilities for the F2a treatment groups from Day 4 to Day 21 were significantly decreased from the controls. The Chi-square significance in the 300 ppm group could be attributed to the total litter loss of female No. 1443. Application of Wilcoxon Rank Sum analysis did not indicate a significant difference. The pup losses at the high treatment level were distributed among eight dams.

TABLE I-E-12

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE F

SUMMARY OF SECOND GENERATION - SECOND MATING (F2b)

| | DOSE (PPM) 0 | | 300 | | 3000 | |
|---|---|---|---|---|---|---|
| | RATIO | PERCENT | RATIO | PERCENT | RATIO | PERCENT |
| **Indices** | | | | | | |
| Male virility (males producing litter/mated) | 10/10 | 100 | 10/10 | 100 | 10/10 | 100 |
| Female fertility (females producing litter/mated) | 18/20 | 90 | 17/20 | 85 | 18/20 | 90 |
| Gestation (females live litter/pregnant) | 18/18 | 100 | 17/17 | 100 | 18/18 | 100 |
| Newborn viability (live pups/total pups) | 250/256 | 98 | 228/230 | 99 | 233/235 | 99 |
| Pup viability (pups Day 4/pups Day 0)[a] | 242/250 | 97 | 222/228 | 97 | 230/233 | 99 |
| Lactation (pups Day 21/pups Day 4)[a] | 142/144 | 99 | 135/136 | 99 | 140/141 | 99 |
| **Pup weight in grams (Mean ± S.D.)** | | | | | | |
| Day 0 males | 6±0.6 | | 7±1.0 | | 7±0.8 | |
| Day 0 females | 6±0.6 | | 7±1.0 | | 6±0.6 | |
| Day 21 males | 44±5.5 | | 47±6.3 | | 48±8.7 | |
| Day 21 females | 42±5.4 | | 44±5.0 | | 45±7.0 | |
| Sex ratio offspring (M/F) Day 0 | 119/131 | | 117/111 | | 117/116 | |
| Live pups per litter (Mean ± S.D.) | 14±2.4 | | 13±3.1 | | 13±2.5 | |

[a]After litters were reduced at Day 4.

TABLE I-E-13

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE G

SUMMARY OF THIRD GENERATION - FIRST MATING (F3a)

| | DOSE (PPM) | | | | | |
|---|---|---|---|---|---|---|
| | 0 | | 300 | | 3000 | |
| | RATIO | PERCENT | RATIO | PERCENT | RATIO | PERCENT |
| **Indices** | | | | | | |
| Male virility (males producing litter/mated) | 10/10 | 100 | 10/10 | 100 | 9/10 | 90 |
| Female fertility (females producing litter/mated) | 18/20 | 90 | 17/20 | 85 | 18/20 | 90 |
| Gestation (females live litter/pregnant) | 18/18 | 100 | 17/17 | 100 | 18/18 | 100 |
| Newborn viability (live pups/total pups) | 210/212 | 99 | 212/212 | 100 | 219/221 | 99 |
| Pup viability (pups Day 4/pups Day 0) | 202/210 | 96 | 204/212 | 96 | 217/219 | 99 |
| Lactation (pups Day 21/pups Day 4)[a] | 128/129 | 99 | 116/129 | 90* | 108/138 | 78* |
| **Pup weight in grams (Mean ± S.D.)** | | | | | | |
| Day 0 males | 6±0.9 | | 6±0.7 | | 7±1.0 | |
| Day 0 females | 6±1.0 | | 6±0.8 | | 6±1.1 | |
| Day 21 males | 42±6.2 | | 39±7.2 | | 32±7.9 | |
| Day 21 females | 41±7.1 | | 37±7.2 | | 30±8.1 | |
| Sex ratio offspring (M/F) Day 0 | 108/102 | | 127/85 | | 124/95 | |
| Live pups per litter (Mean ± S.D.) | 12±3.7 | | 13±4.[illegible] | | 12±3.3 | |

[a]After litters were reduced at Day 4.

*$p < 0.05$, Chi-square with correction for continuity.

TABLE I-E-14

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE H

SUMMARY OF THIRD GENERATION - SECOND MATING (F3b)

| | DOSE (PPM) | | | | | |
|---|---|---|---|---|---|---|
| | 0 | | 300 | | 3000 | |
| | RATIO | PERCENT | RATIO | PERCENT | RATIO | PERCENT |
| **Indices** | | | | | | |
| Male virility (males producing litter/mated) | 10/10 | 100 | 10/10 | 100 | 10/10 | 100 |
| Female fertility (females producing litter/mated) | 20/20 | 100 | 19/20 | 95 | 18/20 | 90 |
| Gestation (females live litter/pregnant) | 20/20 | 100 | 19/19 | 100 | 18/18 | 100 |
| Newborn viability (live pups/total pups) | 287/290 | 99 | 256/257 | 100 | 242/246 | 98 |
| Pup viability (pups Day 4/pups Day 0) | 279/287 | 97 | 249/256 | 97 | 217/242 | 90* |
| Lactation (pups Day 21/pups Day 4)[a] | 138/157 | 88 | 145/149 | 97 | 126/133 | 95 |
| **Pup weight in grams (Mean ± S.D.)** | | | | | | |
| Day 0 males | 6±0.7 | | 6±0.7 | | 6±0.7 | |
| Day 0 females | 5±0.6 | | 6±0.7 | | 6±0.9 | |
| Day 21 males | 49±5.3 | | 47±5.1 | | 46±5.4 | |
| Day 21 females | 45±5.0 | | 43±5.9 | | 41±4.5 | |
| Sex ratio offspring (M/F) Day 0 | 159/128 | | 136/120 | | 115/127 | |
| Live pups per litter (Mean ± S.D.) | 14±3.5 | | 13±3.7 | | 13±2.9 | |

[a]After litters were reduced at Day 4.

*$p < 0.05$, Chi-square with correction for continuity.

4. RESULTS (Continued)

C. Third Generation (F2b Parents, F3a and F3b Offspring)

The F3b pup weights at Day 21 were 9 to 30% greater than the F3a pup weights. A similar trend was observed in the second generation matings.

The only statistically significant feature of the parent body weight and food consumption data, appended in Table 23, was the 7% weight reduction of the high dose level females recorded at Week 20. Dunnett's t-test of analysis of the Week 20 male and female parent weights showed that there was a statistical equivalence among the three generations for the control and treatment groups.

Pup appearance and necropsy observations did not show any evidence of treatment-related effects for the F3a and F3b litters. These data have been detailed in Tables 18, 19, 21 and 22, respectively, of the Appendix.

Observations for the F2b parents have been detailed in Appendix Table 24. The clinical signs listed were not judged to be treatment related.

There were numerous incidences of kidney mottling recorded during the necropsy of the F2b parents (Appendix Table 25). They were divided across treatment and control groups for both sexes, and were therefore judged unrelated to treatment. The only other significant finding was the presence of a mammary mass in female No. 1444 (3000 ppm).

Thirty days after transmittal of this report, original data from the Department of Toxicology will be transferred to the LBI Archivist, 5516 Nicholson Lane, Kensington, Maryland, for distribution to the proper repositories. A copy of this report was reviewed by the LBI Quality Assurance Unit.

## 5. CONCLUSION

Dietary incorporation of DIMP at levels of 300 and 3000 ppm produced no dose-related reproductive response in the rat for three successive generations with two matings per generation. The first mating of the third generation resulted in significant pup losses from Day 4 to Day 21 for the treatment groups. This decrease was not evidenced for the second mating. Food consumption and body weight data for the parent (F0), second generation (F1b) and third generation (F2b) rats, indicated statistical equivalence with the controls for all treatment levels except the high dose F2b female group. Litter and necropsy observations for the first breeding of the three generations were unremarkable and free of any dose-dependent relationship.

Submitted by:

A. P. D'Addario — 14MAY 79

Anthony P. D'Addario, Ph.D. — Date
Post Doctoral Fellow
Department of Toxicology

Robert O Beliles — 5/15/79

Robert P. Beliles, Ph.D. — Date
Director
Department of Toxicology

Reviewed by:

Robert J. Weir — 5/16/79

Robert J. Weir, Ph.D. — Date
Vice President

E. Ross Hart — 5/15/79

E. Ross Hart, Ph.D. — Date
Study Director

# APPENDIX A

# TABLE I-E-15

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 1

RESULTS OF FIRST GENERATION - FIRST MATING (F1a)

DOSE - 0 PPM

| | | DAY 0 | | | | | DAY 4 | | | | DAY 21 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT | DEATHS DAY 1-4 | LIVE PUPS | SEX M/F | LITTER REDUCED M/F | DEATHS DAY 4-21 | LIVE PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT |
| 5030 | 5020 | 16 | | 8/8 | 6 | 6 | | 16 | 8/8 | 4/4 | | 8 | 4/4 | 45 | 45 |
| 5031 | 5020 | 15 | | 7/8 | 6 | 6 | | 15 | 7/8 | 4/4 | | 8 | 4/4 | 56 | 55 |
| 5032 | 5021 | 11 | | 2/9 | 6 | 6 | | 11 | 2/9 | 2/6 | | 8 | 2/6 | 41 | 45 |
| 5033 | 5021 | 14 | | 9/5 | 6 | 6 | 1 | 13 | 8/5 | 4/4 | | 8 | 4/4 | 44 | 40 |
| 5034 | 5022 | 6 | | 2/4 | 11 | 9 | | 6 | 2/4 | 2/4 | | 6 | 2/4 | 66 | 57 |
| 5035 | 5022 | | | | | | | | | | | | | | |
| 5036 | 5023 | 14 | | 9/5 | 6 | 5 | | 14 | 9/5 | 4/4 | | 8 | 4/4 | 57 | 49 |
| 5037 | 5023 | 16 | | 10/6 | 6 | 5 | | 16 | 10/6 | 4/4 | | 8 | 4/4 | 44 | 43 |
| 5038 | 5024 | 14 | | 9/5 | 6 | 6 | | 14 | 9/5 | 4/4 | 1 | 7 | 4/3 | 60 | 52 |
| 5039 | 5024 | 14 | | 8/6 | 7 | 6 | | 14 | 8/6 | 4/4 | | 8 | 4/4 | 53 | 49 |
| 5040 | 5025 | 16 | | 9/7 | 6 | 6 | | 16 | 9/7 | 4/4 | | 8 | 4/4 | 51 | 50 |
| 5041 | 5025 | 10 | | 2/8 | 6 | 6 | | 10 | 2/8 | 2/6 | | 8 | 2/6 | 51 | 45 |
| 5042 | 5026 | 12 | | 3/9 | 7 | 6 | | 12 | 3/9 | 3/5 | | 8 | 3/5 | 59 | 57 |
| 5043 | 5026 | 15 | | 6/9 | 6 | 6 | | 15 | 6/9 | 4/4 | | 8 | 4/4 | 47 | 47 |
| 5044 | 5027 | | | | | | | | | | | | | | |
| 5045 | 5027 | | | | | | | | | | | | | | |
| 5046 | 5028 | 14 | | 6/8 | 7 | 6 | | 14 | 6/8 | 4/4 | | 8 | 4/4 | 60 | 49 |
| 5047 | 5028 | 14 | | 5/9 | 7 | 6 | | 14 | 5/9 | 4/4 | | 8 | 4/4 | 56 | 51 |
| 5048 | 5029 | 14 | | 4/10 | 7 | 7 | | 14 | 4/10 | 4/4 | | 8 | 4/4 | 57 | 52 |
| 5049 | 5029 | 12 | | 5/7 | 7 | 6 | | 12 | 5/7 | 4/4 | | 8 | 4/4 | 51 | 50 |
| TOTAL | | 227 | | 104/123 | | | 1 | 226 | 103/123 | 61/73 | 1 | 133 | 61/72 | | |
| MEAN | | 13 | | | 7 | 6 | | 13 | | | | 8 | | 53 | 49 |
| SD | | 2.6 | | | 1.2 | 0.9 | | 2.5 | | | | 0.5 | | 6.9 | 4.7 |
| SE | | 0.6 | | | 0.3 | 0.2 | | 0.6 | | | | 0.1 | | 1.7 | 1.1 |
| N | | 17 | | | | | | 17 | | | | 17 | | | |

# TABLE I-E-15 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 1 (Continued)

RESULTS OF FIRST GENERATION - FIRST MATING (F1a)

DOSE - 300 PPM

| | | DAY 0 | | | | | DAY 4 | | | | DAY 21 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT | DEATHS DAY 1-4 | LIVE PUPS | SEX M/F | LITTER REDUCED M/F | DEATHS DAY 4-21 | LIVE PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT |
| 5060 | 5050 | 16 | | 8/8 | 6 | 6 | | 16 | 8/8 | 4/4 | | 8 | 4/4 | 49 | 45 |
| 5061 | 5050 | 12 | | 6/6 | 6 | 6 | | 12 | 6/6 | 4/4 | | 8 | 4/4 | 52 | 50 |
| 5062 | 5051 | | | | | | | | | | | | | | |
| 5063 | 5051 | 13 | 1 | 7/6 | 6 | 6 | | 13 | 7/6 | 4/4 | | 8 | 4/4 | 56 | 51 |
| 5064 | 5052 | 14 | | 7/7 | 7 | 6 | | 14 | 7/7 | 4/4 | | 8 | 4/4 | 49 | 45 |
| 5065 | 5052 | 14 | | 7/7 | 6 | 6 | | 14 | 7/7 | 4/4 | | 8 | 4/4 | 46 | 47 |
| 5066 | 5053 | 14 | 1 | 7/7 | 6 | 6 | | 14 | 7/7 | 4/4 | | 8 | 4/4 | 45 | 44 |
| 5067 | 5053 | 11 | | 5/6 | 6 | 6 | 1 | 10 | 4/6 | 4/4 | | 8 | 4/4 | 48 | 53 |
| 5068 | 5054 | 7 | 4 | 5/2 | 6 | 6 | | 7 | 5/2 | 5/2 | 1 | 6 | 4/2 | 47 | 60 |
| 5069 | 5054 | 14 | | 7/7 | 6 | 6 | 1 | 13 | 7/6 | 4/4 | | 8 | 4/4 | 58 | 44 |
| 5070 | 5055 | 15 | | 5/10 | 6 | 6 | | 15 | 5/10 | 4/4 | | 8 | 4/4 | 49 | 44 |
| 5071 | 5055 | 17 | | 7/10 [a] | 5 | 6 | 1 | 16 | 7/9 | 4/4 | | 8 | 4/4 | 44 | 44 |
| 5072 | 5056 | 13 | | 4/9 | 7 | 6 | 1 | 12 | 3/9 | 3/5 | | 8 | 3/5 | 50 | 46 |
| 5073 | 5056 | | | | | | | | | | | | | | |
| 5074 | 5057 | 16 | | 6/10 | 7 | 6 | | 16 | 6/10 | 4/4 | | 8 | 4/4 | 47 | 45 |
| 5075 | 5057 | 18 | | 7/11 | 6 | 6 | 1 | 17 | 6/11 | 4/4 | | 8 | 4/4 | 48 | 47 |
| 5076 | 5058 | 15 | | 5/10 | 7 | 6 | | 15 | 5/10 | 4/4 | | 8 | 4/4 | 60 | 57 |
| 5077 | 5058 | | | | | | | | | | | | | | |
| 5078 | 5059 | 11 | | 6/5 | 7 | 6 | | 11 | 6/5 | 4/4 | | 8 | 4/4 | 56 | 51 |
| 5079 | 5059 | 11 | | 8/3 | 6 | 6 | | 11 | 8/3 | 5/3 | | 8 | 5/3 | 52 | 49 |
| TOTAL | | 231 | 6 | 107/124 | | | 5 | 226 | 104/122 | 69/66 | 1 | 134 | 68/66 | | |
| MEAN | | 14 | | | 6 | 6 | | 13 | | | | 8 | | 50 | 48 |
| SD | | 2.7 | | | 0.6 | 0.0 | | 2.6 | | | | 0.5 | | 4.7 | 4.7 |
| SE | | 0.7 | | | 0.1 | 0.0 | | 0.6 | | | | 0.1 | | 1.1 | 1.1 |
| N | | 17 | | | | | | 17 | | | | 17 | | | |

[a] Pup mis-sexed at Day 0.

# TABLE I-E-15 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 1 (Continued)

RESULTS OF FIRST GENERATION - FIRST MATING (F1a)

DOSE - 3000 PPM

| | | DAY 0 | | | | | DAY 4 | | | | DAY 21 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT | DEATHS DAY 1-4 | LIVE PUPS | SEX M/F | LITTER REDUCED M/F | DEATHS DAY 4-21 | LIVE PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT |
| 5090 | 5080 | | | | | | | | | | | | | | |
| 5091 | 5080 | 13 | | 4/9 | 6 | 6 | | 13 | 4/9 | 4/4 | | 8 | 4/4 | 52 | 52 |
| 5092 | 5081 | 14 | | 10/4 | 7 | 7 | | 14 | 10/4 | 4/4 | | 8 | 4/4 | 51 | 48 |
| 5093 | 5081 | 11 | | 6/5 | 8 | 8 | | 11 | 6/5 | 4/4 | | 8 | 4/4 | 63 | 60 |
| 5094 | 5082 | | | | | | | | | | | | | | |
| 5095 | 5082 | 13 | | 9/4 | 8 | 7 | | 13 | 9/4 | 4/4 | | 8 | 4/4 | 57 | 59 |
| 5096 | 5083 | 18 | | 11/7 | 6 | 6 | | 18 | 11/7 | 4/4 | | 8 | 4/4 | 54 | 51 |
| 5097 | 5083 | 14 | | 5/9 | 7 | 6 | | 14 | 5/9 | 4/4 | | 8 | 4/4 | 59 | 57 |
| 5098 | 5084 | 11 | | 5/6 | 7 | 6 | | 11 | 5/6 | 4/4 | | 8 | 4/4 | 59 | 50 |
| 5099 | 5084 | 12 | | 5/7 | 7 | 6 | | 12 | 5/7 | 4/4 | | 8 | 4/4 | 49 | 45 |
| 5100 | 5085 | 14 | | 4/10 | 8 | 7 | | 14 | 4/10 | 4/4 | | 8 | 4/4 | 46 | 45 |
| 5101 | 5085 | 12 | | 4/8 | 7 | 7 | | 12 | 4/8 | 4/4 | | 8 | 4/4 | 51 | 52 |
| 5102 | 5086 | 13 | | 8/5 | 7 | 6 | | 13 | 8/5 | 4/4 | | 8 | 4/4 | 51 | 47 |
| 5103 | 5086 | | | | | | | | | | | | | | |
| 5104 | 5087 | 13 | | 7/6 | 8 | 7 | | 13 | 7/6 | 4/4 | | 8 | 4/4 | 51 | 48 |
| 5105 | 5087 | 12 | 2 | 3/9 | 7 | 6 | | 12 | 3/9 | 3/5 | | 8 | 3/5 | 59 | 56 |
| 5106 | 5088 | 14 | | 7/7 | 7 | 6 | | 14 | 7/7 | 4/4 | | 8 | 4/4 | 48 | 46 |
| 5107 | 5088 | 11 | | 7/4 | 7 | 7 | | 11 | 7/4 | 4/4 | | 8 | 4/4 | 58 | 56 |
| 5108 | 5089 | 11 | | 5/6 | 6 | 6 | | 11 | 5/6 | 4/4 | | 8 | 4/4 | 41 | 41 |
| 5109[a] | | | | | | | | | | | | | | | |
| TOTAL | | 206 | 2 | 100/106 | | | | 206 | 100/106 | 63/65 | | 128 | 63/65 | | |
| MEAN | | 13 | | | 7 | 7 | | 13 | | | | 8 | | 53 | 51 |
| SD | | 1.8 | | | 0.7 | 0.6 | | 1.8 | | | | 0.0 | | 5.8 | 5.6 |
| SE | | 1.5 | | | 0.2 | 0.2 | | 0.5 | | | | 0.0 | | 1.4 | 1.4 |
| N | | 16 | | | | | | 16 | | | | 16 | | | |

[a]Death recorded during sixth study week.

TABLE I-E-16

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 2

LITTER OBSERVATIONS

FIRST GENERATION - FIRST MATING (F1a)

| DOSE (PPM) | FEMALE NUMBER | DAY OF LACTATION | OBSERVATION |
|---|---|---|---|
| 0 | 5033 | 2 | ONE MALE PUP - FOUND DEAD; NO ABNORMALITIES NOTED. |
| | 5038 | 19 | ONE FEMALE PUP - FOUND DEAD. |
| | 5042 | 21 | ONE FEMALE PUP - OPACITY RIGHT EYE. |
| 300 | 5063 | 0 | ONE MALE PUP - FOUND DEAD. |
| | 5066 | 0 | ONE MALE PUP - FOUND DEAD. |
| | 5068 | 0 | ONE MALE PUP - FOUND DEAD. |
| | | 0 | ONE FEMALE PUP - FOUND DEAD. |
| | 5071 | 2 | ONE MALE PUP - FOUND DEAD. |
| | 5072 | 2 | ONE MALE PUP - FOUND DEAD. |
| | 5075 | 2 | ONE MALE PUP - FOUND DEAD. |
| 3000 | 5105 | 0 | TWO MALE PUPS - FOUND DEAD. |

TABLE I-E-17

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 3

PUP NECROPSY OBSERVATIONS (F1a) AT DAY 21

| DOSE (PPM) | FEMALE NUMBER | NUMBER OF PUPS | OBSERVATION |
|---|---|---|---|
| 0 | 5030 | 8 | ALL TISSUES APPEAR NORMAL |
| | 5031 | 8 | ALL TISSUES APPEAR NORMAL |
| | 5033 | 8 | ALL TISSUES APPEAR NORMAL |
| | 5037 | 8 | ALL TISSUES APPEAR NORMAL |
| | 5039 | 8 | ALL TISSUES APPEAR NORMAL |
| 300 | 5060 | 8 | ALL TISSUES APPEAR NORMAL |
| | 5064 | 8 | ALL TISSUES APPEAR NORMAL |
| | 5069 | 8 | ALL TISSUES APPEAR NORMAL |
| | 5070 | 8 | ALL TISSUES APPEAR NORMAL |
| | 5074 | 8 | ALL TISSUES APPEAR NORMAL |
| | 5075 | 8 | ALL TISSUES APPEAR NORMAL |
| 3000 | 5093 | 8 | ALL TISSUES APPEAR NORMAL |
| | 5095 | 8 | ALL TISSUES APPEAR NORMAL |
| | 5098 | 8 | ALL TISSUES APPEAR NORMAL |
| | 5104 | 8 | ALL TISSUES APPEAR NORMAL |
| | 5106 | 8 | ALL TISSUES APPEAR NORMAL |
| | 5107 | 8 | ALL TISSUES APPEAR NORMAL |

# TABLE I-E-18

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 4

RESULTS OF FIRST GENERATION - SECOND MATING (F1b)

DOSE - 0 PPM

| | | DAY 0 | | | | | DAY 4 | | | | DAY 21 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT | DEATHS DAY 1-4 | LIVE PUPS | SEX M/F | LITTER REDUCED M/F | DEATHS DAY 4-21 | LIVE PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT |
| 5030 | 5029 | 15 | | 7/8 | 7 | 6 | | 15 | 7/8 | 4/4 | | 8 | 4/4 | 50 | 45 |
| 5031 | 5029 | 16 | | 7/9 | 6 | 6 | | 16 | 7/9 | 4/4 | | 8 | 4/4 | 51 | 45 |
| 5032 | 5028 | 12 | | 5/7 | 6 | 7 | 2 | 10 | 4/6 | 4/4 | | 8 | 4/4 | 45 | 40 |
| 5033 | 5028 | 15 | | 6/9 | 6 | 6 | | 15 | 6/9 | 4/4 | 1 | 7 | 3/4 | 46 | 48 |
| 5034 | 5027 | | | | | | | | | | | | | | |
| 5035 | 5027 | | | | | | | | | | | | | | |
| 5036 | 5026 | 15 | | 9/6 | 6 | 6 | 1 | 14 | 8/6 | 4/4 | | 8 | 4/4 | 50 | 48 |
| 5037 | 5026 | 14 | | 4/10 | 6 | 6 | 1 | 13 | 3/10 | 3/5 | | 8 | 4/4[a] | 40 | 37 |
| 5038 | 5025 | 13 | | 9/4 | | 6 | | 13 | 9/4 | 4/4 | | 8 | 4/4 | 40 | 40 |
| 5039 | 5025 | | | | | | | | | | | | | | |
| 5040 | 5024 | 16 | | 11/5 | 8 | 7 | | 16 | 11/5 | 4/4 | | 8 | 4/4 | 51 | 47 |
| 5041 | 5024 | 13 | | 7/6 | 6 | 6 | 1 | 12 | 6/6 | 4/4 | | 8 | 4/4 | 42 | 38 |
| 5042 | 5023 | 15 | | 4/11 | 6 | 6 | 1 | 14 | 4/10 | 4/4 | | 8 | 4/4 | 50 | 45 |
| 5043 | 5023 | 11 | | 5/6 | 7 | 6 | | 11 | 5/6 | 4/4 | | 8 | 4/4 | 46 | 43 |
| 5044 | 5022 | 11 | | 4/7 | 8 | 8 | | 11 | 4/7 | 4/4 | | 8 | 4/4 | 45 | 43 |
| 5045 | 5022 | | | | | | | | | | | | | | |
| 5046 | 5021 | 10 | | 4/6 | 7 | 8 | 1 | 9 | 3/6 | 3/5 | 1 | 7 | 3/4 | 56 | 54 |
| 5047 | 5021 | 13 | | 7/6 | 6 | 6 | 2 | 11 | 6/5 | 4/4 | | 8 | 4/4 | 29 | 26 |
| 5048 | 5020 | 12 | 2 | 6/6 | 7 | 6 | | 12 | 6/6 | 4/4 | | 8 | 4/4 | 39 | 32 |
| 5049 | 5020 | 14 | | 5/9 | 8 | 7 | | 14 | 5/9 | 4/4 | | 8 | 4/4 | 53 | 52 |
| TOTAL | | 204 | 2 | 96/108 | | | 9 | 195 | 90/105 | 58/62 | 2 | 118 | 58/60 | | |
| MEAN | | 14 | | | 7 | 6 | | 13 | | | | 8 | | 46 | 43 |
| SD | | 1.8 | | | 0.7 | 0.6 | | 2.1 | | | | 0.4 | | 7.0 | 7.8 |
| SE | | 0.5 | | | 0.2 | 0.2 | | 0.6 | | | | 0.1 | | 1.9 | 2.0 |
| N | | 16 | | | | | | 16 | | | | 16 | | | |

[a]Pup mis-sexed at Day 4; corrected at Day 21.

# TABLE I-E-18 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 4 (Continued)

RESULTS OF FIRST GENERATION - SECOND MATING (F1b)

DOSE - 300 PPM

| | | DAY 0 | | | | | DAY 4 | | | | DAY 21 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT | DEATHS DAY 1-4 | LIVE PUPS | SEX M/F | LITTER REDUCED M/F | DEATHS DAY 4-21 | LIVE PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT |
| 5060 | 5059 | 12 | 2 | 7/5 | 7 | 7 | | 12 | 7/5 | 4/4 | | 8 | 4/4 | 46 | 45 |
| 5061 | 5059 | 13 | | 8/5 | 7 | 6 | | 13 | 8/5 | 4/4 | | 8 | 4/4 | 52 | 49 |
| 5062 | 5058 | | | | | | | | | | | | | | |
| 5063 | 5058 | 17 | | 4/13 | 7 | 6 | 1 | 16 | 4/12 | 4/4 | | 8 | 4/4 | 54 | 48 |
| 5064 | 5057 | 19 | | 8/11 | 6 | 6 | 1 | 18 | 7/11 | 4/4 | | 8 | 4/4 | 35 | 33 |
| 5065 | 5057 | 15 | | 0/15[a] | | 8 | | 15 | 0/15 | 4/4 | | 8 | 4/4 | 51 | 51 |
| 5066 | 5056 | 10 | | 3/7 | 6 | 7 | | 10 | 3/7 | 3/5 | | 8 | 3/5 | 49 | 50 |
| 5067 | 5056 | 12 | | 4/8 | 6 | 6 | | 12 | 4/8 | 4/4 | | 8 | 4/4 | 49 | 45 |
| 5068 | 5055 | 15 | | 9/6 | 6 | 6 | 1 | 14 | 8/6 | 4/4 | | 8 | 4/4 | 50 | 50 |
| 5069 | 5055 | 15 | | 6/9 | 7 | 6 | | 15 | 6/9 | 4/4 | | 8 | 4/4 | 52 | 50 |
| 5070 | 5054 | 14 | | 7/7 | 6 | 6 | 1 | 13 | 7/6 | 4/4 | | 8 | 4/4 | 50 | 46 |
| 5071 | 5054 | | | | | | | | | | | | | | |
| 5072 | 5053 | 12 | | 8/4 | 6 | 6 | | 12 | 8/4 | 4/4 | | 8 | 4/4 | 40 | 40 |
| 5073 | 5053 | 13 | | 6/7 | 6 | 6 | | 13 | 6/7 | 4/4 | | 8 | 4/4 | 53 | 54 |
| 5074 | 5052 | 13 | | 5/8 | 7 | 8 | | 13 | 5/8 | 4/4 | | 8 | 4/4 | 42 | 42 |
| 5075 | 5052 | 10 | | 6/4 | 7 | 7 | | 10 | 6/4 | 4/4 | | 8 | 4/4 | 54 | 54 |
| 5076 | 5051 | 13 | 1 | 6/7 | 8 | 7 | | 13 | 6/7 | 4/4 | | 8 | 4/4 | 51 | 52 |
| 5077 | 5051 | 14 | | 7/7 | 7 | 7 | | 14 | 7/7 | 4/4 | | 8 | 4/4 | 53 | 52 |
| 5078 | 5050 | 12 | | 6/6 | 7 | 7 | | 12 | 6/6 | 4/4 | | 8 | 4/4 | 56 | 54 |
| 5079 | 5050 | 14 | | 7/7 | 6 | 6 | | 14 | 7/7 | 4/4 | | 8 | 4/4 | 41 | 41 |
| TOTAL | | 243 | 3 | 107/136 | | | 4 | 239 | 105/134 | 71/73 | 0 | 144 | 71/73 | | |
| MEAN | | 14 | | | 7 | 7 | | 13 | | | | 8 | | 49 | 48 |
| SD | | 2.2 | | | 0.6 | 0.7 | | 2.0 | | | | 0.0 | | 5.7 | 5.7 |
| SE | | 0.5 | | | 0.2 | 0.2 | | 0.5 | | | | 0.0 | | 1.3 | 1.3 |
| N | | 18 | | | | | | 18 | | | | 18 | | | |

[a]Pups mis-sexed at Day 0.

# TABLE I-E-18 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 4 (Continued)

RESULTS OF FIRST GENERATION - SECOND MATING (F1b)

DOSE - 3000 PPM

| | | DAY 0 | | | | | DAY 4 | | | | DAY 21 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT | DEATHS DAY 1-4 | LIVE PUPS | SEX M/F | LITTER REJECTED M/F | DEATHS DAY 4-21 | LIVE PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT |
| 5090 | 5089 | 11 | | 4/7 | 7 | 6 | | 11 | 4/7 | 4/4 | | 8 | 4/4 | 57 | 52 |
| 5091 | 5089 | 14 | | 6/8 | 8 | 8 | | 14 | 6/8 | 4/4 | | 8 | 4/4 | 41 | 45 |
| 5092 | 5088 | 14 | | 7/7 | 7 | 7 | | 14 | 7/7 | 4/4 | | 8 | 4/4 | 53 | 51 |
| 5093 | 5088 | 16 | | 11/5 | 7 | 7 | | 16 | 11/5 | 4/4 | | 8 | 4/4 | 54 | 50 |
| 5094 | 5087 | 12 | | 4/8 | 7 | 7 | | 12 | 4/8 | 4/4 | | 8 | 4/4 | 52 | 47 |
| 5095 | 5087 | 12 | | 5/7 | 7 | 7 | | 12 | 5/7 | 4/4 | | 8 | 4/4 | 65 | 58 |
| 5096 | 5086 | 14 | | 6/8 | 7 | 7 | | 14 | 6/8 | 4/4 | | 8 | 4/4 | 61 | 58 |
| 5097 | 5086 | | | | | | | | | | | | | | |
| 5098 | 5085 | 11 | 2 | 7/4 | 7 | 6 | | 11 | 7/4 | 4/4 | | 8 | 4/4 | 54 | 49 |
| 5099 | 5085 | 16 | | 11/5 | 7 | 6 | | 16 | 11/5 | 4/4 | | 8 | 4/4 | 34 | 29 |
| 5100 | 5084 | 14 | | 8/6 | 7 | 7 | | 14 | 8/6 | 4/4 | | 8 | 4/4 | 54 | 51 |
| 5101 | 5084 | 13 | | 7/6 | 7 | 6 | | 13 | 7/6 | 4/4 | | 8 | 4/4 | 61 | 59 |
| 5102 | 5083 | | | | | | | | | | | | | | |
| 5103 | 5083 | 15 | | 11/4 | 7 | 7 | 1 | 14 | 10/4 | 4/4 | | 8 | 4/4 | 39 | 38 |
| 5104 | 5082 | 14 | | 6/8 | 7 | 7 | | 14 | 6/8 | 4/4 | 1 | 7 | 3/4 | 54 | 54 |
| 5105 | 5082 | 8 | | 3/5 | 8 | 7 | | 8 | 3/5 | 3/5 | | 8 | 3/5 | 54 | 49 |
| 5106 | 5081 | 10 | 5 | 4/6 | 8 | 7 | | 10 | 4/6 | 4/4 | 1 | 7 | 3/4 | 54 | 49 |
| 5107 | 5081 | 4 | | 2/2 | 8 | 8 | | 4 | 2/2 | 2/2 | | 4 | 2/2 | 60 | 60 |
| 5108 | 5080 | 11 | | 6/5 | 6 | 6 | | 11 | 6/5 | 4/4 | | 8 | 4/4 | 43 | 43 |
| TOTAL | | 209 | 7 | 108/101 | | | 1 | 208 | 107/101 | 65/67 | 2 | 130 | 63/67 | | |
| MEAN | | 12 | | | 7 | 7 | | 12 | | | | 8 | | 53 | 50 |
| SD | | 3.0 | | | 0.6 | 0.7 | | 3.2 | | | | 1.0 | | 8.2 | 7.8 |
| SE | | 0.7 | | | 0.1 | 0.2 | | 0.8 | | | | 0.2 | | 2.1 | 2.0 |
| N | | 17 | | | | | | 17 | | | | 17 | | | |

TABLE I-E-19

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 5

LITTER OBSERVATIONS

FIRST GENERATION - SECOND MATING (F1b)

| DOSE (PPM) | FEMALE NUMBER | DAY OF LACTATION | OBSERVATION |
|---|---|---|---|
| 0 | 5040 | 0 | ONE FEMALE PUP - SUBCUTANEOUS HEMATOMA, DORSAL-THORACIC AREA. |
| 3000 | 5092 | 0 | ONE FEMALE PUP - SUBCUTANEOUS HEMATOMA, TOP OF NOSE. |
| | 5095 | 0 | ONE FEMALE PUP - BLEEDING FROM LACERATION, RIGHT EAR. |
| | 5096 | 0 | ONE FEMALE PUP - SUBCUTANEOUS HEMATOMA, TOP OF NOSE. |
| | 5096 | 0 | ONE FEMALE PUP - SUBCUTANEOUS HEMATOMA, RIGHT EAR |

TABLE I-E-20

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 6

BODY WEIGHTS AND FOOD CONSUMPTION (G) OF PARENT RATS (Fo)

BODY WEIGHTS

| DOSE (PPM) | | MALES WK 4 | WK 9 | WK 11 | WK 20 |
|---|---|---|---|---|---|
| 0 | MEAN | 301 | 435 | 458 | 551 |
| | SD | 21.2 | 34.2 | 42.3 | 45.5 |
| | SE | 6.7 | 10.8 | 13.4 | 14.4 |
| | N | 10 | 10 | 10 | 10 |
| 300 | MEAN | 290 | 438 | 468 | 562 |
| | SD | 26.1 | 38.5 | 42.2 | 50.6 |
| | SE | 8.3 | 12.2 | 13.4 | 16.0 |
| | N | 10 | 10 | 10 | 10 |
| 3000 | MEAN | 288 | 426 | 453 | 532 |
| | SD | 20.0 | 30.8 | 38.7 | 42.4 |
| | SE | 6.3 | 9.7 | 12.2 | 13.4 |
| | N | 10 | 10 | 10 | 10 |

FOOD CONSUMPTION

| DOSE (PPM) | | MALES WK 4 | WK 9 | WK 11 | WK 20 |
|---|---|---|---|---|---|
| 0 | MEAN | 22.0 | 25.4 | 23.8 | 23.2 |
| | SD | 2.2 | 2.5 | 3.8 | 4.0 |
| | SE | 0.7 | 0.8 | 1.2 | 1.3 |
| | N | 10 | 9 | 10 | 10 |
| 300 | MEAN | 21.7 | 24.9 | 24.2 | 22.9 |
| | SD | 1.5 | 1.0 | 1.4 | 2.4 |
| | SE | 0.6 | 0.4 | 0.5 | 0.8 |
| | N | 7 | 7 | 8 | 10 |
| 3000 | MEAN | 21.7 | 24.6 | 23.7 | 24.5 |
| | SD | 1.5 | 1.6 | 2.1 | 2.9 |
| | SE | 0.5 | 0.6 | 0.8 | 0.9 |
| | N | 10 | 8 | 7 | 10 |

TABLE I-E-20 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 6 (Continued)

BODY WEIGHTS AND FOOD CONSUMPTION (G) OF PARENT RATS (Fo)

BODY WEIGHTS

| DOSE (PPM) | | FEMALES WK 4 | WK 9 | WK 11 | WK 20 |
|---|---|---|---|---|---|
| 0 | MEAN | 189 | 246 | 255 | 299 |
| | SD | 11.7 | 14.8 | 26.0 | 14.7 |
| | SE | 2.6 | 3.3 | 5.8 | 3.3 |
| | N | 20 | 20 | 20 | 20 |
| 300 | MEAN | 193 | 249 | 261 | 301 |
| | SD | 11.5 | 15.7 | 17.4 | 18.0 |
| | SE | 2.6 | 3.5 | 3.9 | 4.0 |
| | N | 20 | 20 | 20 | 20 |
| 3000 | MEAN | 195 | 252 | 263 | 296 |
| | SD | 19.0 | 26.0 | 26.1 | 24.3 |
| | SE | 4.2 | 6.0 | 6.0 | 5.6 |
| | N | 20 | 19 | 19 | 19 |

FOOD CONSUMPTION

| DOSE (PPM) | | FEMALES WK 4 | WK 9 | WK 11 | WK 20 |
|---|---|---|---|---|---|
| 0 | MEAN | 16.1 | 19.3 | 19.3 | 21.2 |
| | SD | 2.0 | 2.5 | 3.3 | 3.2 |
| | SE | 0.5 | 0.6 | 0.8 | 0.7 |
| | N | 18 | 19 | 19 | 19 |
| 300 | MEAN | 15.9 | 19.1 | 18.8 | 20.6 |
| | SD | 1.8 | 3.1 | 3.0 | 3.2 |
| | SE | 0.4 | 0.7 | 0.7 | 0.7 |
| | N | 19 | 20 | 20 | 19 |
| 3000 | MEAN | 16.9 | 19.9 | 18.9 | 21.9 |
| | SD | 2.4 | 3.4 | 3.6 | 4.5 |
| | SE | 0.5 | 0.8 | 0.8 | 1.0 |
| | N | 20 | 19 | 19 | 19 |

TABLE 7

:OXICOLOGY OBSERVATION REPORT

LINICAL SIGNS
PROJECT NUMBER - 10734-06

| /EEK IO. | ** DOSE GROUP/SEX * | ANIMAL NUMBER ***** | OBSERVATIONS : QUALIFIER COMMENTS ********** |
|---|---|---|---|
| ·001 | CONTROL MALE | 05020 | STARTED |
| | | ***** | APRIL 8,1977 |
| | | | 3 GENERATION REPRODUCTION-RAT |
| 001 | CONTROL FEMALE | 05030 | EYE OPACITY-RIGHT EYE |
| 002 | CONTROL FEMALE | 05030 | EYE OPACITY-RIGHT EYE |
| | 300 PPM MALE | 05050 | SKIN REDNESS : EYE-RIGHT |
| 003 | CONTROL FEMALE | 05030 | EYE OPACITY-RIGHT EYE |
| | 300 PPM MALE | 05052 | SOFT STOOL |
| | FEMALE | 05075 | EAR TAG LOST |
| | 3000 PPM | 05094 | EAR TAG LOST |
| 004 | CONTROL FEMALE | 05030 | EYE OPACITY-RIGHT EYE |
| | 300 PPM MALE | 05055 | ULCERATION : LATERAL-RIGHT,NECK |
| | FEMALE | 05070 | EAR TAG LOST |
| | 3000 PPM MALE | 05087 | EAR TAG LOST |
| | FEMALE | 05090 | EAR TAG LOST |
| 005 | CONTROL FEMALE | 05030 | EYE OPACITY-RIGHT EYE |
| | 300 PPM MALE | 05055 | ULCERATION : LATERAL-RIGHT,NECK |
| | 3000 PPM FEMALE | 05109 | FOUND DEAD |
| 006 | CONTROL FEMALE | 05030 | EYE OPACITY-RIGHT EYE |
| | 300 PPM MALE | 05055 | ULCERATION : LATERAL-RIGHT,NECK |
| | 3000 PPM FEMALE | 05093 | LOCAL HAIR LOSS : LIMBS-FORE |
| 007 | CONTROL MALE | 05023 | MISSING EAR TAG |
| | FEMALE | 05030 | EYE OPACITY-RIGHT EYE |
| | 300 PPM MALE | 05055 | LOCAL HAIR LOSS : LATERAL-RIGHT,NECK |
| | 3000 PPM FEMALE | 05093 | LOCAL HAIR LOSS : LIMBS-FORE |
| 008 | CONTROL FEMALE | 05030 | EYE OPACITY-RIGHT EYE |
| | 3000 PPM | 05093 | LOCAL HAIR LOSS : LIMBS-FORE |
| 009 | CONTROL FEMALE | 05030 | EYE OPACITY-RIGHT EYE |
| | 3000 PPM | 05093 | LOCAL HAIR LOSS : LIMBS-FORE |
| 010 | CONTROL FEMALE | 05030 | EYE OPACITY-RIGHT EYE |
| | 3000 PPM | 05091 | EYE DISCHARGE : EYE-RIGHT:AROUND |
| | | 05093 | LOCAL HAIR LOSS : LIMBS-FORE |

TABLE 7 (CONTINUED)

TOXICOLOGY OBSERVATION REPORT

CLINICAL SIGNS
PROJECT NO. - 10734-06

| WEEK NO. | ** DOSE GROUP/SEX * | ANIMAL NUMBER | ***** OBSERVATIONS : QUALIFIER COMMENTS ********** |
|---|---|---|---|
| 011 | CONTROL MALE | 05020 | MATE TO GET F1A |
| | FEMALE | 05030 | EYE OPACITY-RIGHT EYE |
| | 300 PPM | 05066 | LOCAL HAIR LOSS : LIMB-FORE,RIGHT |
| 012 | CONTROL FEMALE | 05030 | EYE OPACITY-RIGHT EYE |
| | 300 PPM | 05066 | LOCAL HAIR LOSS : LIMB-FORE,RIGHT |
| 013 | CONTROL FEMALE | 05030 | EYE OPACITY-RIGHT EYE |
| | 300 PPM | 05066 | LOCAL HAIR LOSS : LIMB-FORE,RIGHT |
| 014 | CONTROL FEMALE | 05030 | EYE OPACITY-RIGHT EYE |
| | 300 PPM | 05066 | LOCAL HAIR LOSS : LIMB-FORE,RIGHT |
| 015 | CONTROL FEMALE | 05030 | EYE OPACITY-RIGHT EYE |
| | 300 PPM | 05066 | LOCAL HAIR LOSS : LIMB-FORE,RIGHT |
| | 3000 PPM MALE | 05083 | EYE PARTIALLY CLOSED : EYE-LEFT |
| 016 | CONTROL FEMALE | 05030 | EYE OPACITY-RIGHT EYE |
| | 300 PPM | 05066 | LOCAL HAIR LOSS : LIMB-FORE,RIGHT |
| | 3000 PPM MALE | 05083 | EYE PARTIALLY CLOSED : EYE-LEFT |
| 017 | CONTROL FEMALE | 05030 | EYE OPACITY-RIGHT EYE |
| | 300 PPM | 05066 | LOCAL HAIR LOSS : LIMB-FORE,RIGHT |
| | 3000 PPM MALE | 05083 | EYE PARTIALLY CLOSED : EYE-LEFT |
| 018 | CONTROL FEMALE | 05030 | EYE OPACITY-RIGHT EYE |
| | 300 PPM MALE | 05052 | CRUST : NOSE:AROUND |
| | | ***** | RED |
| | 3000 PPM | 05083 | EYE PARTIALLY CLOSED : EYE-LEFT |
| 019 | CONTROL FEMALE | 05030 | LOCAL HAIR LOSS : LIMBS-FORE |
| | | | EYE OPACITY-RIGHT EYE |
| | | 05034 | LOCAL HAIR LOSS : LIMB-FORE,LEFT |
| 020 | CONTROL MALE | 05020 | MATE TO GET F1B |
| | | | MATE TO GET F1B |
| | FEMALE | 05030 | LOCAL HAIR LOSS : LIMBS-FORE |
| | | | EYE OPACITY-RIGHT EYE |
| | | 05034 | LOCAL HAIR LOSS : LIMB-FORE,LEFT |
| 021 | CONTROL FEMALE | 05030 | EYE OPACITY-RIGHT EYE |
| | 3000 PPM | 05102 | LOCAL HAIR LOSS : LIMBS-FORE |
| | | 05103 | LOCAL HAIR LOSS : LIMB-FORE,RIGHT |
| 022 | CONTROL FEMALE | 05030 | EYE OPACITY-RIGHT EYE |
| | 3000 PPM | 05102 | LOCAL HAIR LOSS : LIMBS-FORE |
| | | 05103 | LOCAL HAIR LOSS : LIMB-FORE,RIGHT |

TABLE 7 (CONTINUED)

TOXICOLOGY OBSERVATION REPORT

CLINICAL SIGNS
PROJECT NO. - 10734-06

| WEEK NO. | ** DOSE GROUP/SEX * | | ANIMAL NUMBER | ***** OBSERVATIONS : QUALIFIER COMMENTS ********** |
|---|---|---|---|---|
| 023 | CONTROL | FEMALE | 05030 | EYE OPACITY-RIGHT EYE |
| | 3000 PPM | | 05102 | LOCAL HAIR LOSS : LIMBS-FORE |
| | | | 05103 | LOCAL HAIR LOSS : LIMB-FORE,RIGHT |
| 024 | CONTROL | FEMALE | 05030 | EYE OPACITY-RIGHT EYE |
| | 3000 PPM | | 05102 | LOCAL HAIR LOSS : LIMBS-FORE |
| | | | 05103 | LOCAL HAIR LOSS : LIMB-FORE,RIGHT |
| 025 | CONTROL | FEMALE | 05030 | EYE OPACITY-RIGHT EYE |
| | 3000 PPM | | 05102 | LOCAL HAIR LOSS : LIMBS-FORE |
| | | | 05103 | LOCAL HAIR LOSS : LIMB-FORE,RIGHT |
| 026 | CONTROL | FEMALE | 05030 | EYE OPACITY-RIGHT EYE |
| | 3000 PPM | | 05102 | LOCAL HAIR LOSS : LIMBS-FORE |
| | | | 05103 | LOCAL HAIR LOSS : LIMB-FORE,RIGHT |
| 027 | CONTROL | FEMALE | 05030 | EYE OPACITY-RIGHT EYE |
| | 3000 PPM | | 05102 | LOCAL HAIR LOSS : LIMBS-FORE |
| | | | 05103 | LOCAL HAIR LOSS : LIMB-FORE,RIGHT |

TABLE I-E-22

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 8

PARENT NECROPSY OBSERVATIONS (F0) - MALES

| DOSE (PPM) | MALE NUMBER | OBSERVATION |
|---|---|---|
| 0 | 5020 | ALL TISSUES APPEAR NORMAL |
| | 5021 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5022 | ALL TISSUES APPEAR NORMAL |
| | 5023 | ALL TISSUES APPEAR NORMAL |
| | 5024 | ALL TISSUES APPEAR NORMAL |
| | 5025 | ALL TISSUES APPEAR NORMAL |
| | 5026 | ALL TISSUES APPEAR NORMAL |
| | 5027 | ALL TISSUES APPEAR NORMAL |
| | 5028 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5029 | ULCERATION (3 X 3 CM) RIGHT LATERAL THORACIC REGION; ALL TISSUES APPEAR NORMAL |
| 300 | 5050 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5051 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5052 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5053 | ALL TISSUES APPEAR NORMAL |
| | 5054 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5055 | ALL TISSUES APPEAR NORMAL |
| | 5056 | ALL TISSUES APPEAR NORMAL |
| | 5057 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5058 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5059 | ALL TISSUES APPEAR NORMAL |
| 3000 | 5080 | ALL TISSUES APPEAR NORMAL |
| | 5081 | ALL TISSUES APPEAR NORMAL |
| | 5082 | ALL TISSUES APPEAR NORMAL |
| | 5083 | ALL TISSUES APPEAR NORMAL |
| | 5084 | ALL TISSUES APPEAR NORMAL |
| | 5085 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5086 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5087 | BOTH KIDNEYS PALE AND PITTED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5088 | ALL TISSUES APPEAR NORMAL |
| | 5089 | ALL TISSUES APPEAR NORMAL |

TABLE I-E-22 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 8 (Continued)

PARENT NECROPSY OBSERVATIONS (FO) - FEMALES

| DOSE (PPM) | FEMALE NUMBER | OBSERVATION |
|---|---|---|
| 0 | 5030 | RIGHT EYE OPAQUE; ALL TISSUES APPEAR NORMAL |
| | 5031 | ALL TISSUES APPEAR NORMAL |
| | 5032 | ALL TISSUES APPEAR NORMAL |
| | 5033 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5034 | DIARRHEA, BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5035 | ALL TISSUES APPEAR NORMAL |
| | 5036 | ALL TISSUES APPEAR NORMAL |
| | 5037 | ALL TISSUES APPEAR NORMAL |
| | 5038 | ALL TISSUES APPEAR NORMAL |
| | 5039 | ALL TISSUES APPEAR NORMAL |
| | 5040 | ALL TISSUES APPEAR NORMAL |
| | 5041 | ALL TISSUES APPEAR NORMAL |
| | 5042 | ALL TISSUES APPEAR NORMAL |
| | 5043 | ALL TISSUES APPEAR NORMAL |
| | 5044 | ALL TISSUES APPEAR NORMAL |
| | 5045 | ALL TISSUES APPEAR NORMAL |
| | 5046 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5047 | ALL TISSUES APPEAR NORMAL |
| | 5048 | ALL TISSUES APPEAR NORMAL |
| | 5049 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| 300 | 5060 | ALL TISSUES APPEAR NORMAL |
| | 5061 | ALL TISSUES APPEAR NORMAL |
| | 5062 | ALL TISSUES APPEAR NORMAL |
| | 5063 | ALL TISSUES APPEAR NORMAL |
| | 5064 | NECROPSY NOT PERFORMED |
| | 5065 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5066 | ALL TISSUES APPEAR NORMAL |
| | 5067 | ALL TISSUES APPEAR NORMAL |
| | 5068 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5069 | ALL TISSUES APPEAR NORMAL |

TABLE I-E-22 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 8 (Continued)

PARENT NECROPSY OBSERVATIONS (FO) - FEMALES

| DOSE (PPM) | FEMALE NUMBER | OBSERVATION |
|---|---|---|
| 300 | 5070 | ALL TISSUES APPEAR NORMAL |
| | 5071 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5072 | ALL TISSUES APPEAR NORMAL |
| | 5073 | ALL TISSUES APPEAR NORMAL |
| | 5074 | ALL TISSUES APPEAR NORMAL |
| | 5075 | ALL TISSUES APPEAR NORMAL |
| | 5076 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5077 | ALL TISSUES APPEAR NORMAL |
| | 5078 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5079 | ALL TISSUES APPEAR NORMAL |
| 3000 | 5090 | ALL TISSUES APPEAR NORMAL |
| | 5091 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5092 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5093 | ALL TISSUES APPEAR NORMAL |
| | 5094 | ALL TISSUES APPEAR NORMAL |
| | 5095 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5096 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5097 | ALL TISSUES APPEAR NORMAL |
| | 5098 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5099 | ALL TISSUES APPEAR NORMAL |
| | 5100 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5101 | ALL TISSUES APPEAR NORMAL |
| | 5102 | ALL TISSUES APPEAR NORMAL |
| | 5103 | ALL TISSUES APPEAR NORMAL |
| | 5104 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5105 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5106 | ALL TISSUES APPEAR NORMAL |
| | 5107 | ALL TISSUES APPEAR NORMAL |
| | 5108 | ALL TISSUES APPEAR NORMAL |

# TABLE I-E-23

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 9

RESULTS OF SECOND GENERATION - FIRST MATING (F2a)

DOSE - 0 PPM

| | | DAY 0 | | | | | DAY 4 | | | | DAY 21 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT | DEATHS DAY 1-4 | LIVE PUPS | SEX M/F | LITTER REDUCED M/F | DEATHS DAY 4-21 | LIVE PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT |
| 5456 | 5455 | 11 | | 4/7 | 6 | 5 | 2 | 9 | 3/6 | 3/5 | 8 | 0 | | | |
| 5457 | 5455 | 13 | | 8/5 | 5 | 6 | | 13 | 8/5 | 4/4[a] | | 8 | 3/5 | 40 | 38 |
| 5458 | 5447 | 14 | | 8/6 | 6 | 5 | 1 | 13 | 8/5 | 4/4 | | 8 | 4/4 | 37 | 39 |
| 5459 | 5447 | 15 | | 9/6 | 5 | 4 | | 15 | 7/8 | 4/4 | | 8 | 4/4 | 37 | 33 |
| 5460 | 5448 | 11 | | 6/5 | 5 | 5 | 11 | 0 | | | | 0 | | | |
| 5461 | 5448 | 12 | | 8/4 | 6 | 5 | 4 | 8 | 6/2 | 6/2 | | 8 | 6/2 | 45 | 41 |
| 5462 | 5449 | 12 | | 6/6 | 6 | 5 | | 12 | 6/6 | 4/4 | | 8 | 4/4 | 40 | 38 |
| 5463 | 5449 | 13 | | 6/7 | 6 | 6 | | 13 | 6/7 | 4/4 | | 8 | 4/4 | 47 | 43 |
| 5464 | 5450 | 13 | | 6/7 | 6 | 6 | 1 | 12 | 5/7 | 4/4 | | 8 | 4/4 | 39 | 36 |
| 5465 | 5450 | 13 | | 4/9 | 8 | 8 | | 13 | 4/9 | 4/4 | | 8 | 4/4 | 25 | 26 |
| 5466 | 5451 | 14 | | 8/6 | 7 | 7 | | 14 | 8/6 | 4/4 | | 8 | 4/4 | 41 | 39 |
| 5467 | 5451 | 3 | 7 | 2/1 | 5 | 5 | 3 | 0 | | | | 0 | | | |
| 5468 | 5452 | | | | | | | | | | | | | | |
| 5469 | 5452 | 13 | 2 | 6/7 | 6 | 6 | 1 | 12 | 5/7 | 4/4 | | 8 | 4/4 | 43 | 39 |
| 5470 | 5453 | 12 | | 6/6 | 7 | 7 | 2 | 10 | 6/4 | 4/4 | | 8 | 4/4 | 42 | 42 |
| 5471 | 5453 | | | | | | | | | | | | | | |
| 5472 | 5454 | 14 | | 4/10 | 7 | 6 | | 14 | 4/10 | 4/4 | | 8 | 4/4 | 45 | 43 |
| 5473 | 5454 | 12 | | 7/5 | 7 | 7 | | 12 | 7/5 | 4/4 | | 8 | 4/4 | 47 | 52 |
| 5474 | 5446 | 13 | | 6/7 | 5 | 4 | 12 | 1 | 0/1 | 0/1 | 1 | 0 | | | |
| 5475 | 5446 | 15 | 1 | 2/13 | 7 | 6 | | 15 | 2/13 | 2/6 | | 8 | 2/6 | 22 | 20 |
| TOTAL | | 223 | 10 | 106/117 | | | 37 | 186 | 85/101 | 59/62 | 9 | 112 | 55/57 | | |
| MEAN | | 12 | | | 6 | 6 | | 10 | | | | 6 | | 39 | 38 |
| SD | | 2.6 | | | 0.9 | 1.1 | | 5.0 | | | | 3.4 | | 7.5 | 7.7 |
| SE | | 0.6 | | | 0.2 | 0.2 | | 1.2 | | | | 0.8 | | 2.0 | 2.1 |
| N | | 18 | | | | | | 18 | | | | 18 | | | |

[a]One pup mis-sexed, corrected at Day 21.

# TABLE I-E-23 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 9 (Continued)

RESULTS OF SECOND GENERATION - FIRST MATING (F2a)

DOSE - 300 PPM

| | | DAY 0 | | | | | DAY 4 | | | | DAY 21 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT | DEATHS DAY 1-4 | LIVE PUPS | SEX M/F | LITTER REDUCED M/F | DEATHS DAY 4-21 | LIVE PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT |
| 5486 | 5485 | 14 | | 7/7 | 6 | 5 | | 14 | 7/7 | 4/4 | | 8 | 4/4 | 48 | 43 |
| 5487 | 5485 | 9 | | 4/5 | 7 | 7 | | 9 | 4/5 | 4/4 | | 8 | 4/4 | 52 | 48 |
| 5488 | 5477 | | | | | | | | | | | | | | |
| 5489 | 5477 | | | | | | | | | | | | | | |
| 5490 | 5478 | 14 | 1 | 10/4[a] | 6 | 6 | | 14 | 4/10[b] | 4/4 | | 8 | 4/4 | 23 | 24 |
| 5491 | 5478 | 10 | | 2/8 | 7 | 7 | | 11 | 2/9[b] | 2/6 | | 8 | 2/6 | 48 | 46 |
| 5492 | 5479 | 7 | | 3/4[a] | 7 | 7 | | 7 | 4/3 | 4/3 | | 7 | 4/3 | 43 | 41 |
| 5493 | 5479 | 8 | | 4/4 | 10 | 8 | | 8 | 4/4 | 4/4 | | 8 | 4/4 | 55 | 48 |
| 5494 | 5480 | 11 | 1 | 6/5 | 6 | 5 | | 11 | 6/5 | 4/4 | | 8 | 4/4 | 42 | 36 |
| 5495 | 5480 | 13 | | 6/7 | 5 | 5 | 1 | 12 | 6/6 | 4/4 | 1 | 7 | 4/3 | 35 | 38 |
| 5496 | 5481 | 13 | | 4/9 | 6 | 5 | | 13 | 4/9 | 4/4 | | 8 | 4/4 | 38 | 35 |
| 5497 | 5481 | 13 | 1 | 8/5 | 7 | 7 | | 13 | 8/5 | 4/4 | | 8 | 4/4 | 50 | 47 |
| 5498 | 5482 | 11 | | 7/4 | 6 | 5 | | 11 | 8/3 | 5/3 | | 8 | 5/3 | 42 | 41 |
| 5499 | 5482 | 12 | 1 | 6/6 | 6 | 6 | | 12 | 6/6 | 4/4 | 8 | 0 | | | |
| 5500 | 5483 | 15 | | 4/11[a] | 5 | 5 | | 15 | 3/12 | 3/5 | | 8 | 3/5 | 41 | 37 |
| 5501 | 5483 | | | | | | | | | | | | | | |
| 5502 | 5484 | 10 | | 4/6 | 6 | 6 | 3 | 7 | 3/4 | 3/4 | | 7 | 3/4 | 39 | 22 |
| 5503 | 5484 | 13 | 1 | 7/6 | 5 | 5 | 3 | 10 | 5/5 | 4/4 | | 8 | 4/4 | 40 | 38 |
| 5504 | 5476 | | | | | | | | | | | | | | |
| 5505 | 5476 | | | | | | | | | | | | | | |
| TOTAL | | 173 | 5 | 82/91 | | | 7 | 167 | 74/93 | 57/61 | 9 | 109 | 53/56 | | |
| MEAN | | 12 | | | 6 | 6 | | 11 | | | | 7 | | 43 | 39 |
| SD | | 2.4 | | | 1.2 | 1.0 | | 2.5 | | | | 2.1 | | 8.1 | 8.1 |
| SE | | 0.6 | | | 0.3 | 0.3 | | 0.7 | | | | 0.5 | | 2.1 | 2.1 |
| N | | 15 | | | | | | 15 | | | | 15 | | | |

[a] Mis-sexed at Day 0, corrected at Day 4.
[b] Late birth recorded after Day 0.

# TABLE I-E-23 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 9 (Continued)

RESULTS OF SECOND GENERATION - FIRST MATING (F2a)

DOSE - 3000 PPM

| | | DAY 0 | | | | | DAY 4 | | | | DAY 21 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT | DEATHS DAY 1-4 | LIVE PUPS | SEX M/F | LITTER REDUCED M/F | DEATHS DAY 4-21 | LIVE PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT |
| 5516 | 5515 | 13 | | 5/8 | 7 | 7 | | 13 | 5/8 | 4/4[a] | | 8 | 5/3 | 46 | 45 |
| 5517 | 5515 | | | | | | | | | | | | | | |
| 5518 | 5507 | | | | | | | | | | | | | | |
| 5519 | 5507 | | | | | | | | | | | | | | |
| 5520 | 5508 | 12 | | 6/6[b] | 7 | 7 | | 12 | 5/7 | 4/4 | | 8 | 4/4 | 42 | 39 |
| 5521 | 5508 | 12 | | 6/6 | 7 | 6 | | 12 | 6/6 | 4/4 | | 8 | 4/4 | 50 | 48 |
| 5522 | 5509 | 10 | | 2/8[b] | 7 | 7 | | 10 | 2/8 | 2/6[a] | | 8 | 2/6 | 41 | 35 |
| 5523 | 5509 | 7 | 1 | 2/5 | 7 | 6 | | 7 | 3/4 | 3/4[a] | | 7 | 2/5 | 28 | 29 |
| 5524 | 5510 | 14 | 1 | 5/9 | 7 | 7 | 1 | 13 | 5/8 | 4/4 | | 8 | 4/4 | 36 | 37 |
| 5525 | 5510 | 15 | | 8/7 | 6 | 6 | 1 | 14 | 8/6 | 4/4 | | 8 | 4/4 | 40 | 37 |
| 5526 | 5511 | 10 | | 6/4 | 7 | 7 | | 10 | 6/4 | 4/4 | 1 | 7 | 4/3 | 41 | 37 |
| 5527 | 5511 | 10 | 2[c] | 4/6 | 7 | 7 | | 10 | 4/6 | 4/4 | | 8 | 4/4 | 38 | 36 |
| 5528 | 5512 | 13 | | 5/8 | 8 | 8 | | 13 | 5/8 | 4/4 | | 8 | 4/4 | 40 | 40 |
| 5529 | 5512 | | | | | | | | | | | | | | |
| 5530 | 5513 | 11 | | 4/7 | 8 | 7 | | 11 | 4/7 | 4/4 | | 8 | 4/4 | 40 | 42 |
| 5531 | 5513 | 10 | 1 | 3/7 | 7 | 7 | | 10 | 3/7 | 3/5 | | 8 | 3/5 | 38 | 40 |
| 5532 | 5514 | 12 | | 4/8 | 7 | 7 | | 12 | 4/8 | 4/4 | | P | 4/4 | 38 | 34 |
| 5533 | 5514 | 12 | | 8/4 | 6 | 6 | | 12 | 8/4 | 4/4 | | | 4/4 | 39 | 39 |
| 5534 | 5506 | 10 | | 6/4 | 7 | 6 | | 10 | 6/4 | 4/4 | | 8 | 4/4 | 31 | 35 |
| 5535 | 5506 | 13 | | 5/8 | 5 | 4 | 7 | 6 | 2/4 | 2/4 | | 6 | 2/4 | 38 | 34 |
| TOTAL | | 184 | 5 | 79/105 | | | 9 | 175 | 76/99 | 58/67 | 1 | 124 | 58/66 | | |
| MEAN | | 12 | | | 7 | 7 | | 11 | | | | 8 | | 39 | 38 |
| SD | | 2.0 | | | 0.7 | 0.9 | | 2.2 | | | | 0.6 | | 4.1 | 3.8 |
| SE | | 0.5 | | | 0.2 | 0.2 | | 0.5 | | | | 0.1 | | 1.1 | 1.0 |
| N | | 16 | | | | | | 16 | | | | 16 | | | |

[a]Mis-sexed pup, corrected at Day 21.
[b]Mis-sexed pup, corrected at Day 4.
[c]Siamese birth, recorded as 2 male pups.

TABLE I-E-24

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 10

LITTER OBSERVATIONS

SECOND GENERATION - FIRST MATING (F2a)

| DOSE (PPM) | FEMALE NUMBER | DAY OF LACTATION | OBSERVATION |
|---|---|---|---|
| 0 | 5463 | 0 | ONE FEMALE PUP - HEMATOMA, NOSE; AND TOP OF HEAD. |
| | 5461 | 1 | ONE MALE PUP AND ONE FEMALE PUP - FOUND DEAD; NO VISIBLE ABNORMALITIES. |
| | 5467 | 1 | SURVIVING PUPS - TWO MALE AND ONE FEMALE - DRY SPLITTING SKIN AROUND AXILLA AND VENTRAL SIDE OF NECK. |
| | 5474 | 1 | ONE MALE PUP - FOUND DEAD; NO VISIBLE ABNORMALITIES. |
| | 5458 | 21 | ONE MALE PUP - FOUND DEAD; NO VISIBLE ABNORMALITIES. |
| 300 | 5503 | 0 | ONE FEMALE PUP - HEMATOMA, RIGHT SIDE OF FACE. |
| | 5495 | 2 | ONE FEMALE PUP - FOUND DEAD; NO VISIBLE ABNORMALITIES. |
| 3000 | 5527 | 0 | TWO MALE PUPS CONNECTED AT VENTRAL THORACIC REGION - FOUND DEAD; EACH HAS A COMPLETE SET OF LIMBS, ONE HAS COMPLETELY FORMED HEAD AND FACE, THE OTHER HAS ONLY TWO PROTRUSIONS FROM THE ANTERIOR NECK. |
| | 5533 | 2 | ONE PUP - FOUND DEAD; UNABLE TO DETERMINE SEX DUE TO CANNIBALIZATION. |
| | 5526 | 21 | ONE MALE AND TWO FEMALE PUPS - BOTH EYES CLOSED. |
| | 5527 | 21 | THREE MALE AND THREE FEMALE PUPS - PARTIALLY CLOSED EYES |
| | 5534 | 26 | ONE MALE PUP - VERY EMACIATED AND SMALL, RIGHT EYE CLOSED |

TABLE I-E-25

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 11

PUP NECROPSY OBSERVATIONS (F2a) AT DAY 21

| DOSE (PPM) | FEMALE NUMBER | NUMBER OF PUPS | OBSERVATION |
|---|---|---|---|
| 0 | 5456 | 8 | ALL TISSUES APPEAR NORMAL |
| | 5458 | 6 | ALL TISSUES APPEAR NORMAL |
| | 5462 | 8 | ALL TISSUES APPEAR NORMAL |
| | 5463 | 8 | ALL TISSUES APPEAR NORMAL |
| | 5466 | 8 | ALL TISSUES APPEAR NORMAL |
| | 5470 | 8 | ALL TISSUES APPEAR NORMAL |
| 300 | 5490 | 8 | ALL TISSUES APPEAR NORMAL |
| | 5491 | 8 | ALL TISSUES APPEAR NORMAL |
| | 5494 | 8 | ALL TISSUES APPEAR NORMAL |
| | 5496 | 8 | ALL TISSUES APPEAR NORMAL |
| | 5499 | 6 | ALL TISSUES APPEAR NORMAL |
| | 5502 | 7 | ALL TISSUES APPEAR NORMAL |
| 3000 | 5520 | 8 | ALL TISSUES APPEAR NORMAL |
| | 5523 | 7 | ALL TISSUES APPEAR NORMAL |
| | 5524 | 8 | ALL TISSUES APPEAR NORMAL |
| | 5530 | 8 | ALL TISSUES APPEAR NORMAL |
| | 5533 | 8 | ALL TISSUES APPEAR NORMAL |
| | 5534 | 8 | ALL TISSUES APPEAR NORMAL |

# TABLE I-E-26

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 12

RESULTS OF SECOND GENERATION - SECOND MATING (F2b)

DOSE - 0 PPM

| | | DAY 0 | | | | | DAY 4 | | | | DAY 21 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT | DEATHS DAY 1-4 | LIVE PUPS | SEX M/F | LITTER REDUCED M/F | DEATHS DAY 4-21 | LIVE PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT |
| 5456 | 5455 | 12 | | 6/6 | 6 | 5 | | 12 | 6/6 | 4/4 | | 8 | 4/4 | 44 | 46 |
| 5457 | 5455 | 15 | | 8/7 | 6 | 6 | | 15 | 8/7 | 4/4 | | 8 | 4/4 | 41 | 40 |
| 5458 | 5454 | 14 | | 5/9 | 7 | 6 | | 14 | 5/9 | 4/4 | | 8 | 4/4 | 46 | 46 |
| 5459 | 5454 | 16 | | 7/9 | 6 | 6 | | 16 | 7/9 | 4/4 | | 8 | 4/4 | 42 | 41 |
| 5460 | 5453 | 11 | | 3/8 | 6 | 6 | | 11 | 3/8 | 3/5 | | 8 | 3/5 | 38 | 35 |
| 5461 | 5453 | 16 | | 8/8 | 6 | 5 | 1 | 15 | 8/7 | 4/4 | | 8 | 4/4 | 40 | 37 |
| 5462 | 5452 | 12 | | 7/5 | 7 | 7 | | 12 | 7/5 | 4/4 | | 8 | 4/4 | 54 | 50 |
| 5463 | 5452 | 14 | | 8/6[a] | 6 | 6 | | 14 | 9/5 | 4/4 | | 8 | 4/4 | 46 | 48 |
| 5464 | 5451 | | | | | | | | | | | | | | |
| 5465 | 5451 | 15 | | 9/6 | 6 | 6 | | 15 | 9/6 | 4/4 | | 8 | 4/4 | 46 | 40 |
| 5466 | 5450 | 12 | | 7/5 | 6 | 6 | 1 | 11 | 6/5 | 4/4 | | 8 | 4/4 | 38 | 35 |
| 5467 | 5450 | | | | | | | | | | | | | | |
| 5468 | 5449 | 8 | 2 | 1/7 | 6 | 7 | | 8 | 1/7 | 1/7 | | 8 | 1/7 | 47 | 48 |
| 5469 | 5449 | 15 | | 6/9 | 7 | 7 | | 15 | 6/9 | 4/4 | | 8 | 4/4 | 50 | 45 |
| 5470 | 5448 | 17 | 1 | 9/8 | 7 | 6 | | 17 | 9/8 | 4/4 | 1 | 7 | 4/3 | 51 | 49 |
| 5471 | 5448 | 13 | 1 | 8/5 | 6 | 5 | 5 | 8 | 7/1 | 7/1 | 1 | 7 | 6/1 | 44 | 36 |
| 5472 | 5447 | 13 | 1 | 5/8 | 8 | 7 | | 13 | 5/8 | 4/4 | | 8 | 4/4 | 52 | 48 |
| 5473 | 5447 | 16 | | 7/9 | 6 | 6 | | 16 | 7/9 | 4/4 | | 8 | 4/4 | 36 | 33 |
| 5474 | 5446 | 13 | | 6/7 | 6 | 6 | | 13 | 6/7 | 4/4 | | 8 | 4/4 | 46 | 44 |
| 5475 | 5446 | 18 | 1 | 9/9 | 6 | 6 | 1 | 17 | 9/8 | 4/4 | | 8 | 4/4 | 39 | 41 |
| TOTAL | | 250 | 6 | 119/131 | | | 8 | 242 | 118/124 | 71/73 | 2 | 142 | 70/72 | | |
| MEAN | | 14 | | | 6 | 6 | | 13 | | | | 8 | | 44 | 42 |
| SD | | 2.4 | | | 0.6 | 0.6 | | 2.7 | | | | 0.3 | | 5.5 | 5.4 |
| SE | | 0.6 | | | 0.2 | 0.2 | | 0.6 | | | | 0.1 | | 1.4 | 1.4 |
| N | | 18 | | | | | | 18 | | | | 18 | | | |

[a]Mis-sexed at Day 0, corrected at Day 4.

# TABLE I-E-26 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 12 (Continued)

RESULTS OF SECOND GENERATION - SECOND MATING (F2b)

DOSE - 300 PPM

| | | DAY 0 | | | | | DAY 4 | | | | DAY 21 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT | DEATHS DAY 1-4 | LIVE PUPS | SEX M/F | LITTER REDUCED M/F | DEATHS DAY 4-21 | LIVE PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT |
| 5486 | 5485 | 16 | | 8/8 | 6 | 6 | 1 | 15 | 7/8 | 4/4 | | 8 | 4/4 | 46 | 46 |
| 5487 | 5485 | 13 | | 2/11[a] | 6 | 7 | | 13 | 3/10 | 3/5 | | 8 | 3/5 | 52 | 47 |
| 5488 | 5484 | 12 | | 7/5 | 7 | 7 | 1 | 11 | 7/4 | 4/4 | | 8 | 4/4 | 50 | 48 |
| 5489 | 5484 | | | | | | | | | | | | | | |
| 5490 | 5483 | 13 | | 8/5[a] | 7 | 6 | | 13 | 7/6 | 4/4 | 1 | 7 | 4/3 | 55 | 50 |
| 5491 | 5483 | 8 | | 8/0 | 7 | | | 8 | 8/0 | 8/0 | | 8 | 8/0 | 46 | |
| 5492 | 5482 | 12 | | 6/6 | 7 | 8 | | 12 | 6/6 | 4/4 | | 8 | 4/4 | 39 | 42 |
| 5493 | 5482 | 18 | | 8/10 | 8 | 7 | | 18 | 8/10 | 4/4 | | 8 | 4/4 | 54 | 49 |
| 5494 | 5481 | 15 | 2 | 5/10 | 6 | 6 | 1 | 14 | 5/9 | 4/4 | | 8 | 4/4 | 51 | 50 |
| 5495 | 5481 | 17 | | 8/9[a] | 6 | 6 | | 17 | 7/10 | 4/4 | | 8 | 4/4 | 49 | 49 |
| 5496 | 5480 | 16 | | 7/9 | 6 | 6 | | 16 | 7/9 | 4/4 | | 8 | 4/4 | 39 | 41 |
| 5497 | 5480 | 17 | | 10/7 | 9 | 9 | | 17 | 10/7 | 4/4 | | 8 | 4/4 | 36 | 33 |
| 5498 | 5479 | 16 | | 8/8 | 6 | 5 | 2 | 14 | 8/6 | 4/4 | | 8 | 4/4 | 44 | 40 |
| 5499 | 5479 | | | | | | | | | | | | | | |
| 5500 | 5478 | 10 | | 9/1 | | 7 | | 10 | 9/1 | 7/1 | | 8 | 7/1 | 56 | 44 |
| 5501 | 5478 | 9 | | 5/4 | 6 | 6 | | 9 | 5/4 | 4/4 | | 8 | 4/4 | 54 | 49 |
| 5502 | 5477 | 9 | | 4/5[a] | 6 | 7 | | 9 | 5/4 | 4/4 | | 8 | 3/5 | 47 | 43 |
| 5503 | 5477 | 12 | | 6/6 | 6 | 6 | | 12 | 6/6 | 4/4 | | 8 | 4/4 | 44 | 40 |
| 5504 | 5476 | 15 | | 8/7 | 6 | 6 | 1 | 14 | 7/7 | 4/4 | | 8 | 4/4 | 43 | 46 |
| 5505 | 5476 | | | | | | | | | | | | | | |
| TOTAL | | 228 | 2 | 117/111 | | | 6 | 222 | 115/107 | 74/62 | 1 | 135 | 73/62 | | |
| MEAN | | 13 | | | 7 | 7 | | 13 | | | | 8 | | 47 | 44 |
| SD | | 3.1 | | | 1.0 | 1.0 | | 3.0 | | | | 0.2 | | 6.3 | 5.0 |
| SE | | 0.8 | | | 0.2 | 0.3 | | 0.7 | | | | 0.1 | | 1.7 | 1.4 |
| N | | 17 | | | | | | 17 | | | | 17 | | | |

[a]Mis-sexed at Day 0, corrected at Day 4.

# TABLE I-E-26 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 12 (Continued)

RESULTS OF SECOND GENERATION - SECOND MATING (F2b)

DOSE - 3000 PPM

| | | DAY 0 | | | | | DAY 4 | | | | DAY 21 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT | DEATHS DAY 1-4 | LIVE PUPS | SEX M/F | LITTER REDUCED M/F | DEATHS DAY 4-21 | LIVE PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT |
| 5516 | 5515 | 12 | | 6/6 | 6 | 6 | | 12 | 6/6 | 4/4 | | 8 | 4/4 | 56 | 49 |
| 5517 | 5515 | | | | | | | | | | | | | | |
| 5518 | 5514 | 12 | | 10/2 | 7 | 7 | | 12 | 10/2 | 6/2 | | 8 | 6/2 | 51 | 51 |
| 5519 | 5514 | 14 | | 9/5 | 7 | 7 | | 14 | 9/5 | 4/4 | | 8 | 4/4 | 46 | 45 |
| 5520 | 5513 | 14 | | 8/6[a] | 6 | 6 | | 14 | 6/8 | 4/4 | | 8 | 4/4 | 42 | 39 |
| 5521 | 5513 | 14 | | 6/8 | 8 | 7 | | 14 | 6/8 | 4/4 | | 8 | 4/4 | 68 | 62 |
| 5522 | 5512 | 7 | | 5/2 | 8 | 7 | 1 | 6 | 5/1 | 5/1 | | 6 | 5/1 | 57 | 50 |
| 5523 | 5512 | 7 | | 3/4 | 6 | 5 | | 7 | 3/4 | 3/4 | | 7 | 3/4 | 30 | 31 |
| 5524 | 5511 | 14 | | 8/6 | 6 | 6 | | 14 | 8/6 | 4/4 | | 8 | 4/4 | 43 | 44 |
| 5525 | 5511 | 14 | | 4/10[a] | 6 | 6 | | 14 | 5/9 | 4/4 | | 8 | 4/4 | 46 | 43 |
| 5526 | 5510 | 11 | | 6/5 | 7 | 7 | | 11 | 6/5 | 4/4 | | 8 | 4/4 | 51 | 44 |
| 5527 | 5510 | 14 | | 8/6 | 6 | 6 | | 14 | 8/6 | 4/4 | | 8 | 4/4 | 44 | 42 |
| 5528 | 5509 | | | | | | | | | | | | | | |
| 5529 | 5509 | 13 | | 4/9 | 8 | 7 | | 13 | 4/9 | 4/4 | | 8 | 4/4 | 49 | 49 |
| 5530 | 5508 | 15 | | 5/10 | 7 | 6 | | 15 | 5/10 | 4/4 | | 8 | 4/4 | 51 | 47 |
| 5531 | 5508 | 13 | | 8/5 | 6 | 6 | | 13 | 8/5 | 4/4 | | 8 | 4/4 | 44 | 44 |
| 5532 | 5507 | 14 | | 4/10 | 8 | 7 | 1 | 13 | 4/9 | 4/4 | | 8 | 4/4 | 38 | 36 |
| 5533 | 5507 | 16 | | 10/6 | 6 | 7 | | 16 | 10/6 | 4/4 | | 8 | 5/3 | 46 | 45 |
| 5534 | 5506 | 13 | 2 | 7/6 | 6 | 6 | | 13 | 7/6 | 4/4 | | 8 | 4/4 | 50 | 46 |
| 5535 | 5506 | 16 | | 6/10 | 6 | 6 | 1 | 15 | 6/9 | 4/4 | 1 | 7 | 3/4 | 54 | 50 |
| TOTAL | | 233 | 2 | 117/116 | | | 3 | 230 | 116/114 | 74/67 | 1 | 140 | 74/66 | | |
| MEAN | | 13 | | | 7 | 6 | | 13 | | | | 8 | | 48 | 45 |
| SD | | 2.5 | | | 0.8 | 0.6 | | 2.6 | | | | 0.5 | | 8.7 | 7.0 |
| SE | | 0.6 | | | 0.2 | 0.1 | | 0.6 | | | | 0.1 | | 2.2 | 1.7 |
| N | | 18 | | | | | | 18 | | | | 18 | | | |

[a]Mis-sexed at Day 0, corrected at Day 4.

TABLE I-E-27

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 13

LITTER OBSERVATIONS

SECOND GENERATION - SECOND MATING (F2b)

| DOSE (PPM) | FEMALE NUMBER | DAY OF LACTATION | OBSERVATION |
|---|---|---|---|
| 0 | 5471 | 0 | ONE MALE PUP - PALE AND INACTIVE; DEATH RECORDED SUBSEQUENTLY. |
| | 5471 | 21 | ONE PUP - FOUND DEAD; CANNIBALIZED. |
| | 5472 | 0 | ONE FEMALE PUP - HEMATOMA, MID-DORSAL THORACIC REGION. |
| 300 | 5504 | 1 | ONE MALE PUP - FOUND DEAD; NO VISIBLE ABNORMALITIES. |
| | 5494 | 4 | ONE FEMALE PUP - FOUND DEAD. |
| | 5497 | 6 | ONE FEMALE PUP - FOUND DEAD; NO VISIBLE ABNORMALITIES. |
| | 5490 | 9 | ONE FEMALE PUP - FOUND DEAD. |
| 3000 | 5524 | 21 | ONE FEMALE PUP - ACCIDENTALLY DIED DURING HANDLING. |

TABLE I-E-28

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 14

BODY WEIGHTS AND FOOD CONSUMPTION (G) OF PARENT RATS (F1b)

BODY WEIGHTS

| DOSE (PPM) | | MALES WK 4 | WK 9 | WK 11 | WK 20 |
|---|---|---|---|---|---|
| 0 | MEAN | 341 | 464 | 468 | 578 |
| | SD | 27.6 | 30.4 | 37.2 | 45.3 |
| | SE | 8.7 | 9.6 | 11.8 | 14.3 |
| | N | 10 | 10 | 10 | 10 |
| 300 | MEAN | 313 | 445 | 451 | 572 |
| | SD | 32.2 | 22.2 | 27.5 | 41.4 |
| | SE | 10.2 | 7.0 | 8.7 | 13.1 |
| | N | 10 | 10 | 10 | 10 |
| 3000 | MEAN | 310* | 438 | 442 | 541 |
| | SD | 27.3 | 31.5 | 33.7 | 38.6 |
| | SE | 8.6 | 10.0 | 10.7 | 12.2 |
| | N | 10 | 10 | 10 | 10 |

FOOD CONSUMPTION

| DOSE (PPM) | | MALES WK 4 | WK 9 | WK 11 | WK 20 |
|---|---|---|---|---|---|
| 0 | MEAN | 24.3 | 25.3 | 26.0 | 32.0 |
| | SD | 2.2 | 1.4 | 2. 5 | 5.4 |
| | SE | 0.7 | 0.6 | 1.0 | 1.8 |
| | N | 9 | 5 | 6 | 9 |
| 300 | MEAN | 24.0 | 25.9 | 23.9 | 31.7 |
| | SD | 1.8 | 2.9 | 6.1 | 3.9 |
| | SE | 0.6 | 1.2 | 2.1 | 1.2 |
| | N | 9 | 6 | 8 | 10 |
| 3000 | MEAN | 24.6 | 27.3 | 27.9 | 28.6 |
| | SD | 2.1 | 2.4 | 2.5 | 4.2 |
| | SE | 0.7 | 0.9 | 0.9 | 1.4 |
| | N | 9 | 7 | 8 | 9 |

*$p < 0.05$ as compared to controls: Dunnett's t-test.

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 14 (Continued)

BODY WEIGHTS AND FOOD CONSUMPTION (G) OF PARENT RATS (F1b)

BODY WEIGHTS

| DOSE (PPM) | | FEMALES WK 4 | WK 9 | WK 11 | WK 20 |
|---|---|---|---|---|---|
| 0 | MEAN | 200 | 246 | 249 | 295 |
| | SD | 20.9 | 18.6 | 22.0 | 16.6 |
| | SE | 4.7 | 4.2 | 4.9 | 3.7 |
| | N | 20 | 20 | 20 | 20 |
| 300 | MEAN | 203 | 261 | 259 | 308 |
| | SD | 24.0 | 25.2 | 24.3 | 26.5 |
| | SE | 5.4 | 5.6 | 5.4 | 5.9 |
| | N | 20 | 20 | 20 | 20 |
| 3000 | MEAN | 194 | 247 | 243 | 287 |
| | SD | 18.6 | 22.3 | 22.0 | 23.3 |
| | SE | 4.2 | 5.0 | 4.9 | 5.2 |
| | N | 20 | 20 | 20 | 20 |

FOOD CONSUMPTION

| DOSE (PPM) | | FEMALES WK 4 | WK 9 | WK 11 | WK 20 |
|---|---|---|---|---|---|
| 0 | MEAN | 17.4 | 23.1 | 22.7 | 31.0 |
| | SD | 3.7 | 4.7 | 4.9 | 4.7 |
| | SE | 0.8 | 1.2 | 1.1 | 1.3 |
| | N | 19 | 17 | 20 | 14 |
| 300 | MEAN | 18.8 | 21.9 | 22.5 | 31.4 |
| | SD | 2.7 | 4.1 | 4.2 | 5.7 |
| | SE | 0.6 | 1.0 | 1.0 | 1.3 |
| | N | 20 | 18 | 19 | 18 |
| 3000 | MEAN | 17.2 | 24.2 | 23.1 | 31.4 |
| | SD | 2.7 | 3.1 | 3.4 | 6.1 |
| | SE | 0.6 | 0.7 | 0.7 | 1.4 |
| | N | 18 | 17 | 20 | 20 |

TABLE 15

TOXICOLOGY OBSERVATION REPORT

CLINICAL SIGNS
PROJECT NUMBER - 10734-06

| WEEK NO. | ** DOSE GROUP/SEX * | ANIMAL NUMBER | ***** OBSERVATIONS : QUALIFIER COMMENTS ********** |
|---|---|---|---|
| -001 | CONTROL MALE | 05446 | STARTED |
| | | ***** | OCT. 20,1977 |
| 001 | CONTROL MALE | 05446 | ALL ANIMALS NORMAL |
| 002 | CONTROL MALE | 05446 | ALL ANIMALS NORMAL |
| 003 | CONTROL MALE | 05446 | ALL ANIMALS NORMAL |
| 004 | CONTROL MALE | 05446 | ALL ANIMALS NORMAL |
| 005 | CONTROL MALE | 05446 | ALL ANIMALS NORMAL |
| 006 | CONTROL MALE | 05446 | ALL ANIMALS NORMAL |
| 007 | CONTROL MALE | 05446 | ALL ANIMALS NORMAL |
| 008 | CONTROL MALE | 05446 | ALL ANIMALS APPEAR NORMAL |
| 009 | CONTROL MALE | 05446 | ALL ANIMALS NORMAL |
| | 3000 PPM FEMALE | 05524 | ULCERATION : HEAD |
| | | ***** | RIGHT SIDE |
| | | | LOSS OF : EAR-RIGHT |
| 010 | 3000 PPM FEMALE | 05524 | MEDIUM ULCERATION(1-5CM) : EAR-RIGHT |
| | | | MEDIUM SCAB(1-5CM) : EAR-RIGHT |
| | | ***** | RT EAR MISSING; SCAB ON RT SIDE OF HEAD |
| | | | LOSS OF : EAR-RIGHT |
| 011 | 3000 PPM FEMALE | 05524 | MEDIUM ULCERATION(1-5CM) : EAR-RIGHT |
| | | | LOSS OF : EAR-RIGHT |
| | | | MATE TO GET F2A |
| 012 | 300 PPM FEMALE | 05489 | LOCAL HAIR LOSS : LIMBS-FORE |
| | 3000 PPM | 05524 | MEDIUM SCAB(1-5CM) : EAR-RIGHT |
| | | ***** | RIGHT EAR MISSING SCAB ON RT SIDE OF HEAD |
| | | | LOSS OF : EAR-RIGHT |
| 013 | CONTROL MALE | 05446 | REMOVED FROM MATING |
| | 300 PPM FEMALE | 05489 | LOCAL HAIR LOSS : LIMBS-FORE |
| | 3000 PPM | 05524 | LOSS OF : EAR-RIGHT |
| 014 | 300 PPM FEMALE | 05489 | LOCAL HAIR LOSS : LIMBS-FORE |

TABLE 15 (CONTINUED)

TOXICOLOGY OBSERVATION REPORT

CLINICAL SIGNS
PROJECT NO. - 10734-06

| WEEK NO. | ** DOSE GROUP/SEX | * ANIMAL NUMBER | ***** OBSERVATIONS : QUALIFIER COMMENTS ********** |
|---|---|---|---|
| | 3000 PPM | 05524 | LOSS OF : EAR-RIGHT |
| 015 | 300 PPM FEMALE | 05489 | LOCAL HAIR LOSS : LIMBS-FORE |
| | 3000 PPM | 05524 | LOSS OF : EAR-RIGHT |
| 016 | 300 PPM FEMALE | 05489 | LOCAL HAIR LOSS : LIMBS-FORE |
| | 3000 PPM | 05524 | LOSS OF : EAR-RIGHT |
| 017 | 300 PPM FEMALE | 05489 | LOCAL HAIR LOSS : LIMBS-FORE |
| 018 | 300 PPM FEMALE | 05489 | LOCAL HAIR LOSS : LIMBS-FORE |
| | 3000 PPM | 05524 | LOSS OF : EAR-RIGHT |
| 020 | 300 PPM FEMALE | 05489 | LOCAL HAIR LOSS : LIMBS-FORE |
| | 3000 PPM | 05524 | LOSS OF : EAR-RIGHT |
| 021 | CONTROL MALE | 05446 | MATE TO GET F2B |
| | 300 PPM FEMALE | 05489 | LOCAL HAIR LOSS : LIMBS-FORE |
| 022 | 300 PPM FEMALE | 05489 | LOCAL HAIR LOSS : LIMBS-FORE |
| 023 | CONTROL MALE | 05446 | REMOVED FROM MATING |
| | 300 PPM FEMALE | 05489 | LOCAL HAIR LOSS : LIMBS-FORE |
| 024 | 300 PPM FEMALE | 05489 | LOCAL HAIR LOSS : LIMBS-FORE<br>LOCAL HAIR LOSS : LIMBS-FORE |
| 025 | CONTROL FEMALE | 05468 | EYE DISCHARGE : EYE-LEFT |
| | 300 PPM | 05489 | LOCAL HAIR LOSS : LIMBS-FORE |
| 026 | 300 PPM FEMALE | 05489 | LOCAL HAIR LOSS : LIMBS-FORE |
| 027 | CONTROL MALE | 05446 | ALL MALES SACRIFICED-GROSS NECROPSY<br>ALL TISSUES NORMAL |
| | FEMALE | 05456 | ALL FEMALES SACRIFICED ON OR<br>BEFORE WEEK 29<br>GROSS NECROPSY-ABNORMALS LISTED |
| | 300 PPM | 05489 | LOCAL HAIR LOSS : LIMBS-FORE |
| 028 | 300 PPM FEMALE | 05489 | LOCAL HAIR LOSS : LIMBS-FORE |

TABLE I-E-30

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 16

PARENT NECROPSY OBSERVATIONS (F1b) - MALES

| DOSE (PPM) | MALE NUMBER | OBSERVATION |
|---|---|---|
| 0 | 5446 | ALL TISSUES APPEAR NORMAL |
| | 5447 | ALL TISSUES APPEAR NORMAL |
| | 5448 | ALL TISSUES APPEAR NORMAL |
| | 5449 | ALL TISSUES APPEAR NORMAL |
| | 5450 | ALL TISSUES APPEAR NORMAL |
| | 5451 | ALL TISSUES APPEAR NORMAL |
| | 5452 | ALL TISSUES APPEAR NORMAL |
| | 5453 | ALL TISSUES APPEAR NORMAL |
| | 5454 | ALL TISSUES APPEAR NORMAL |
| | 5455 | ALL TISSUES APPEAR NORMAL |
| 300 | 5476 | ALL TISSUES APPEAR NORMAL |
| | 5477 | ALL TISSUES APPEAR NORMAL |
| | 5478 | ALL TISSUES APPEAR NORMAL |
| | 5479 | ALL TISSUES APPEAR NORMAL |
| | 5480 | ALL TISSUES APPEAR NORMAL |
| | 5481 | ALL TISSUES APPEAR NORMAL |
| | 5482 | ALL TISSUES APPEAR NORMAL |
| | 5483 | ALL TISSUES APPEAR NORMAL |
| | 5484 | ALL TISSUES APPEAR NORMAL |
| | 5485 | ALL TISSUES APPEAR NORMAL |
| 3000 | 5506 | ALL TISSUES APPEAR NORMAL |
| | 5507 | ALL TISSUES APPEAR NORMAL |
| | 5508 | ALL TISSUES APPEAR NORMAL |
| | 5509 | ALL TISSUES APPEAR NORMAL |
| | 5510 | ALL TISSUES APPEAR NORMAL |
| | 5511 | ALL TISSUES APPEAR NORMAL |
| | 5512 | ALL TISSUES APPEAR NORMAL |
| | 5513 | ALL TISSUES APPEAR NORMAL |
| | 5514 | ALL TISSUES APPEAR NORMAL |
| | 5515 | ALL TISSUES APPEAR NORMAL |

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 16 (Continued)

PARENT NECROPSY OBSERVATIONS (F1b) - FEMALES

| DOSE (PPM) | FEMALE NUMBER | OBSERVATION |
|---|---|---|
| 0 | 5456 | ALL TISSUES APPEAR NORMAL |
| | 5457 | CYST ON RIGHT OVARY (10 X 15 X 10 MM) |
| | 5458 | CYST ON UTERUS (13 X 10 MM) |
| | 5459 | ALL TISSUES APPEAR NORMAL |
| | 5460 | ALL TISSUES APPEAR NORMAL |
| | 5461 | ALL TISSUES APPEAR NORMAL |
| | 5462 | ALL TISSUES APPEAR NORMAL |
| | 5463 | ALL TISSUES APPEAR NORMAL |
| | 5464 | ALL TISSUES APPEAR NORMAL |
| | 5465 | ALL TISSUES APPEAR NORMAL |
| | 5466 | ALL TISSUES APPEAR NORMAL |
| | 5467 | ALL TISSUES APPEAR NORMAL |
| | 5468 | ALL TISSUES APPEAR NORMAL |
| | 5469 | ALL TISSUES APPEAR NORMAL |
| | 5470 | ALL TISSUES APPEAR NORMAL |
| | 5471 | ALL TISSUES APPEAR NORMAL |
| | 5472 | ALL TISSUES APPEAR NORMAL |
| | 5473 | ALL TISSUES APPEAR NORMAL |
| | 5474 | ALL TISSUES APPEAR NORMAL |
| | 5475 | ALL TISSUES APPEAR NORMAL |
| 300 | 5486 | ALL TISSUES APPEAR NORMAL |
| | 5487 | ALL TISSUES APPEAR NORMAL |
| | 5488 | ALL TISSUES APPEAR NORMAL |
| | 5489 | ALL TISSUES APPEAR NORMAL |
| | 5490 | SMALL CYST ON RIGHT OVARY; ALL OTHER TISSUES APPEAR NORMAL |
| | 5491 | ALL TISSUES APPEAR NORMAL |
| | 5492 | ALL TISSUES APPEAR NORMAL |
| | 5493 | ALL TISSUES APPEAR NORMAL |
| | 5494 | ALL TISSUES APPEAR NORMAL |
| | 5495 | ALL TISSUES APPEAR NORMAL |
| | 5496 | ALL TISSUES APPEAR NORMAL |
| | 5497 | ALL TISSUES APPEAR NORMAL |
| | 5498 | ALL TISSUES APPEAR NORMAL |
| | 5499 | ALL TISSUES APPEAR NORMAL |
| | 5500 | ALL TISSUES APPEAR NORMAL |
| | 5501 | ALL TISSUES APPEAR NORMAL |
| | 5502 | ALL TISSUES APPEAR NORMAL |
| | 5503 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 5504 | ALL TISSUES APPEAR NORMAL |
| | 5505 | ALL TISSUES APPEAR NORMAL |

TABLE I-E-30 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 16 (Continued)

PARENT NECROPSY OBSERVATIONS (F1b) - FEMALES

| DOSE (PPM) | FEMALE NUMBER | OBSERVATION |
|---|---|---|
| 3000 | 5516 | ALL TISSUES APPEAR NORMAL |
| | 5517 | ALL TISSUES APPEAR NORMAL |
| | 5518 | ALL TISSUES APPEAR NORMAL |
| | 5519 | ALL TISSUES APPEAR NORMAL |
| | 5520 | ALL TISSUES APPEAR NORMAL |
| | 5521 | ALL TISSUES APPEAR NORMAL |
| | 5522 | ALL TISSUES APPEAR NORMAL |
| | 5523 | FOUR STONES IN URINARY BLADDER, EACH APPROXIMATELY 1 $CM^3$ |
| | 5524 | ALL TISSUES APPEAR NORMAL |
| | 5525 | ALL TISSUES APPEAR NORMAL |
| | 5526 | ALL TISSUES APPEAR NORMAL |
| | 5527 | ALL TISSUES APPEAR NORMAL |
| | 5528 | ALL TISSUES APPEAR NORMAL |
| | 5529 | ALL TISSUES APPEAR NORMAL |
| | 5530 | CYST ON RIGHT FALLOPIAN TUBE NEAR UTERUS (5 X 5 X 5 MM) |
| | 5531 | ALL TISSUES APPEAR NORMAL |
| | 5532 | ALL TISSUES APPEAR NORMAL |
| | 5534 | ALL TISSUES APPEAR NORMAL |
| | 5535 | ALL TISSUES APPEAR NORMAL |

# TABLE I-E-31

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 17

RESULTS OF THIRD GENERATION - FIRST MATING (F3a)

DOSE - 0 PPM

| | | DAY 0 | | | | | DAY 4 | | | | DAY 21 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT | DEATHS DAY 1-4 | LIVE PUPS | SEX M/F | LITTER REDUCED M/F | DEATHS DAY 4-21 | LIVE PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT |
| 1407 | 1405 | 13 | | 8/5 | 7 | 6 | | 13 | 8/5 | 4/4 | | 8 | 4/4 | 34 | 31 |
| 1408 | 1406 | 13 | 1 | 6/7 | 6 | 5 | 1 | 12 | 5/7 | 4/4 | | 8 | 4/4 | 39 | 36 |
| 1409 | 1406 | 16 | | 10/6 | 6 | 6 | | 16 | 10/6 | 4/4[a] | | 8 | 5/3 | 38 | 44 |
| 1410 | 1397 | 15 | | 5/10 | 6 | 5 | | 15 | 5/10 | 4/4 | | 8 | 4/4 | 47 | 45 |
| 1411 | 1397 | 13 | | 7/6 | 6 | 6 | | 13 | 7/6 | 4/4 | | 8 | 4/4 | 40 | 36 |
| 1412 | 1398 | 6 | | 4/2 | 7 | 7 | | 6 | 4/2 | 4/2 | | 6 | 4/2 | 46 | 46 |
| 1413 | 1398 | | | | | | | | | | | | | | |
| 1414 | 1399 | 14 | | 10/4 | 6 | 6 | 1 | 13 | 9/4 | 4/4 | | 8 | 4/4 | 45 | 42 |
| 1415 | 1399 | 12 | | 5/7 | 8 | 8 | | 12 | 5/7 | 4/4 | | 8 | 4/4 | 46 | 40 |
| 1416 | 1400 | 12 | 1 | 6/6 | 7 | 6 | | 12 | 6/6 | 4/4 | | 8 | 4/4 | 41 | 38 |
| 1417 | 1400 | 11 | | 5/6 | 6 | 6 | | 11 | 5/6 | 4/4 | | 8 | 4/4 | 43 | 42 |
| 1418 | 1401 | | | | | | | | | | | | | | |
| 1419 | 1401 | 9 | | 5/4 | 7 | 6 | | 9 | 5/4 | 4/4 | | 8 | 4/4 | 56 | 49 |
| 1420 | 1402 | 5 | | 1/4 | 4 | 4 | 5 | 0 | | | | | | | |
| 1421 | 1402 | 14 | | 8/6 | 6 | 7 | | 14 | 8/6 | 4/4 | | 8 | 4/4 | 41 | 40 |
| 1422 | 1403 | 14 | | 8/6 | 6 | 6 | 1 | 13 | 8/5 | 4/4 | | 8 | 4/4 | 50 | 47 |
| 1423 | 1403 | 15 | | 8/7 | 6 | 6 | | 15 | 8/7 | 4/4 | | 8 | 4/4 | 45 | 43 |
| 1424 | 1404 | 11 | | 6/5 | 7 | 6 | | 11 | 6/5 | 4/4 | 1 | 7 | 3/4 | 33 | 33 |
| 1425 | 1404 | 3 | | 0/3 | | 8 | | 3 | 0/3 | 0/3 | | 3 | 0/3 | | 58 |
| 1426 | 1405 | 14 | | 6/8 | 7 | 6 | | 14 | 6/8 | 4/4 | | 8 | 4/4 | 34 | 28 |
| TOTAL | | 210 | 2 | 108/102 | | | 8 | 202 | 105/97 | 64/65 | 1 | 128 | 64/64 | | |
| MEAN | | 12 | | | 6 | 6 | | 12 | | | | 8 | | 42 | 41 |
| SD | | 3.7 | | | 0.9 | 1.0 | | 3.3 | | | | 1.3 | | 6.2 | 7.1 |
| SE | | 0.9 | | | 0.2 | 0.2 | | 0.8 | | | | 0.3 | | 1.6 | 1.7 |
| N | | 18 | | | | | | 17 | | | | 17 | | | |

[a]One pup mis-sexed, corrected at Day 21.

# TABLE I-E-31 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 17 (Continued)

RESULTS OF THIRD GENERATION - FIRST MATING (F3a)

DOSE - 300 PPM

| | | DAY 0 | | | | | DAY 4 | | | | DAY 21 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT | DEATHS DAY 1-4 | LIVE PUPS | SEX M/F | LITTER REDUCED M/F | DEATHS DAY 4-21 | LIVE PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT |
| 1437 | 1428 | 12 | | 8/4 | 5 | 5 | 3 | 9 | 6/3 | 5/3 | | 8 | 5/3 | 33 | 29 |
| 1438 | 1428 | 14 | | 9/5 | 5 | 5 | 3 | 11 | 6/5 | 4/4 | 4 | 4 | 2/2 | 31 | 27 |
| 1439 | 1429 | | | | | | | | | | | | | | |
| 1440 | 1429 | 16 | | 13/3 | 6 | 6 | | 16 | 13/3 | 5/3 | | 8 | 5/3 | 40 | 40 |
| 1441 | 1430 | 13 | | 10/3 | 6 | 6 | 1 | 12 | 9/3 | 5/3 | | 8 | 5/3 | 40 | 41 |
| 1442 | 1430 | 11 | | 9/2 | 6 | 6 | 1 | 10 | 9/1 | 7/1 | 1 | 7 | 7/0 | 45 | |
| 1443 | 1431 | 12 | | 5/7 | 7 | 6 | | 12 | 5/7 | 4/4 | 8 | 0 | | | |
| 1444 | 1431 | 11 | | 6/5 | 7 | 7 | | 11 | 6/5 | 4/4 | | 8 | 4/4 | 45 | 42 |
| 1445 | 1432 | 14 | | 11/3 | 6 | 6 | | 14 | 11/3 | 5/3 | | 8 | 5/3 | 29 | 29 |
| 1446 | 1432 | | | | | | | | | | | | | | |
| 1447 | 1433 | 13 | | 9/4 | 7 | 7 | | 13 | 9/4 | 4/4 | | 8 | 4/4 | 46 | 42 |
| 1448 | 1433 | 7 | | 4/3 | 7 | 7 | | 7 | 4/3 | 4/3 | | 7 | 4/3 | 48 | 45 |
| 1459 | 1434 | 22 | | 11/11 | 7 | 7 | | 22 | 11/11 | 4/4 | | 8 | 4/4 | 37 | 39 |
| 1450 | 1434 | 12 | | 8/4 | 6 | 5 | | 12 | 8/4 | 4/4 | | 8 | 4/4 | 28 | 28 |
| 1451 | 1435 | 12 | | 8/4 | 6 | 7 | | 12 | 8/4 | 4/4 | | 8 | 4/4 | 28 | 28 |
| 1452 | 1435 | 13 | | 6/7 | 7 | 6 | | 13 | 6/7 | 4/4 | | 8 | 4/4 | 48 | 42 |
| 1453 | 1436 | | | | | | | | | | | | | | |
| 1454 | 1436 | 2 | | 0/2 | | | | 2 | 0/2 | 0/2 | | 2 | 0/2 | | 50 |
| 1455 | 1427 | 13 | | 4/9 | 7 | 6 | | 13 | 4/9 | 4/4 | | 8 | 4/4 | 38 | 35 |
| 1456 | 1427 | 15 | | 6/9 | 7 | 7 | | 15 | 6/9 | 4/4 | | 8 | 4/4 | 41 | 39 |
| TOTAL | | 212 | | 127/85 | | | 8 | 204 | 121/83 | 71/58 | 13 | 116 | 65/51 | | |
| MEAN | | 13 | | | 6 | 6 | | 13 | | | | 7 | | 39 | 37 |
| SD | | 4.0 | | | 0.7 | 0.8 | | 3.3 | | | | 2.4 | | 7.2 | 7.2 |
| SE | | 1.0 | | | 0.2 | 0.2 | | 0.8 | | | | 0.6 | | 1.9 | 1.9 |
| N | | 17 | | | | | | 16 | | | | 17 | | | |

# TABLE I-E-31 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 17 (Continued)

RESULTS OF THIRD GENERATION - FIRST MATING (F3a)

DOSE - 3000 PPM

| | | DAY 0 | | | | | DAY 4 | | | | DAY 21 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT | DEATHS DAY 1-4 | LIVE PUPS | SEX M/F | LITTER REDUCED M/F | DEATHS DAY 4-21 | LIVE PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT |
| 1467 | 1465 | 17 | | 10/7 | 6 | 6 | | 17 | 10/7 | 4/4 | | 8 | 4/4 | 33 | 32 |
| 1468 | 1466 | 16 | 1 | 10/6 | 6 | 6 | | 16 | 10/6 | 4/4 | 1 | 7 | 4/3 | 32 | 33 |
| 1469 | 1466 | 13 | | 7/6 | 6 | 6 | 1 | 12 | 7/5 | 4/4 | 1 | 7 | 3/4 | 33 | 31 |
| 1470 | 1457 | 5 | | 4/1 | 7 | 7 | | 5 | 4/1 | 4/1 | | 5 | 4/1 | 31 | 29 |
| 1471 | 1457 | 14 | | 9/5 | 6 | 6 | | 14 | 9/5 | 4/4 | 2 | 6 | 2/4 | 26 | 28 |
| 1472 | 1458 | 13 | | 5/8 | 7 | 6 | | 13 | 5/8 | 4/4 | | 8 | 4/4 | 33 | 33 |
| 1473 | 1458 | 13 | | 8/5 | 6 | 6 | | 13 | 8/5 | 4/4 | | 8 | 4/4 | 31 | 31 |
| 1474 | 1459 | | | | | | | | | | | | | | |
| 1475 | 1459 | | | | | | | | | | | | | | |
| 1476 | 1460 | 10 | | 4/6 | 7 | 7 | | 10 | 4/6 | 4/4 | | 8 | 4/4 | 20 | 21 |
| 1477 | 1460 | 8 | | 4/4 | 8 | 8 | | 8 | 4/4 | 4/4 | 1 | 7 | 3/4 | 31 | 30 |
| 1478 | 1461 | 12 | | 4/8 | 7 | 7 | | 12 | 4/8 | 4/4 | 8 | | | | |
| 1479 | 1461 | 11 | | 6/5 | 4 | 4 | | 11 | 6/5 | 4/4 | | 8 | 4/4 | 30 | 30 |
| 1480 | 1462 | 13 | | 8/5 | 7 | 7 | | 13 | 8/5 | 4/4 | | 8 | 4/4 | 28 | 26 |
| 1481 | 1462 | 14 | 1 | 11/3 | 6 | 5 | | 14 | 11/3 | 5/3 | 5 | 3 | 2/1 | 26 | 14 |
| 1482 | 1463 | 5 | | 3/2 | 9 | 9 | | 5 | 3/2 | 3/2 | | 5 | 3/2 | 58 | 55 |
| 1483 | 1463 | 15 | | 9/7 | 6 | 6 | | 15 | 8/7 | 4/4 | 2 | 6 | 2/4 | 27 | 26 |
| 1484 | 1464 | 14 | | 8/6 | 7 | 7 | | 14 | 8/6 | 4/4 | 4 | 4 | 2/2 | 34 | 28 |
| 1485 | 1464 | 14 | | 9/5 | 7 | 6 | | 14 | 9/5 | 4/4 | | 8 | 4/4 | 31 | 30 |
| 1586 | 1465 | 12 | | 6/6 | 6 | 6 | 1 | 11 | 5/6 | 4/4 | 6 | 2 | 0/2 | | 26 |
| TOTAL | | 219 | 2 | 124/95 | | | 2 | 217 | 123/94 | 72/66 | 30 | 108 | 53/55 | | |
| MEAN | | 12 | | | 7 | 6 | | 12 | | | | 6 | | 32 | 30 |
| SD | | 3.3 | | | 1.0 | 1.1 | | 3.3 | | | | 1.9 | | 7.9 | 8.1 |
| SE | | 0.8 | | | 0.2 | 0.3 | | 0.8 | | | | 0.5 | | 2.0 | 2.0 |
| N | | 18 | | | | | | 18 | | | | 17 | | | |

TABLE I-E-32

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 18

LITTER OBSERVATIONS

THIRD GENERATION - FIRST MATING (F3a)

| DOSE (PPM) | FEMALE NUMBER | DAY OF LACTATION | OBSERVATION |
|---|---|---|---|
| 300 | 1438 | 20 | ONE MALE AND TWO FEMALE PUPS - FOUND DEAD; ONE PUP - CANNIBALIZED. |
| 3000 | 1478 | 9 | ALL PUPS (EIGHT) - FOUND DEAD. |
| | 1484 | 14 | THREE FEMALE PUPS - FOUND DEAD; ONE PUP - CANNIBALIZED. |
| | 1469 | 17 | ONE MALE PUP - FOUND DEAD. |
| | 1477 | 19 | ONE MALE PUP - FOUND DEAD. |
| | 1471 | 20 | ONE MALE PUP - FOUND DEAD; ONE PUP - CANNIBALIZED. |
| | 1486 | 20 | TWO FEMALE AND TWO MALE PUPS - FOUND DEAD; ONE PUP - CANNIBALIZED. |
| | 1481 | 21 | FOUR FEMALE PUPS - FOUND DEAD; ONE PUP - CANNIBALIZED. |
| | 1481 | 23 | ONE PUP - CANNIBALIZED. |

TABLE I-E-33

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 19

PUP NECROPSY OBSERVATIONS (F3a) AT DAY 21

| DOSE (PPM) | FEMALE NUMBER | NUMBER OF PUPS | OBSERVATION |
|---|---|---|---|
| 0 | 1408 | 8 | ALL TISSUES APPEAR NORMAL |
| | 1410 | 8 | ALL TISSUES APPEAR NORMAL |
| | 1415 | 8 | ALL TISSUES APPEAR NORMAL |
| | 1423 | 8 | ALL TISSUES APPEAR NORMAL |
| | 1424 | 7 | ALL TISSUES APPEAR NORMAL |
| | 1426 | 8 | ALL TISSUES APPEAR NORMAL |
| 300 | 1437 | 8 | ALL TISSUES APPEAR NORMAL |
| | 1438 | 4 | ALL TISSUES APPEAR NORMAL |
| | 1440 | 8 | ALL TISSUES APPEAR NORMAL |
| | 1442 | 7 | ALL TISSUES APPEAR NORMAL |
| | 1449 | 8 | ALL TISSUES APPEAR NORMAL |
| | 1454 | 2 | ALL TISSUES APPEAR NORMAL |
| 3000 | 1468 | 7 | ALL TISSUES APPEAR NORMAL |
| | 1470 | 5 | ALL TISSUES APPEAR NORMAL |
| | 1476 | 8 | ALL TISSUES APPEAR NORMAL |
| | 1480 | 8 | ALL TISSUES APPEAR NORMAL |
| | 1484 | 4 | ALL TISSUES APPEAR NORMAL |
| | 1485 | 8 | ALL TISSUES APPEAR NORMAL |

# TABLE I-E-34

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 20

RESULTS OF THIRD GENERATION - SECOND MATING (F3b)

DOSE - 0 PPM

| | | DAY 0 | | | | | DAY 4 | | | | DAY 21 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT | DEATHS DAY 1-4 | LIVE PUPS | SEX M/F | LITTER REDUCED M/F | DEATHS DAY 4-21 | LIVE PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT |
| 1407 | 1402 | 17 | | 5/12[a] | 5 | 5 | 2 | 15 | 3/12 | 3/5 | 8 | | | | |
| 1408 | 1405 | 7 | | 5/2 | 5 | 5 | | 7 | 5/2 | 4/2 | | 6 | 4/2 | 47 | 47 |
| 1409 | 1405 | 20 | | 13/7 | 6 | 5 | 1 | 19 | 12/7 | 4/4 | | 8 | 4/4 | 43 | 39 |
| 1410 | 1406 | 16 | | 8/8 | 6 | 6 | | 16 | 8/8 | 4/4 | | 8 | 4/4 | 46 | 42 |
| 1411 | 1406 | 17 | | 12/5 | 6 | 6 | | 17 | 12/5 | 4/4 | | 8 | 4/4 | 54 | 53 |
| 1412 | 1397 | 11 | | 11/0 | 7 | | | 11 | 11/0 | 8/0 | | 8 | 8/0 | 46 | |
| 1413 | 1397 | 13 | | 8/5 | 5 | 5 | | 13 | 8/5 | 4/4 | 8 | | | | |
| 1414 | 1398 | 18 | | 12/6 | 6 | 6 | | 18 | 12/6 | 4/4 | | 8 | 4/4 | 44 | 41 |
| 1415 | 1398 | 12 | | 6/6 | 7 | 7 | | 12 | 6/6 | 4/4 | | 8 | 4/4 | 61 | 58 |
| 1416 | 1399 | 15 | 1 | 10/5 | 6 | 5 | 1 | 14 | 9/5 | 4/4 | | 8 | 4/4 | 50 | 44 |
| 1417 | 1399 | 15 | 1 | 13/2 | 6 | 5 | 3 | 12 | 10/2 | 6/2 | | 8 | 6/2 | 59 | 46 |
| 1418 | 1400 | 13 | 1 | 6/7 | 6 | 6 | | 13 | 6/7 | 4/4 | | 8 | 4/4 | 49 | 44 |
| 1419 | 1400 | 16 | | 4/12 | 5 | 5 | 1 | 15 | 4/11 | 4/4 | 3 | 5 | 4/1 | 49 | 47 |
| 1420 | 1401 | 7 | | 5/2 | 7 | 6 | | 7 | 5/2 | 5/2 | | 7 | 5/2 | 54 | 48 |
| 1421 | 1401 | 15 | | 5/10 | 6 | 5 | | 15 | 5/10 | 4/4 | | 8 | 4/4 | 55 | 47 |
| 1422 | 1402 | 18 | | 10/8 | 6 | 6 | | 18 | 10/8 | 4/4 | | 8 | 4/4 | 50 | 45 |
| 1423 | 1403 | 18 | | 9/9 | 6 | 5 | | 18 | 9/9 | 4/4 | | 8 | 4/4 | 48 | 46 |
| 1424 | 1403 | 12 | | 7/5 | 7 | 6 | | 12 | 7/5 | 4/4 | | 8 | 4/4 | 47 | 39 |
| 1425 | 1404 | 13 | | 2/13 | 5 | 5 | 2 | 13 | 7/6 | 4/4 | | 8 | 4/4 | 45 | 38 |
| 1426 | 1404 | 14 | | 3/11 | 5 | 5 | | 14 | 3/11 | 3/5 | | 8 | 3/5 | 42 | 47 |
| TOTAL | | 287 | 3 | 159/128 | | | 10 | 279 | 152/127 | 85/72 | 19 | 138 | 78/60 | | |
| MEAN | | 14 | | | 6 | 5 | | 14 | | | | 8 | | 49 | 45 |
| SD | | 3.5 | | | 0.7 | 0.6 | | 3.3 | | | | 0.8 | | 5.3 | 5.0 |
| SE | | 0.8 | | | 0.2 | 0.1 | | 0.7 | | | | 0.2 | | 1.3 | 1.2 |
| N | | 20 | | | | | | 20 | | | | 17 | | | |

[a]Pups initially mis-sexed.

# TABLE I-E-34 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 20 (Continued)

RESULTS OF THIRD GENERATION - SECOND MATING (F3b)

DOSE - 300 PPM

| | | DAY 0 | | | | | DAY 4 | | | | DAY 21 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT | DEATHS DAY 1-4 | LIVE PUPS | SEX M/F | LITTER REDUCED M/F | DEATHS DAY 4-21 | LIVE PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT |
| 1437 | 1436 | | | | | | | | | | | | | | |
| 1438 | 1436 | 9 | | 4/5 | 7 | 6 | | 9 | 4/5 | 4/4 | | 8 | 4/4 | 49 | 49 |
| 1439 | 1428 | 6 | | 2/4 | 7 | 7 | | 6 | 2/4 | 2/4 | | 6 | 2/4 | 49 | 44 |
| 1440 | 1428 | 12 | | 5/7 | 6 | 6 | | 12 | 5/7 | 4/4 | 2 | 6 | 3/3 | 46 | 42 |
| 1441 | 1429 | 13 | | 7/6[a] | 5 | 6 | | 13 | 7/6 | 4/4 | | 8 | 4/4 | 36 | 36 |
| 1442 | 1429 | 13 | | 4/9 | 6 | 6 | | 13 | 4/9 | 4/4 | | 8 | 4/4 | 54 | 53 |
| 1443 | 1430 | 16 | | 8/8 | 6 | 5 | | 16 | 8/8 | 4/4 | | 8 | 4/4 | 50 | 45 |
| 1444 | 1430 | 14 | | 11/3 | 7 | 6 | | 14 | 11/3 | 5/3 | | 8 | 5/3 | 51 | 48 |
| 1445 | 1431 | 15 | | 9/6[a] | 5 | 5 | 1 | 14 | 8/6 | 4/4 | | 8 | 4/4 | 51 | 40 |
| 1446 | 1431 | 7 | | 5/2 | 7 | 7 | | 7 | 5/2 | 5/2 | | 7 | 5/2 | 46 | 39 |
| 1447 | 1432 | 14 | | 10/4 | 6 | 4 | | 14 | 10/4 | 4/4 | | 8 | 4/4 | 38 | 31 |
| 1448 | 1432 | 17 | 1 | 10/7 | 7 | 6 | 1 | 16 | 10/6 | 4/4 | | 8 | 4/4 | 53 | 42 |
| 1449 | 1433 | 15 | | 6/9 | 7 | 6 | 3 | 12 | 4/8 | 4/4 | | 8 | 4/4 | 48 | 45 |
| 1450 | 1433 | 20 | | 10/10[a] | 6 | 6 | 1 | 19 | 10/9 | 4/4 | | 8 | 4/4 | 53 | 46 |
| 1451 | 1434 | 13 | | 10/3 | 6 | 6 | | 13 | 10/3 | 5/3 | | 8 | 4/4 | 48 | 51 |
| 1452 | 1434 | 17 | | 8/9 | 6 | 6 | 1 | 16 | 7/9 | 4/4 | 2 | 6 | 2/4 | 40 | 34 |
| 1453 | 1435 | 11 | | 4/7 | 6 | 6 | | 11 | 4/7 | 4/4 | | 8 | 4/4 | 49 | 44 |
| 1454 | 1427 | 10 | | 5/5 | 6 | 6 | | 10 | 5/5 | 4/4 | | 8 | 4/4 | 49 | 44 |
| 1455 | 1427 | 17 | | 8/9 | 7 | 5 | | 17 | 8/9 | 4/4 | | 8 | 4/4 | 50 | 40 |
| 1456 | 1435 | 17 | | 10/7[a] | 5 | 5 | | 17 | 10/7 | 4/4 | | 8 | 4/4 | 41 | 34 |
| TOTAL | | 256 | 1 | 136/120 | | | 7 | 249 | 132/117 | 77/72 | 4 | 145 | 73/72 | | |
| MEAN | | 13 | | | 6 | 6 | | 13 | | | | 8 | | 47 | 43 |
| SD | | 3.7 | | | 0.7 | 0.7 | | 3.4 | | | | 0.8 | | 5.1 | 5.9 |
| SE | | 0.8 | | | 0.2 | 0.2 | | 0.8 | | | | 0.2 | | 1.2 | 1.4 |
| N | | 19 | | | | | | 19 | | | | 19 | | | |

[a]Pups initially mis-sexed.

# TABLE I-E-34 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 20 (Continued)

RESULTS OF THIRD GENERATION - SECOND MATING (F3b)

DOSE - 3000 PPM

| | | DAY 0 | | | | | DAY 4 | | | | DAY 21 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT | DEATHS DAY 1-4 | LIVE PUPS | SEX M/F | LITTER REDUCED M/F | DEATHS DAY 4-21 | LIVE PUPS | SEX M/F | MEAN M PUP WT | MEAN F PUP WT |
| 1467 | 1466 | 16 | | 8/8[a] | 6 | 6 | | 16 | 8/8 | 4/4 | | 8 | 4/4 | 52 | 45 |
| 1468 | 1457 | 15 | | 9/6[a] | 7 | 7 | 1 | 14 | 8/6 | 4/4 | | 8 | 4/4 | 47 | 44 |
| 1469 | 1457 | 12 | | 7/5[a] | 7 | 7 | | 12 | 7/5 | 4/4 | | 8 | 4/4 | 45 | 36 |
| 1470 | 1458 | 12 | | 3/9[a] | 6 | 5 | | 12 | 3/9 | 3/5 | | 8 | 3/5 | 48 | 43 |
| 1471 | 1458 | 18 | 1 | 8/10 | 6 | 5 | 1 | 17 | 8/9 | 4/4 | | 8 | 4/4 | 47 | 37 |
| 1472 | 1459 | 6 | | 3/3 | 8 | 7 | | 6 | 3/3 | 3/3 | 6 | 0 | | | |
| 1473 | 1459 | 13 | | 3/10[a] | 5 | 5 | | 13 | 3/10 | 3/5 | | 8 | 3/5 | 60 | 49 |
| 1474 | 1460 | | | | | | | | | | | | | | |
| 1475 | 1460 | 15 | | 6/9 | 6 | 5 | 15 | | | | | | | | |
| 1476 | 1461 | 11 | | 4/7 | 7 | 5 | 2 | 9 | 3/6 | 3/5 | | 8 | 3/5 | 46 | 39 |
| 1477 | 1461 | 12 | | 4/8 | 6 | 6 | | 12 | 4/8 | 4/4 | | 8 | 4/4 | 46 | 40 |
| 1478 | 1562 | 12 | | 6/6 | 7 | 7 | | 12 | 6/6 | 4/4 | | 8 | 4/4 | 39 | 36 |
| 1479 | 1462 | 17 | | 10/7[a] | 6 | 6 | | 17 | 10/7 | 4/4 | | 8 | 4/4 | 41 | 35 |
| 1480 | 1466 | 13 | 3 | 4/9 | 5 | 5 | 6 | 7 | 5/2 | 5/2 | 1 | 6 | 4/2 | 42 | 41 |
| 1481 | 1463 | 17 | | 9/8 | 6 | 5 | | 17 | 9/8 | 4/4 | | 8 | 4/4 | 46 | 42 |
| 1482 | 1464 | 10 | | 4/6 | 6 | 5 | | 10 | 4/6 | 4/4 | | 8 | 4/4 | 39 | 37 |
| 1483 | 1464 | | | | | | | | | | | | | | |
| 1484 | 1465 | 14 | | 10/4 | 6 | 7 | | 14 | 10/4 | 4/4 | | 8 | 4/4 | 45 | 38 |
| 1485 | 1465 | 15 | | 10/5 | 6 | 5 | | 15 | 10/5 | 4/4 | | 8 | 4/4 | 39 | 39 |
| 1486 | 1463 | 14 | | 7/7 | 6 | 6 | | 14 | 7/7 | 4/4 | | 8 | 4/4 | 50 | 45 |
| TOTAL | | 242 | 4 | 115/127 | | | 25 | 217 | 108/109 | 65/68 | 7 | 126 | 61/65 | | |
| MEAN | | 13 | | | 6 | 6 | | 13 | | | | 7 | | 46 | 41 |
| SD | | 2.9 | | | 0.7 | 0.9 | | 3.3 | | | | 2.0 | | 5.4 | 4.5 |
| SE | | 0.7 | | | 0.2 | 0.2 | | 0.8 | | | | 0.5 | | 1.4 | 1.1 |
| N | | 18 | | | | | | 17 | | | | 17 | | | |

[a]Pups initially mis-sexed.

TABLE I-E-35

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 21

LITTER OBSERVATIONS

THIRD GENERATION - SECOND MATING (F3b)

| DOSE (PPM) | FEMALE NUMBER | DAY OF LACTATION | OBSERVATION |
|---|---|---|---|
| 0 | 1414 | 4 | ALL PUPS (EXCEPT ONE MALE PUP) - FOUND DEAD. |
| 300 | 1453 | 2 | ONE PUP - FOUND CANNIBALIZED. |
| | 1452 | 16 | TWO PUPS - FOUND CANNIBALIZED. |
| | 1440 | 25 | TWO PUPS (ONE CANNIBALIZED) - FOUND DEAD. |
| 3000 | 1480 | 15 | ONE PUP - FOUND CANNIBALIZED. |

TABLE I-E-36

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 22

PUP NECROPSY OBSERVATIONS (F3b) AT DAY 21

| DOSE (PPM) | FEMALE NUMBER | NUMBER OF PUPS | OBSERVATION |
|---|---|---|---|
| 0 | 1408 | 6 | ALL TISSUES APPEAR NORMAL |
| | 1410 | 8 | ALL TISSUES APPEAR NORMAL |
| | 1411 | 8 | ALL TISSUES APPEAR NORMAL |
| | 1421 | 5 | ALL TISSUES APPEAR NORMAL |
| | 1422 | 8 | ALL TISSUES APPEAR NORMAL |
| | 1425 | 8 | ALL TISSUES APPEAR NORMAL |
| 300 | 1439 | 6 | ALL TISSUES APPEAR NORMAL |
| | 1440 | 6 | ALL TISSUES APPEAR NORMAL |
| | 1443 | 8 | ALL TISSUES APPEAR NORMAL |
| | 1447 | 8 | ALL TISSUES APPEAR NORMAL |
| | 1453 | 8 | ALL TISSUES APPEAR NORMAL |
| | 1455 | 8 | ALL TISSUES APPEAR NORMAL |
| 3000 | 1471 | 8 | ALL TISSUES APPEAR NORMAL |
| | 1477 | 8 | ALL TISSUES APPEAR NORMAL |
| | 1478 | 8 | ALL TISSUES APPEAR NORMAL |
| | 1482 | 8 | ALL TISSUES APPEAR NORMAL |
| | 1484 | 8 | ALL TISSUES APPEAR NORMAL |
| | 1485 | 8 | ALL TISSUES APPEAR NORMAL |

TABLE I-E-37

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 23

BODY WEIGHTS AND FOOD CONSUMPTION (G) OF PARENT RATS (F2b)

BODY WEIGHTS

| DOSE (PPM) | | MALES WK 4 | WK 9 | WK 11 | WK 20 |
|---|---|---|---|---|---|
| 0 | MEAN | 338 | 481 | 504 | 564 |
| | SD | 26.1 | 40.7 | 41.2 | 43.6 |
| | SE | 8.2 | 12.9 | 13.0 | 13.8 |
| | N | 10 | 10 | 10 | 10 |
| 300 | MEAN | 328 | 441 | 482 | 553 |
| | SD | 19.1 | 30.7 | 41.1 | 51.0 |
| | SE | 6.0 | 9.7 | 13.0 | 16.1 |
| | N | 10 | 10 | 10 | 10 |
| 3000 | MEAN | 328 | 449 | 480 | 538 |
| | SD | 32.0 | 45.9 | 49.7 | 68.2 |
| | SE | 10.1 | 14.5 | 15.7 | 21.6 |
| | N | 10 | 10 | 10 | 10 |

FOOD CONSUMPTION

| DOSE (PPM) | | MALES WK 4 | WK 9 | WK 11 | WK 20 |
|---|---|---|---|---|---|
| 0 | MEAN | 38.6 | 33.7 | 30.4 | 29.4 |
| | SD | 2.4 | 4.3 | 3.9 | 3.6 |
| | SE | 0.9 | 1.3 | 1.2 | 1.1 |
| | N | 7 | 10 | 10 | 10 |
| 300 | MEAN | 39.1 | 31.4 | 29.3 | 29.2 |
| | SD | 3.6 | 2.4 | 2.8 | 3.9 |
| | SE | 1.3 | 0.9 | 0.9 | 1.2 |
| | N | 8 | 8 | 10 | 10 |
| 3000 | MEAN | 38.2 | 31.2 | 28.8 | 28.9 |
| | SD | 3.8 | 4.4 | 3.7 | 4.0 |
| | SE | 1.3 | 1.4 | 1.2 | 1.3 |
| | N | 9 | 10 | 10 | 10 |

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 23 (Continued)

BODY WEIGHTS AND FOOD CONSUMPTION (G) OF PARENT RATS (F2b)

BODY WEIGHTS

| DOSE (PPM) | | FEMALES WK 4 | WK 9 | WK 11 | WK 20 |
|---|---|---|---|---|---|
| 0 | MEAN | 212 | 264 | 278 | 300 |
| | SD | 19.7 | 24.9 | 26.6 | 23.5 |
| | SE | 4.4 | 5.6 | 6.0 | 5.2 |
| | N | 20 | 20 | 20 | 20 |
| 300 | MEAN | 210 | 255 | 269 | 297 |
| | SD | 31.2 | 17.5 | 17.8 | 20.2 |
| | SE | 7.0 | 3.9 | 4.0 | 4.5 |
| | N | 20 | 20 | 20 | 20 |
| 3000 | MEAN | 204 | 250 | 265 | 281* |
| | SD | 18.9 | 22.2 | 24.4 | 23.7 |
| | SE | 4.3 | 5.0 | 5.5 | 5.3 |
| | N | 19 | 20 | 20 | 20 |

FOOD CONSUMPTION

| DOSE (PPM) | | FEMALES WK 4 | WK 9 | WK 11 | WK 20 |
|---|---|---|---|---|---|
| 0 | MEAN | 34.8 | 29.8 | 29.3 | 30.0 |
| | SD | 5.1 | 4.2 | 6.7 | 2.2 |
| | SE | 1.1 | 1.0 | 1.5 | 0.6 |
| | N | 20 | 18 | 20 | 15 |
| 300 | MEAN | 33.2 | 25.4 | 25.9 | 29.5 |
| | SD | 5.8 | 5.5 | 6.8 | 6.4 |
| | SE | 1.3 | 1.3 | 1.5 | 1.5 |
| | N | 19 | 19 | 20 | 18 |
| 3000 | MEAN | 33.6 | 27.4 | 25.4 | 29.2 |
| | SD | 6.4 | 6.0 | 5.9 | 4.4 |
| | SE | 1.6 | 1.5 | 1.4 | 1.1 |
| | N | 16 | 17 | 18 | 16 |

*$p<0.05$ as compared to controls: Dunnett's t-test.

TABLE 24

TOXICOLOGY OBSERVATION REPORT

CLINICAL SIGNS
PROJECT NUMBER - 10734-06

| WEEK NO. ** | DOSE GROUP/SEX * | ANIMAL NUMBER ***** | OBSERVATIONS : QUALIFIER COMMENTS ********** |
|---|---|---|---|
| -001 | CONTROL MALE | 01397 | STARTED |
| | | ***** | MAY 11, 1978 |
| 001 | CONTROL MALE | 01397 | ALL ANIMALS NORMAL |
| 002 | CONTROL MALE | 01397 | ALL ANIMALS NORMAL |
| 003 | CONTROL MALE | 01397 | ALL ANIMALS NORMAL |
| 004 | CONTROL MALE | 01402 | MISSING |
| | | | FOUND-RETURNED TO STUDY |
| 005 | CONTROL MALE | 01397 | ALL ANIMALS NORMAL |
| 006 | CONTROL MALE | 01397 | ALL ANIMALS NORMAL |
| 007 | CONTROL MALE | 01397 | ALL ANIMALS NORMAL |
| 008 | CONTROL MALE | 01397 | ALL ANIMALS NORMAL |
| 009 | CONTROL MALE | 01397 | ALL ANIMALS NORMAL |
| 010 | CONTROL MALE | 01397 | ALL ANIMALS NORMAL |
| 011 | CONTROL MALE | 01397 | ALL ANIMALS NORMAL |
| 012 | CONTROL MALE | 01397 | MATE TO GET F3A |
| | | | ALL ANIMALS NORMAL |
| 013 | CONTROL MALE | 01397 | ALL ANIMALS NORMAL |
| 014 | CONTROL MALE | 01397 | REMOVED FROM MATING |
| | FEMALE | 01409 | LOCAL HAIR LOSS : LATERAL-RIGHT,POSTERIOR |
| | | | LOCAL HAIR LOSS : LATERAL-LEFT,POSTERIOR |
| 015 | CONTROL FEMALE | 01409 | LOCAL HAIR LOSS : LATERAL-RIGHT,THORACIC |
| | | | LOCAL HAIR LOSS : LATERAL-LEFT,THORACIC |
| | 300 PPM | 01444 | SMALL MASS(<1CM) : VENTRAL-AXILLARY,LEFT |
| 016 | CONTROL FEMALE | 01409 | LOCAL HAIR LOSS : LATERAL-RIGHT,THORACIC |
| | | | LOCAL HAIR LOSS : LATERAL-LEFT,THORACIC |
| | 300 PPM | 01444 | MEDIUM MASS(1-5CM) : VENTRAL-AXILLARY,LEFT |

TABLE 24 (CONTINUED)

TOXICOLOGY OBSERVATION REPORT

CLINICAL SIGNS
PROJECT NO. - 10734-06

| WEEK NO. | ** DOSE GROUP/SEX * | ANIMAL NUMBER | ***** OBSERVATIONS : QUALIFIER COMMENTS ********** : |
|---|---|---|---|
| 017 | CONTROL FEMALE | 01409 | LOCAL HAIR LOSS : LATERAL-RIGHT,THORACIC |
| | | | LOCAL HAIR LOSS : LATERAL-LEFT,THORACIC |
| | 300 PPM | 01444 | MEDIUM MASS(1-5CM) : VENTRAL-AXILLARY,LEFT |
| 018 | CONTROL FEMALE | 01409 | LOCAL HAIR LOSS : LATERAL-RIGHT,THORACIC |
| | | | LOCAL HAIR LOSS : LATERAL-LEFT,THORACIC |
| | 300 PPM | 01444 | MEDIUM MASS(1-5CM) : VENTRAL-AXILLARY,LEFT |
| 019 | CONTROL FEMALE | 01409 | LOCAL HAIR LOSS : LATERAL-RIGHT,THORACIC |
| | | | LOCAL HAIR LOSS : LATERAL-LEFT,THORACIC |
| | 300 PPM | 01444 | MEDIUM MASS(1-5CM) : VENTRAL-AXILLARY,LEFT |
| | 3000 PPM | 01477 | LOCAL HAIR LOSS : DORSAL-LUMBAR,MID |
| 020 | CONTROL MALE | 01397 | MATE TO GET F3B |
| | FEMALE | 01409 | LOCAL HAIR LOSS : LATERAL-RIGHT,THORACIC |
| | | | LOCAL HAIR LOSS : LATERAL-LEFT,THORACIC |
| | 300 PPM | 01444 | MEDIUM MASS(1-5CM) : VENTRAL-AXILLARY,LEFT |
| | 3000 PPM | 01477 | LOCAL HAIR LOSS : DORSAL-LUMBAR,MID |
| 021 | CONTROL FEMALE | 01409 | LOCAL HAIR LOSS : LATERAL-RIGHT,THORACIC |
| | | | LOCAL HAIR LOSS : LATERAL-LEFT,THORACIC |
| | 300 PPM | 01444 | MEDIUM MASS(1-5CM) : VENTRAL-AXILLARY,LEFT |
| 022 | CONTROL MALE | 01397 | REMOVED FROM MATING |
| | FEMALE | 01409 | LOCAL HAIR LOSS : LATERAL-RIGHT,THORACIC |
| | | | LOCAL HAIR LOSS : LATERAL-LEFT,THORACIC |
| | 300 PPM | 01444 | MEDIUM MASS(1-5CM) : VENTRAL-AXILLARY,LEFT |
| 023 | CONTROL FEMALE | 01409 | LOCAL HAIR LOSS : LATERAL-RIGHT,THORACIC |
| | | | LOCAL HAIR LOSS : LATERAL-LEFT,THORACIC |
| | 300 PPM | 01444 | MEDIUM MASS(1-5CM) : VENTRAL-AXILLARY,LEFT |
| 024 | CONTROL FEMALE | 01409 | LOCAL HAIR LOSS : LATERAL-RIGHT,THORACIC |
| | | | LOCAL HAIR LOSS : LATERAL-LEFT,THORACIC |
| | 300 PPM | 01444 | MEDIUM MASS(1-5CM) : VENTRAL-AXILLARY,LEFT |
| 025 | CONTROL FEMALE | 01409 | LOCAL HAIR LOSS : LATERAL-RIGHT,THORACIC |
| | | | LOCAL HAIR LOSS : LATERAL-LEFT,THORACIC |
| | 300 PPM | 01444 | MEDIUM MASS(1-5CM) : VENTRAL-AXILLARY,LEFT |
| 026 | CONTROL FEMALE | 01409 | LOCAL HAIR LOSS : LATERAL-RIGHT,THORACIC |
| | | | LOCAL HAIR LOSS : LATERAL-LEFT,THORACIC |
| | 300 PPM | 01444 | MEDIUM MASS(1-5CM) : VENTRAL-AXILLARY,LEFT |
| 027 | CONTROL FEMALE | 01409 | LOCAL HAIR LOSS : LATERAL-RIGHT,THORACIC |
| | | | LOCAL HAIR LOSS : LATERAL-LEFT,THORACIC |
| | 300 PPM | 01444 | MEDIUM MASS(1-5CM) : VENTRAL-AXILLARY,LEFT |

TABLE 24 (CONTINUED)

TOXICOLOGY OBSERVATION REPORT

CLINICAL SIGNS
PROJECT NO. - 10734-06

| WEEK NO. ** | DOSE GROUP/SEX * | ANIMAL NUMBER | ***** OBSERVATIONS : QUALIFIER COMMENTS ********** |
|---|---|---|---|
| | | 01447 | URINE STAIN ON COAT |
| | | 01451 | EMACIATED |
| | | | NASAL DISCHARGE |
| | | ***** | CRUSTY NOSE |
| | | | URINE STAIN ON COAT |
| | | 01453 | URINE STAIN ON COAT |
| 028 | CONTROL FEMALE | 01409 | LOCAL HAIR LOSS : LATERAL-RIGHT,THORACIC |
| | | | LOCAL HAIR LOSS : LATERAL-LEFT,THORACIC |
| | | 01422 | URINE STAIN ON COAT |
| | 300 PPM | 01444 | MEDIUM MASS(1-5CM) : VENTRAL-AXILLARY,LEFT |
| | | 01451 | EMACIATED |
| 029 | CONTROL FEMALE | 01409 | LOCAL HAIR LOSS : LATERAL-RIGHT,THORACIC |
| | | | LOCAL HAIR LOSS : LATERAL-LEFT,THORACIC |
| | | 01422 | URINE STAIN ON COAT |
| | 300 PPM | 01444 | MEDIUM MASS(1-5CM) : VENTRAL-AXILLARY,LEFT |
| | | 01451 | EMACIATED |

TABLE I-E-39

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 25

PARENT NECROPSY OBSERVATIONS (F2b) - MALES

| DOSE (PPM) | MALE NUMBER | OBSERVATION |
|---|---|---|
| 0 | 1397 | ALL TISSUES APPEAR NORMAL |
| | 1398 | ALL TISSUES APPEAR NORMAL |
| | 1399 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 1400 | ALL TISSUES APPEAR NORMAL |
| | 1401 | ALL TISSUES APPEAR NORMAL |
| | 1402 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 1403 | ALL TISSUES APPEAR NORMAL |
| | 1404 | ALL TISSUES APPEAR NORMAL |
| | 1405 | ALL TISSUES APPEAR NORMAL |
| | 1406 | ALL TISSUES APPEAR NORMAL |
| 300 | 1427 | ALL TISSUES APPEAR NORMAL |
| | 1428 | ALL TISSUES APPEAR NORMAL |
| | 1429 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 1430 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 1431 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 1432 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 1433 | ALL TISSUES APPEAR NORMAL |
| | 1434 | ALL TISSUES APPEAR NORMAL |
| | 1435 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 1436 | ALL TISSUES APPEAR NORMAL |
| 3000 | 1457 | ALL TISSUES APPEAR NORMAL |
| | 1458 | ALL TISSUES APPEAR NORMAL |
| | 1459 | ALL TISSUES APPEAR NORMAL |
| | 1460 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 1461 | ALL TISSUES APPEAR NORMAL |
| | 1462 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 1463 | ALL TISSUES APPEAR NORMAL |
| | 1464 | ALL TISSUES APPEAR NORMAL |
| | 1465 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 1466 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 25 (Continued)

PARENT NECROPSY OBSERVATIONS (F2b) - FEMALES

| DOSE (PPM) | FEMALE NUMBER | OBSERVATION |
|---|---|---|
| 0 | 1407 | ALL TISSUES APPEAR NORMAL |
| | 1408 | ALL TISSUES APPEAR NORMAL |
| | 1409 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 1410 | ALL TISSUES APPEAR NORMAL |
| | 1411 | ALL TISSUES APPEAR NORMAL |
| | 1412 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 1413 | ALL TISSUES APPEAR NORMAL |
| | 1414 | ALL TISSUES APPEAR NORMAL |
| | 1415 | ALL TISSUES APPEAR NORMAL |
| | 1416 | ALL TISSUES APPEAR NORMAL |
| | 1417 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 1418 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 1419 | ALL TISSUES APPEAR NORMAL |
| | 1420 | ALL TISSUES APPEAR NORMAL |
| | 1421 | ALL TISSUES APPEAR NORMAL |
| | 1422 | ALL TISSUES APPEAR NORMAL |
| | 1423 | ALL TISSUES APPEAR NORMAL |
| | 1424 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 1425 | ALL TISSUES APPEAR NORMAL |
| | 1426 | ALL TISSUES APPEAR NORMAL |
| 300 | 1437 | ALL TISSUES APPEAR NORMAL |
| | 1438 | ALL TISSUES APPEAR NORMAL |
| | 1439 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 1440 | ALL TISSUES APPEAR NORMAL |
| | 1441 | ALL TISSUES APPEAR NORMAL |
| | 1442 | ALL TISSUES APPEAR NORMAL |
| | 1443 | ALL TISSUES APPEAR NORMAL |
| | 1444 | BOTH KIDNEYS MOTTLED; SUBCUTANEOUS MAMMARY MASS (1 $CM^2$) ON LEFT AXILLA |
| | 1445 | ALL TISSUES APPEAR NORMAL |
| | 1446 | ALL TISSUES APPEAR NORMAL |
| | 1447 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |

LITTON BIONETICS, INC.
PROJECT NO. 10734-06

TABLE 25 (Continued)

PARENT NECROPSY OBSERVATIONS (F2b) - FEMALES

| DOSE (PPM) | FEMALE NUMBER | OBSERVATION |
|---|---|---|
| 300 | 1448 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 1449 | ALL TISSUES APPEAR NORMAL |
| | 1450 | ALL TISSUES APPEAR NORMAL |
| | 1451 | ALL TISSUES APPEAR NORMAL |
| | 1452 | ALL TISSUES APPEAR NORMAL |
| | 1453 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 1454 | ALL TISSUES APPEAR NORMAL |
| | 1455 | ALL TISSUES APPEAR NORMAL |
| | 1456 | ALL TISSUES APPEAR NORMAL |
| 3000 | 1467 | ALL TISSUES APPEAR NORMAL |
| | 1468 | ALL TISSUES APPEAR NORMAL |
| | 1469 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 1470 | ALL TISSUES APPEAR NORMAL |
| | 1471 | ALL TISSUES APPEAR NORMAL |
| | 1472 | ALL TISSUES APPEAR NORMAL |
| | 1473 | ALL TISSUES APPEAR NORMAL |
| | 1474 | ALL TISSUES APPEAR NORMAL |
| | 1475 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 1476 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 1477 | ALL TISSUES APPEAR NORMAL |
| | 1478 | ALL TISSUES APPEAR NORMAL |
| | 1479 | ALL TISSUES APPEAR NORMAL |
| | 1480 | BOTH KIDNEYS MOTTLED; ALL OTHER TISSUES APPEAR NORMAL |
| | 1481 | ALL TISSUES APPEAR NORMAL |
| | 1482 | ALL TISSUES APPEAR NORMAL |
| | 1483 | ALL TISSUES APPEAR NORMAL |
| | 1484 | ALL TISSUES APPEAR NORMAL |
| | 1485 | ALL TISSUES APPEAR NORMAL |
| | 1486 | ALL TISSUES APPEAR NORMAL |

# APPENDIX B

SPONSOR: Environmental Protection Department,
US Army Medical Bioengineering Research
and Development Laboratory

MATERIAL: Diisopropylmethylphosphonate (DIMP)

SUBJECT: FINAL REPORT
Analysis of Diet Formulations
LBI Project No. 10734

## 1. OBJECTIVE

The purpose of the study was to analyze DIMP in animal chow with regard to stability and formulation content in diet.

## 2. MATERIAL AND EXPERIMENTAL DESIGN

Analysis of the dosed feed was performed by the following chromatographic method:

### Scope

This method describes the analytical procedure for the determination of DIMP in dosed feed used by Litton Bionetics, Inc. (LBI) from July, 1977 to September, 1978.

### Principle

A five gram subsample is extracted with 15 ml of acetone by shaking for 10 minutes in an automatic shaker. The extract is clarified by centrifugation for 10 minutes at 1350 rpm and decanted into a separate tube. A second extraction is performed with 10 ml of acetone in the same manner. The two extracts are combined and centrifuged again prior to analysis by gas-liquid chromatography.

The amount of DIMP found is calculated by reference to calibration curves prepared by analysis of standard solutions of DIMP in acetone.

### Equipment and Suppliers:

50 ml graduated conical Falcon tubes with positive seal caps (available from Becton, Dickinson, and Company, Oxnord, CA 93030), stock number H8292-209811

Short-stem glass funnels (corning 6180).

15 ml graduated glass centrifuge tubes with ground glass stoppers.

Centrifuge.

Volumetric glassware - 1, 4, and 10 ml pipettes; 50 and 100 ml flasks.

2. MATERIALS AND EXPERIMENTAL DESIGN (Continued)

Graduated cylinders - 25 ml capacity.

Mechanical shaker.

Analytical laboratory balance (accurate to 0.01 mg).

Top-loading laboratory balance (accurate to 0.01 g).

Gas-liquid chromatograph - Varian 2100, equipped with 1.8 m x 2 mm I.D. glass column packed with 10% FFAP on 80/100 mesh Supelcoport, flame ionization detectors.

Acetone (Burdick & Jackson).

Preparation of Standard:

Prepare a stock standard solution of DIMP by dissolving 75 mg of DIMP in 50 ml of acetone.

Take a 10 ml aliquot and dilute to 100 ml with acetone in a volumetric flask. This solution has a concentration of 0.15 mg/ml.

Prepare a standard curve by injecting 1, 2 and 3 µl of the standard solution at the following parameters:

| | |
|---|---|
| Column temperature: | 120°C |
| Injector temperature: | 250°C |
| FID temperature: | 275°C |
| Chart: | 6 minutes/inch |
| Carrier gas flow: | 40 cc/min nitrogen |
| Attn: | $16 \times 10^{-11}$ |

Procedure:

Weigh a 5 g sample of the dosed feed to the nearest 0.01 g in a Falcon tube.

Extract the sample with 15 ml of acetone by mixing for 10 min in a mechanical shaker, followed by centrifugation at 1300 rpm for 10 min.

Decant the supernatant into a Falcon tube and tightly seal to prevent solvent loss.

Repeat the extraction one additional time with 10 ml of acetone. Combine the extracts in the Falcon tube. Stopper tightly and mix well. Allow the sample to settle for 1 min, then centrifuge for 10 min at 1350 rpm.

Dilute the high-dose level (3000 ppm) in a 15 ml graduated centrifuge tube by adding a 1 ml aliquot to 4 ml of acetone.

2. MATERIAL AND EXPERIMENTAL DESIGN (Continued)

Repeat above procedure using undosed animal feed of the same lot used for the preparation of the dosed feed. This extract will be used as a negative control to assure that there are no interfering peaks contributed by the feed itself.

Repeat above procedure using undosed animal feed of the same lot which has been spiked in the laboratory with DIMP at corresponding dose levels.

Quantitate the amount of DIMP in solution by comparing to calibration curve prepared above.

Calculations:

Calculate the ppm of DIMP in the dosed feed or spiked (recovery) sample as follows:

To determine mg of sample injected:

$$\frac{5 \text{ g feed}}{25 \text{ ml acetone}} = \frac{200 \text{ mg feed}}{1.0 \text{ ml acetone}}$$

$$\frac{200 \text{ mg feed}}{1.0 \text{ ml acetone}} \times \text{Dilution Factor} = \frac{(x) \text{ mg feed}}{1.0 \text{ ml acetone}}$$

Dilution Factor = 1 for 300 ppm level
= 0.2 for 3000 ppm level

$$\frac{(x) \text{ mg feed}}{1.0 \text{ ml acetone}} \times \frac{\mu\text{l sample}}{1000} = \text{mg of feed injected}$$

Calculate the intercept and slope from standard curve, as determined by linear regression correlation.

$$\frac{\text{Peak Response (peak height)} - \text{intercept}}{\text{slope}} = \text{ng of DIMP in injection}$$

To determine ppm:

$$\frac{\text{ng of DIMP}}{\text{mg of feed injected}} = \text{ppm}$$

Determine method recovery from spiked samples as follows:

$$\text{percent recovery} = \frac{\text{ppm found} \times 100}{\text{ppm added}}$$

Correct the result of the dosed feed sample for method recovery for its corresponding spiked sample.

$$\text{corrected ppm} = \frac{\text{sample ppm} \times 100}{\text{percent recovery}}$$

3. MATERIAL AND EXPERIMENTAL DESIGN

(Method Modification of 17 September 1978)

Scope

This method describes the analytical procedure used for the determination of DIMP in dosed feed used by Litton Bionetics, Inc. (LBI) from 17 September 1978 to the termination of the study.

Principle

A five gram subsample is extracted with 15 ml of acetone by shaking for 10 min in an automatic shaker. The extract is clarified by centrifugation for 10 min at 1350 rpm and decanted into a separate tube. A second extraction is performed with 10 ml of acetone in the same manner. The two extracts are combined and centrifuged again prior to analysis by gas-liquid chromatography.

An aliquot of the extract is diluted with a standard solution of trimethyl phosphate $(CH_3O)_3P(O)$. The trimethyl phosphate serves as an internal standard.

Analysis is performed by gas-liquid chromatography using a Hewlett-Packard 5840A with a 7672 Auto Liquid Sampler. Quantitation is by the automatic internal standard method.

Equipment and Supplies:

The basic laboratory equipment previously listed (see Section 2) is ammended to include:

Gas-liquid chromatograph - Hewlett Packard 5840A with 7672 Auto Liquid Sampler equipped with 1.8 m x 2 mm I.D. glass column packed with 10% FFAP on 80/100 mesh supelcoport flame ionization detector.

Trimethyl phosphate (Aldrich 13,219-5)

Septa vial (Wheaton Industries 07081)

Preparation of Standards:

Prepare a stock standard solution of DIMP by dissolving 75 mg of DIMP in 50 ml of acetone.

Take a 4 ml aliquot and dilute to a final volume of 100 ml in a volumetric flask. This solution has a concentration of 0.06 mg/ml.

Prepare a stock standard solution of Trimethyl phosphate by dissolving 75 mg of trimethyl phosphate in 50 ml of acetone.

Take a 50 ml aliquot and dilute to a final volume of 100 ml in a volumetric flask. This solution has a concentration of 0.75 mg/ml.

3. MATERIAL AND EXPERIMENTAL DESIGN (Continued)

To prepare a working standard, take a 4 ml aliquot of the 0.06 mg/ml DIMP solution and combine with 4 ml of the 0.75 mg/ml trimethyl phosphate solution. Inject 3 µl of the solution 4 times using the internal standard method (see Calculations, section 3 for description).

Procedure:

Weigh a 5 g sample of the dosed feed to the nearest 0.01 g into a Falcon tube.

Extract the sample with 15 ml of acetone by mixing for 10 min in a mechanical shaker followed by centrifugation at 1300 rpm for 10 min.

Decant the supernatant into a second Falcon tube and tightly seal to prevent solvent loss.

Repeat the extraction one additional time with 10 ml of acetone. Combine the extracts in the second Falcon tube. Stopper tightly and mix well. Allow the sample to settle for one minute, then centrifuge for 10 min at 1350 rpm.

Dilute the high-dose level (3000 ppm) in a 15 ml graduated centrifuge tube by taking a 1 ml aliquot with 9 ml of acetone.

Dilute 4 ml of the extract with 4 ml of trim[illegible]sphate. The extract is now ready for analysis by gas [illegible]hy.

Repeat above procedure using undosed anima[illegible] the same lot used for the preparation of the dosed feed. This [illegible]act will be used as a negative control and will assure that there are no interfering peaks contributed by the feed itself.

Repeat above procedure using undosed animal feed of the same lot which has been spiked in the laboratory with DIMP at corresponding dose levels.

Inject 3 µl using the 7672 Auto Liquid Sampler, and calculate using internal standard method.

Calculations:

Calculate the ppm of DIMP in the dosed feed or spiked (recovery) sample as follows:

Determine mg of sample injected.

$$\frac{5 \text{ g feed}}{25 \text{ ml acetone}} = \frac{200 \text{ mg feed}}{1.0 \text{ ml acetone}}$$

$$\frac{200 \text{ mg feed}}{1.0 \text{ ml acetone}} \times \text{Dilution Factor} = \frac{(x) \text{ mg feed}}{1.0 \text{ ml acetone}}$$

Dilution Factor = 1 for 300 ppm level
= 0.1 for 3000 ppm level

3. MATERIAL AND EXPERIMENTAL DESIGN (Continued)

Instrumental Dilution Factor = 1/(x) mg feed injected
= 2.5 for 300 ppm level
= 25 for 3000 ppm level

The 5840A Gas Chromatograph is a microprocessor-based instrument which is capable of automatically calculating analytical results by internal programming. A standard is established by making four equal injections of the DIMP standard solution and averaging the results. The nanograms of DIMP injected using the STND corresponds to the nanograms of DIMP in the samples (achieved by dilution if necessary). The actual analytical sequence used is:

$$\text{Concentration of DIMP (ppm)} = \frac{\text{Area 1} \times \text{Response 1}}{\text{Area 2} \times \text{Response 2}} \times \frac{\text{Amount}}{\text{I.S.}} \times \text{IDF}$$

Area 1 = Area of DIMP peak
Response I = Response of DIMP peak
Area 2 = Area of trimethyl phosphate peak
Response 2 = Response of trimethyl phosphate
Amount I.S. = Amount of trimethyl phosphate present in the injection in ng.
I.D.F. = Instrumental dilution factor (corrects to ppm)

Determine method recovery from spiked samples as follows:

$$\text{Percent recovery} = \frac{\text{ppm found} \times 10}{\text{ppm added}}$$

Correct the result of the dosed feed sample for method recovery of its corresponding spiked sample.

$$\text{corrected ppm} = \frac{\text{sample ppm} \times 100}{\text{Percent recovery}}$$

4. RESULTS

Stability Analysis

Samples were analyzed the day the mix was received by the analytical laboratory. This corresponded to Day 5 of the stability study. Two aliquots of feed were removed from each diet level of samples 0417, 0418, and 0419 and stored at ambient conditions. One aliquot was stored in a closed container, while the other was stored in an open container.

The two aliquots were analyzed five days later (Day 10) by the standard method. Results of the analysis are indicated in Table 1.

In the open containers, the concentration dropped 18.3% for the 300 ppm level and 31.3% for the 3000 ppm level.

In the closed container, the concentration remained the same for the 300 ppm level and dropped 9.3% for the 3000 ppm level.

## 5. DISCUSSION

The results of the stability study indicated that DIMP was not lost from the feed mixes stored in closed containers, whereas considerable loss occurred from open containers. The loss, therefore, appears to result from volatility of the compound.

The concentration of test compound found in feed mixes prepared for the rat reproduction study (Table 2) varied significantly at each dose level. In general, the amount of DIMP found in the 300 ppm diets were 83% of the intended dosage and at the higher dose level, the concentrations found averaged 88% of the theoretical dosage.

The levels of DIMP found in the diet mixes in Table 3 also showed significant variation. The amount of DIMP in the low level diet averaged about 77% of the intended dose level. However, the concentrations found in the two higher levels were usually within ±10% of the theoretical dosage.

LITTON BIONETICS, INC.
Kensington, Maryland 20795

Submitted by:

03/19/79

J.D. Mitchell
Analytical Chemist

Reviewed by:

03/19/79

H.J. Paulin, M.S.
Analytical Chemist

Edward D. Helton

E.D. Helton, Ph.D.
Director, Department of Chemistry

# TABLE I-E-40

## COMPARISON OF EXTRACTION PROCEDURES FOR DIMP

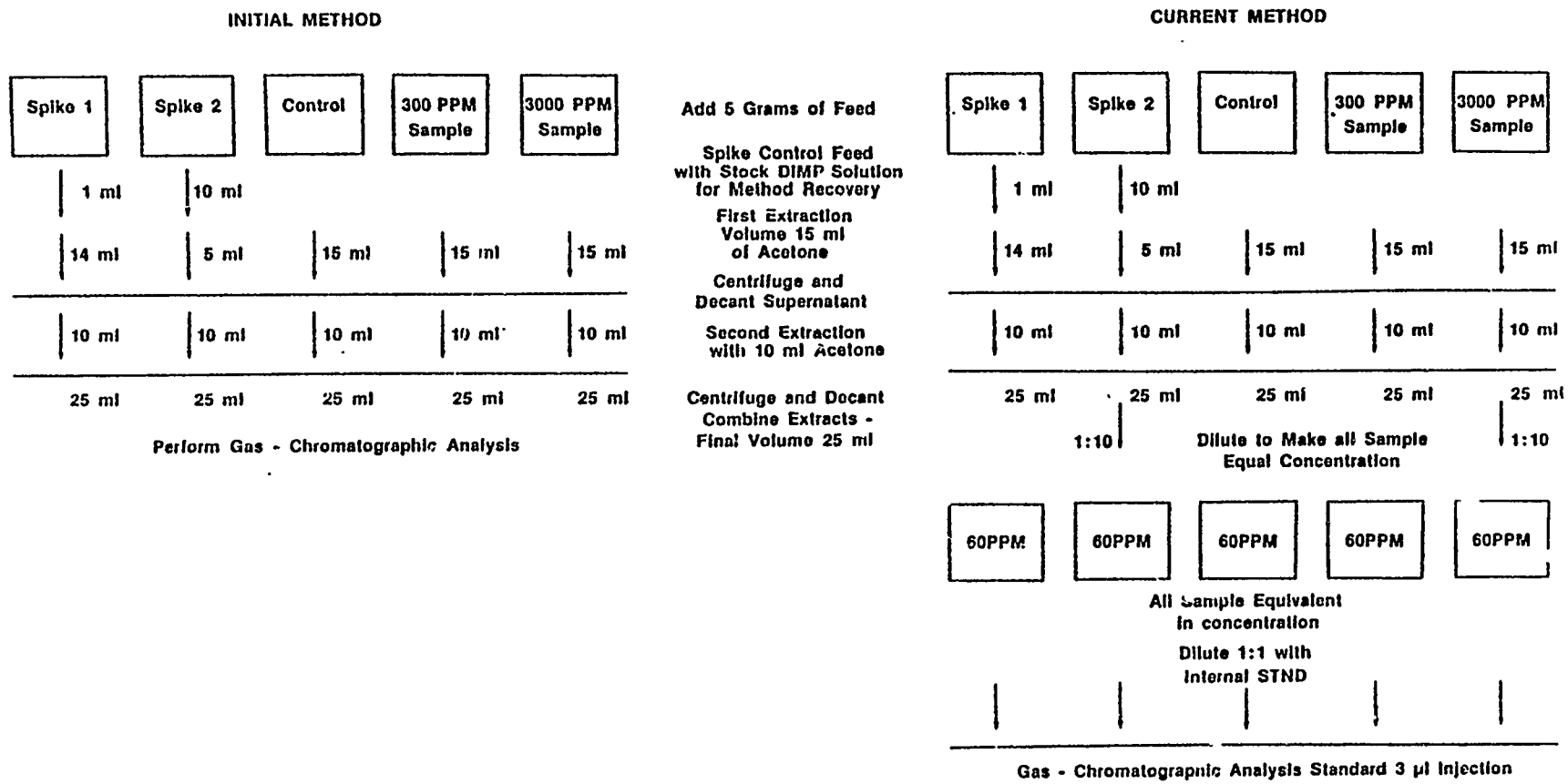


TABLE I-E-41

LITTON BIONETICS, INC.
PROJECT 10715

TABLE 1

STABILITY OF DIMP IN DIET
MIXED 07/14/77

| SAMPLE NUMBER | ANALYSIS DATE | DAY | DOSAGE PPM | ANALYSIS VALUE (PPM)[a] |
|---|---|---|---|---|
| 0417 | 07/19/77 | 5 | 0 | 0 |
| 0418 | 07/19/77 | 5 | 300 | 252 |
| 0419 | 07/19/77 | 5 | 3000 | 2882 |
| Closed Container | | | | |
| 0417 | 07/27/77 | 10 | 0 | 0 |
| 0418 | 07/27/77 | 10 | 300 | 254 |
| 0419 | 07/27/77 | 10 | 3000 | 2614 |
| Open Container | | | | |
| 0417 | 07/27/77 | 10 | 0 | 0 |
| 0418 | 07/27/77 | 10 | 300 | 206 |
| 0419 | 07/27/77 | 10 | 3000 | 1980 |

[a]All values have been corrected for respective method recovery, run simultaneously with analyses.

TABLE I-E-42

LITTON BIONETICS, INC.
PROJECT NO. 10734

TABLE 2

WEEKLY DIMP FEED ANALYSIS - RAT REPRODUCTION STUDY

| STUDY WEEK | MIX DATE | ANALYSIS DATE | SAMPLE NUMBER | PPM LEVEL | ANALYSIS VALUE (ppm)[a] |
|---|---|---|---|---|---|
| 1 | 04/07/77 | 07/18/77 | b | 300 | 194 |
| | | | b | 3000 | 2581 |
| 2 | 04/14/77 | 07/18/77 | b | 300 | 209 |
| | | | b | 3000 | 2452 |
| 3 | 04/21/77 | 07/18/77 | b | 300 | 178 |
| | | | b | 3000 | 2339 |
| 4 | 04/28/77 | 07/18/77 | b | 300 | 218 |
| | | | b | 3000 | 2178 |
| 5 | 05/05/77 | 07/18/77 | b | 300 | 242 |
| | | | b | 3000 | 3226 |
| 6 | 05/12/77 | 07/18/77 | b | 300 | 2581[c] |
| | | | b | 3000 | 306[c] |
| 10 | 06/09/77 | 07/19/77 | 0336 | 0 | 0 |
| | | | 0337 | 300 | 240 |
| | | | 0338 | 3000 | 2282 |
| 11 | 06/16/77 | 07/13/77 | 0366 | 0 | 0 |
| | | | 0367 | 300 | 267 |
| | | | 0368 | 3000 | 2786 |
| 15 | 07/14/77 | 07/19/77 | 0417 | 0 | 0 |
| | | | 0418 | 300 | 252 |
| | | | 0419 | 3000 | 2882 |
| 16 | 07/21/77 | 07/27/77 | 0430 | 0 | 0 |
| | | | 0431 | 300 | 246 |
| | | | 0432 | 3000 | 3010 |
| 17 | 07/28/77 | 08/23/77 | 0459 | 0 | 0 |
| | | | 0460 | 300 | 185 |
| | | | 0461 | 3000 | 2554 |

[a]All values have been corrected for respective method recovery run simultaneously with analysis.
[b]Samples received in quart jars with no I.D. number.
[c]Possible mixup of the jar label indicated.

TABLE I-E-42 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734

TABLE 2 (CONTINUED)

WEEKLY DIMP FEED ANALYSIS - RAT REPRODUCTION STUDY

| STUDY WEEK | MIX DATE | ANALYSIS DATE | SAMPLE NUMBER | PPM LEVEL | ANALYSIS VALUE (ppm)[a] |
|---|---|---|---|---|---|
| 19 | 08/11/77 | 08/23/77 | 0499 | 300 | 199 |
| | | | 0500 | 3000 | 2316 |
| 20 | 08/18/77 | 09/07/77 | b | 300 | 182 |
| | | | | 3000 | 2348 |
| 21 | 08/25/77 | 09/07/77 | 0526 | 0 | 0 |
| | | | 0527 | 300 | 244 |
| | | | 0528 | 3000 | 2386 |
| 24 | 09/15/77 | 09/27/77 | 0616 | 0 | 0 |
| | | | 0617 | 300 | 199 |
| | | | 0618 | 3000 | 2392 |
| 27 | 10/06/77 | 10/25/77 | 0689 | 300 | 316 |
| | | | 0688 | 3000 | 2297 |
| 28 | 10/14/77 | 10/25/77 | 0748 | 300 | 244 |
| | | | 0747 | 3000 | 2511 |
| 29 | 10/20/77 | 10/25/77 | 0796 | 0 | |
| | | | 0797 | 300 | 333 |
| | | | 0798 | 3000 | 2547 |
| 30 | 10/27/77 | 11/03/77 | 0855 | 300 | 189 |
| | | | 0857 | 3000 | 2136 |
| 31 | 11/03/77 | 11/11/77 | 0922 | 300 | 204 |
| | | | 0923 | 3000 | 2294 |
| 36 | 12/09/77 | 12/15/77 | 1095 | 0 | 0 |
| | | | 1096 | 300 | 0[c] |
| | | | 1097 | 3000 | 2516 |
| | | 12/16/77 | 1128 | 300 | 253[d] |

[a]All values have been corrected for respective method recovery run simultaneously with analysis.
[b]Samples received in quart jars with no I.D. number.
[c]Analysis repeated to confirm results, sample resubmitted and analyzed immediately.
[d]Repeat of 1096.

TABLE I-E-42 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734

TABLE 2 (CONTINUED)

WEEKLY DIMP FEED ANALYSIS - RAT REPRODUCTION STUDY

| STUDY WEEK | MIX DATE | ANALYSIS DATE | SAMPLE NUMBER | PPM LEVEL | ANALYSIS VALUE (ppm)[a] |
|---|---|---|---|---|---|
| 38 | 12/22/77 | 12/28/77 | 1161 | 0 | 0 |
| | | | 1162 | 300 | 206 |
| | | | 1163 | 3000 | 3024 |
| 39 | 12/28/77 | 01/05/78 | 1188 | 0 | 0 |
| | | | 1189 | 300 | 234 |
| | | | 1190 | 3000 | 2749 |
| 40 | 01/04/78 | 01/10/78 | 1229 | 0 | 0 |
| | | | 1230 | 300 | 184 |
| | | | 1231 | 3000 | 2285 |
| 41 | 01/11/78 | 01/13/78 | 1262 | 0 | 0 |
| | | | 1263 | 300 | 231 |
| | | | 1264 | 3000 | 2679 |
| 42 | 01/19/78 | 01/22/78 | 1293 | 0 | 0 |
| | | | 1294 | 300 | 247 |
| | | | 1295 | 3000 | 2700 |
| 42 | 01/19/78 | 01/25/78 | 1293 | 0 | 0[b] |
| | | | 1294 | 300 | 239 |
| | | | 1295 | 3000 | 2335 |
| 43 | 01/24/78 | 02/03/78 | 1319 | 0 | 0 |
| | | | 1320 | 300 | 271 |
| | | | 1321 | 3000 | 2860 |
| 44 | 02/01/78 | 02/03/78 | FC0047K78 | 0 | 0 |
| | | | FC0048K78 | 300 | 271 |
| | | | FC0049K78 | 3000 | 3180 |
| 45 | 02/08/78 | 02/13/78 | FC0152K78 | 0 | 0 |
| | | | FC0153K78 | 300 | 255 |
| | | | FC0154K78 | 3000 | 2755 |
| 46 | 02/15/78 | 02/19/78 | FC0212K78 | 0 | 0 |
| | | | FC0213K78 | 300 | 256 |
| | | | FC0214K78 | 3000 | 2836 |

[a]All values have been corrected for respective method recovery run simultaneously with analysis.
[b]Repeat analysis to confirm original results.

TABLE I-E-42 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734

TABLE 2 (CONTINUED)

WEEKLY DIMP FEED ANALYSIS - RAT REPRODUCTION STUDY

| STUDY WEEK | MIX DATE | ANALYSIS DATE | SAMPLE NUMBER | PPM LEVEL | ANALYSIS VALUE (ppm)[a] |
|---|---|---|---|---|---|
| 47 | 02/22/78 | 02/23/78 | FC0306K78 | 0 | 0 |
| | | | FC0307K78 | 300 | 300 |
| | | | FC0308K78 | 3000 | 2912 |
| 48 | 03/02/78 | 03/08/78 | FC0437K78 | 0 | 0 |
| | | | FC0438K78 | 300 | 240 |
| | | | FC0439K78 | 3000 | 2631 |
| 49 | 03/08/78 | 03/13/78 | FC0517K78 | 0 | 0 |
| | | | FC0518K78 | 300 | 301 |
| | | | FC0519K78 | 3000 | 2517 |
| 50 | 03/15/78 | 03/20/78 | FC0653K78 | 0 | 0 |
| | | | FC0654K78 | 300 | 239 |
| | | | FC0655K78 | 3000 | 2732 |
| 51 | 03/21/78 | 03/23/78 | FC0727K78 | 0 | 0 |
| | | | FC0728K78 | 300 | 249 |
| | | | FC0729K78 | 3000 | 2867 |
| 52 | 03/29/78 | 04/02/78 | FC0819K78 | 0 | 0 |
| | | | FC0820K78 | 300 | 231 |
| | | | FC0821K78 | 3000 | 2628 |
| 53 | 04/05/78 | 04/06/78 | FC0901K78 | 0 | 0 |
| | | | FC0902K78 | 300 | 263 |
| | | | FC0903K78 | 3000 | 2452 |
| 54 | 04/12/78 | 04/13/78 | FC0972K78 | 0 | 0 |
| | | | FC0973K78 | 300 | 278 |
| | | | FC0974K78 | 3000 | 2759 |
| 55 | 04/19/78 | 04/19/78 | FC1017K78 | 0 | 0 |
| | | | FC1018K78 | 300 | 269 |
| | | | FC1019K78 | 3000 | 2822 |
| 56 | 04/26/78 | 04/27/78 | FC1087K78 | 0 | 0 |
| | | | FC1088K78 | 300 | 299 |
| | | | FC1089K78 | 3000 | 3022 |

[a]All values have been corrected for respective method recovery run simultaneously with analysis.

LITTON BIONETICS, INC.
PROJECT NO. 10734

TABLE 2 (CONTINUED)

WEEKLY DIMP FEED ANALYSIS - RAT REPRODUCTION STUDY

| STUDY. WEEK | MIX DATE | ANALYSIS DATE | SAMPLE NUMBER | PPM LEVEL | ANALYSIS VALUE (ppm)[a] |
|---|---|---|---|---|---|
| 57 | 05/03/78 | 05/04/78 | FC1143K78 | 0 | 0 |
| | | | FC1144K78 | 300 | 274 |
| | | | FC1145K78 | 3000 | 2821 |
| 58 | 05/10/78 | 05/13/78 | FC1192K78 | 0 | 0 |
| | | | FC1193K78 | 300 | 249 |
| | | | FC1194K78 | 3000 | 2276 |
| 59 | 05/17/78 | 05/21/78 | FC1244K78 | 0 | 0 |
| | | | FC1245K78 | 300 | 275 |
| | | | FC1246K78 | 3000 | 2907 |
| 60 | 05/24/78 | 05/31/78 | FC1302K78 | 0 | 0 |
| | | | FC1303K78 | 300 | 263 |
| | | | FC1304K78 | 3000 | 2619 |
| 61 | 05/31/78 | 06/02/78 | FC1336K78 | 0 | 0 |
| | | | FC13337K78 | 300 | 257 |
| | | | FC13338K78 | 3000 | 3003 |
| 62 | 06/07/78 | 06/11/78 | FC1402K78 | 0 | 0 |
| | | | FC1403K78 | 300 | 316 |
| | | | FC1404K78 | 3000 | 3146 |
| 63 | 06/14/78 | 06/14/78 | FC1467K78 | 0 | 0 |
| | | | FC1468K78 | 300 | 286 |
| | | | FC1469K78 | 3000 | 3133 |
| 64 | 06/21/78 | 06/27/78 | FC1570K78 | 0 | 0 |
| | | | FC1571K78 | 300 | 234 |
| | | | FC1572K78 | 3000 | 2608 |
| 65 | 06/28/78 | 07/08/78 | R0121K78 | 0 | 0 |
| | | | R0122K78 | 300 | 227 |
| | | | R0123K78 | 3000 | 2423 |
| 66 | 07/05/78 | 07/08/78 | R0143K78 | 0 | 0 |
| | | | R0144K78 | 300 | 269 |
| | | | R0145K78 | 3000 | 3033 |

[a]All values have been corrected for respective method recovery run simultaneously with analysis.

LITTON BIONETICS, INC.
PROJECT NO. 10734

TABLE 2 (CONTINUED)

WEEKLY DIMP FEED ANALYSIS - RAT REPRODUCTION STUDY

| STUDY WEEK | MIX DATE | ANALYSIS DATE | SAMPLE NUMBER | PPM LEVEL | ANALYSIS VALUE (ppm)[a] |
|---|---|---|---|---|---|
| 67 | 07/13/78 | 07/16/78 | R0172K78 | 0 | 0 |
| | | | R0173K78 | 300 | 269 |
| | | | R0174K78 | 3000 | 2992 |
| 68 | 07/20/78 | 07/25/78 | [b] | 0 | 0 |
| | | | | 300 | 194 |
| | | | | 3000 | 2101 |
| 69 | 07/26/78 | 07/28/78 | R0220K78 | 0 | 0 |
| | | | R0221K78 | 300 | 198 |
| | | | R0222K78 | 3000 | 2575 |
| 70 | 08/03/78 | 08/07/78 | R0267K78 | 0 | 0 |
| | | | R0268K78 | 300 | 253 |
| | | | R0269K78 | 3000 | 2971 |
| 71 | 08/10/78 | 08/14/78 | R0327K78 | 0 | 0 |
| | | | R0328K78 | 300 | 293 |
| | | | R0329K78 | 3000 | 2851 |
| 72 | 08/17/78 | 08/20/78 | R0376K78 | 0 | 0 |
| | | | R0377K78 | 300 | 270 |
| | | | R0378K78 | 3000 | 2748 |
| 73 | 08/24/78 | 08/27/78 | R0489K78 | 0 | 0 |
| | | | R0490K78 | 300 | 274 |
| | | | R0491K78 | 3000 | 2858 |
| 74 | 08/31/78 | 09/02/78 | R0525K78 | 0 | 0 |
| | | | R0526K78 | 300 | 257 |
| | | | R0527K78 | 3000 | 2870 |
| 76 | 09/14/78 | 09/17/78 | R0595K78 | 0 | 0 |
| | | | R0596K78 | 300 | 267 |
| | | | R0597K78 | 3000 | 2746 |

[a]All values have been corrected for respective method recovery run simultaneously with analysis.
[b]No sample number indicated.

TABLE I-E-42 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734

TABLE 2 (CONTINUED)

WEEKLY DIMP FEED ANALYSIS - RAT REPRODUCTION STUDY

| STUDY WEEK | MIX DATE | ANALYSIS DATE | SAMPLE NUMBER | PPM LEVEL | ANALYSIS VALUE (ppm)[a] |
|---|---|---|---|---|---|
| 77 | 09/20/78 | 09/30/78 | R0617K78 | 0 | 0 |
| | | | R0618K78 | 300 | 279 |
| | | | R0619K78 | 3000 | 1705 |
| 78 | 09/26/78 | 09/30/78 | R0662K78 | 0 | 0 |
| | | | R0663K78 | 300 | 277 |
| | | | R0664K78 | 3000 | 2745 |
| 79 | 10/03/78 | 10/17/78 | R0694K78 | 0 | 0 |
| | | | R0695K78 | 300 | 300 |
| | | | R0696K78 | 3000 | 2799 |
| 81 | 10/17/78 | 10/24/78 | R0754K78 | 0 | 0 |
| | | | R0755K78 | 300 | trace |
| | | | R0756K78 | 3000 | 2760 |
| 82 | 10/25/78 | 10/26/78 | R0782K78 | 0 | 0 |
| | | | R0783K78 | 300 | 293 |
| | | | R0784K78 | 3000 | 3040 |
| 83 | 11/01/78 | 11/05/78 | R0817K78 | 0 | 0 |
| | | | R0818K78 | 300 | 241 |
| | | | R0819K78 | 3000 | 2513 |
| 84 | 11/07/78 | 11/10/78 | R0834K78 | 0 | 0 |
| | | | R0835K78 | 300 | 250 |
| | | | R0836K78 | 3000 | 2698 |
| 85 | 11/14/78 | 11/16/78 | R0874K78 | 0 | 0 |
| | | | R0875K78 | 300 | 242 |
| | | | R0876K78 | 3000 | 2632 |
| 86 | 11/21/78 | 11/25/78 | R0897K78 | 0 | 0 |
| | | | R0898K78 | 300 | 296 |
| | | | R0899K78 | 3000 | 3106 |

[a]All values have been corrected for respective method recovery run simultaneously with analysis.

PART I - SECTION F

DEMYELINATION PARALYSIS IN CHICKENS

DIMP

LBI PROJECT NO. 2566


## SUMMARY

Treatment of atropinized White Leghorn hens with DIMP once at 1500 mg/kg or twice at 1000 or 500 mg/kg did not produce evidence of nerve fiber degeneration after 21 days (animals treated once) or 46 days (animals treated twice) when the sciatic nerve was examined microscopically. Evidence of unsteady gait was easily distinguished clinically from signs exhibited by the positive control animals and was judged to be unrelated to nerve fiber degeneration.

The positive control animals, treated with TOCP once at 500 mg/kg, developed classical progressive clinical signs of nerve fiber degeneration beginning 12 to 14 days after treatment. Most of the animals showed microscopic evidence of nerve fiber degeneration.


## 1. OBJECTIVE

The objective of this study was to determine the potential of the test material to cause demyelination of the sciatic nerve in hens after one or two single oral treatments.

## 2. MATERIAL

Refer to Part I - Section A.

## 3. EXPERIMENTAL DESIGN

Young adult Leghorn hens (weighing 1.1 to 1.8 kg and 18 to 20 weeks of age at the time of treatment, February 10, 1978) were obtained from Bowman's Hatchery, Westminster, Maryland, and acclimated to laboratory conditions for 13 days. The hens were singly housed in stainless steel rabbit cages in a temperature-controlled room with artificial illumination automatically controlled to provide a 12-hour light cycle. Growena chicken meal and water were provided ad libitum, except the night before treatment when food was removed from the cages. No other test chemicals were under concurrent investigation in this animal room. This study was performed in the Falls Church facility of the Toxicology Department.

3. EXPERIMENTAL DESIGN (Continued)

The dose levels of DIMP administered to the test animals were selected based on data generated during the acute oral toxicity study in chickens, dated September 8, 1977. Treatment mixtures of DIMP and TOCP were prepared in corn oil. Atropine sulfate was prepared using deionized water and was made to a concentration of 54 mg/ml. The specific gravities for DIMP and TOCP were 1.0 and 1.16, respectively. Fresh treatment mixtures were prepared for each use.

The study design has been summarized in Text Table A. Each animal received a measured volume of atropine sulfate solution (54 mg/ml) prior to administration of the test compounds or vehicle control so that a dose of 15 mg/kg was received. Typically, 15 minutes elapsed between the time of atropine administration and treatment with the test compound.

The animals were treated and observed for 21 days. At Day 22, surviving animals from the high dose group, the positive control group and half of the negative control animals were killed. The remaining animals were redosed with atropine sulfate and their respective treatment mixtures, and observed for an additional 24 days. This second treatment was performed on the low and intermediate dose level DIMP animals because there were no indications of neural toxicity after 21 days. The hens in the high DIMP dose level were not redosed since significant mortality resulted after the initial treatment.

The animals were observed twice daily for mortality and general appearance. Particular attention was given to observing the gait of the hens, since demyelination of the sciatic nerve and its concomitant disruption of normal walking and standing was the parameter under investigation. All animals were weighed prior to treatment.

Animals dying within 96 hours of treatment were necropsied to ensure proper dosing technique only. Animals dying after 96 hours of treatment, as well as all animals terminated, were subjected to a special truncated necropsy procedure. During this necropsy, the left leg sciatic nerves were dissected and preserved in 10% formalin. The five nerve junctions with the spinal cord were left intact and the entire nerve (encompassing sciatic, tibial and plantar nerves) leading to the foot was removed. No other tissues were observed for gross lesions or preserved.

TABLE I-F-43

LITTON BIONETICS, INC.
PROJECT NO. 20566

TABLE A

STUDY DESIGN

| GROUP NUMBER | GROUP DESIGNATION | COMPOUND | DOSE LEVEL (MG/KG) | TEST MATERIAL CONCENTRATION (MG/ML) | ANIMAL NUMBERS |
|---|---|---|---|---|---|
| 1 | Vehicle Control | Corn Oil | 0 | 0 | 16-35 |
| 2 | Positive Control | TOCP | 500 | 250 | 36-55 |
| 3 | Treatment | DIMP | 500 | 250 | 56-75 |
| 4 | Treatment | DIMP | 1000 | 500 | 76-95 |
| 5 | Treatment | DIMP | 1500 | 750 | 96-115 |

Date of first dose: February 10, 1978, all groups.
Date of second dose: March 3, 1978, groups 1*, 3, 4.
Date of first terminal kill: March 3, 1978, groups 1*, 2, 5.
Date of second terminal kill: March 27, 1978, groups 1, 3, 4.

*Nine animals only.

## 4. RESULTS

Mortality data has been summarized in Appendix Table 1. Two control hens were judged moribund and killed on Days 18 and 41 of study. There were no deaths among the positive control animals. Seven hens in the high dose and five hens in the medium dose were killed shortly after first treatment with DIMP. These deaths were clearly related to treatment with the test compound. One hen in the medium dose and two hens in the low dose were found dead after the second dosing. Additionally, three medium dose hens were judged moribund and killed.

Clinical signs have been summarized in Appendix Table 2. Predictably, animals treated with TOCP developed unsteady gait on Days 12 to 14 (19 hens of the 20 treated were affected). This condition progressed as described below until termination at Day 21, in 17 animals. In two instances the animals finally could neither walk nor stand.

The animals treated with DIMP showed toxic signs, the severity of which was related to the dose administered. Within minutes of treatment, particularly in the high dose, the hens became very quiet and soon were prostrate. While these animals gave the appearance of being very close to death, most recovered. Many of the surviving hens had an unsteady gait on Days 1 to 3 after treatment. This unsteadiness was judged to be related to the test compound.

Among the animals treated with 500 mg/kg of DIMP initially, all animals remained clinically normal throughout the 21 day observation period. When these animals were treated a second time with 500 mg/kg of the compound, five animals (Nos. 57, 58, 60, 65, 67) developed signs of unsteady gait or inability to walk. In four of these animals, the signs were judged unsimilar to those of the positive control. In assessing these signs, they were compared to the characteristics shown by the positive control animals. These characteristics were:

a. The regular onset of "unsteady gait" 12 to 14 days after initial treatment in those animals affected (95% of treated). This regularity was seen both temporally and in severity. Eleven animals were judged, initially, to show "slightly unsteady gait". All of these then progressed to "unsteady gait" and seven also were judged by Day 19 to 20 to show "very unsteady gait". Eight animals were judged, initially, to show "unsteady gait". Five of these progressed to "very unsteady gait" by Day 19 to 20 (with one hen, No. 38, showing "very unsteady gait" as early as Day 16) and two animals (Nos. 38 and 54) progressed to "unable to stand" by Day 19 to 20. Thus, 16 animals showed progressive signs, three showed steady signs and one remained normal.

4. RESULTS (Continued)

b. The gradual progressiveness of the "unsteady gait" once this sign was evidenced.
In general, the "slight" to "unsteady" to "very unsteady" changes in clinical condition were noted on Days 13, 14 and 19. There were no instances of dramatic rapid deterioration of the animals.

c. The failure of any affected animals to improve, clinically, in the time frame of this study.

Among the animals treated with 1000 mg/kg of DIMP, initially, 13 of the surviving 16 animals were normal (neglecting the early signs of toxicity after treatment) for the entire initial observation period. One animal (No. 82) was normal for 20 days, but deteriorated rapidly and was judged moribund on Day 21. Two animals (Nos. 93 and 95) both showed signs relating to unsteady gait, but returned to normal by the end of the initial observation period. Thus, using the criteria above, none of the animals treated once with 1000 mg/kg DIMP developed clinical signs similar to those shown by the positive control TOCP animals.

Among the 15 animals treated a second time with 1000 mg/kg DIMP, one animal died after treatment and eight remained normal (neglecting the initial signs of toxicity after treatment) throughout the additional 24 day observation period. The remaining six animals (three of which were judged moribund) showed signs that were not similar to the positive control animals and it was, again, judged that treatment with 1000 mg/kg DIMP was without similar effect as seen after TOCP treatment.

Among the surviving animals treated once with 1500 mg/kg DIMP, 11 of 12 hens were clinically normal for the 21 day observation period (neglecting the initial signs of toxicity after treatment). One animal (No. 100) was normal through Day 18, developed a slight unsteady gait for two days, but was again normal at Day 21. These signs were judged unsimilar to the positive control animals.

The summary of necropsy findings has been tabulated in Appendix Table 3. One animal (No. 80), treated twice with DIMP at 1000 mg/kg, showed slight muscle wasting on its left leg. There were no other remarkable findings relating to the musculature or sciatic nerve of the left leg of any of the animals.

4. RESULTS (Continued)

The pathology report, written by Herman Seibold, D.M.V. (LBI), has been appended. He examined the sciatic nerve of these hens using two sections of each specimen--one stained with hematoxylin and eosin, and the other stained with luxol-fast blue and counter stained with cresyl violet. It should be noted that the nerve specimens submitted for microscopic evaluation as dissected from the spinal cord to the foot included anatomically the sciatic, tibial and plantar nerves. Microscopic distinction of tibial and plantar segments, however, was not possible; thus, the results are discussed under the one category of sciatic nerve.

There was evidence of nerve fiber degeneration in 13 of the 19 hens that showed signs of unsteady gait after TOCP treatment. The severity of this degeneration averaged 1.8 on a scale that used 1 to indicate minimal, 2 to indicate slight and 3 to indicate moderate nerve fiber degeneration. The absence of microscopic lesions in six animals that showed clinical signs led Dr. Seibold to observe that the clinical manifestation of TOCP toxicity was more sensitive an indicator of TOCP induced nerve damage than routine microscopic evaluation.

There were lesions rated as "trace" in two hens treated with 1000 mg/kg and "slight" in one hen treated with 1500 mg/kg. One hen with trace amounts of degeneration was treated once with DIMP, was normal until Day 20 and became moribund on Day 21. The other hen in the 1000 mg/kg group was treated twice with DIMP. This hen was normal throughout the first observation period, normal for the first 20 days of the second observation period, unable to stand for the next three days but improved at Day 24, in that it was able to stand but unable to walk.

The one hen in the 1500 mg/kg group that had "slight" evidence of nerve lesions was normal (except for signs of initial acute toxicity) throughout its observation period.

There was no evidence of nerve fiber degeneration in any of the other hens receiving the vehicle alone, DIMP at 500 mg/kg, 1000 mg/kg or 1500 mg/kg. Dr. Seibold concluded that the trace lesions in the two hens treated with 1000 mg/kg DIMP were probably not unusual in light of similar lesions reported for normal hens and that the minimal lesion in the 1500 mg/kg hen was coincidental since this animal showed no clinical signs and he concluded that nerve fiber degeneration attributable to delayed neurotoxicity of DIMP was not apparent in these animals.

4. RESULTS (Continued)

These data indicate that DIMP does not induce nerve fiber degeneration in hens after either one treatment at 1500 mg/kg or two treatments at 1000 or 500 mg/kg. The high dose was the maximum that could be administered as judged by the mortality immediately following treatment. The delayed appearance of an unsteady gait observed in one animal (No. 60) after two treatments with 500 mg/kg had similar characteristics of the positive control animals, but is judged to be incidental and not related to nerve fiber degeneration.

The remaining clinical signs were different in one or more respects when compared to the positive control animals. Animals lacked substantive evidence of nerve fiber degeneration and it was judged that DIMP is without effect with regard to nerve fiber degeneration in hens.

Thirty days after transmittal of this report, original data from the Department of Toxicology will be transferred to the LBI Archivist, 5516 Nicholson Lane, Kensington, Maryland, for distribution to the proper repositories. A copy of this report was reviewed by the LBI Quality Assurance Unit.

5. CONCLUSION

Treatment of atropinized White Leghorn hens with DIMP once at 1500 mg/kg or twice at 1000 or 500 mg/kg did not produce evidence of nerve fiber degeneration after 21 days (animals treated once) or 46 days (animals treated twice) when the sciatic nerve was examined microscopically. Evidence of unsteady gait was easily distinguished clinically from signs exhibited by the positive control animals and was judged to be unrelated to nerve fiber degeneration.

The positive control animals, treated with TOCP once at 500 mg/kg, developed classical progressive clinical signs of nerve fiber degeneration beginning 12 to 14 days after treatment. Most of the animals showed microscopic evidence of nerve fiber degeneration.

Submitted by:

Elliot B. Gordon 1/2/79

Elliot B. Gordon, Ph.D. Date
Senior Toxicologist
Department of Toxicology

Reviewed by:

Robert P Beliles 1/3/79

Robert P. Beliles, Ph.D. Date
Director
Department of Toxicology

TABLE I-F-44

LITTON BIONETICS, INC.
PROJECT NO. 20566

TABLE 1

MORTALITY

| GROUP DESIGNATION | COMPOUND | DOSE LEVEL (MG/KG) | INITIAL DOSING | | SECOND DOSING | | TOTAL MORTALITY (DEAD/TREATED) |
|---|---|---|---|---|---|---|---|
| | | | MORTALITY BY DAY | CUMULATIVE MORTALITY (DEAD/TREATED) | MORTALITY BY DAY | CUMULATIVE MORTALITY (DEAD/TREATED) | |
| | | | 1 2 3 4-21 | | 22 23 24 25-46 | | |
| CONTROL | - | 0 | - - - 1 | 1/20 | - - - 1 | 1/ 9 | 2/20 |
| POSITIVE CONTROL | TOCP | 500 | - - - - | 0/20 | NOT TREATED | - | 0/20 |
| TREATMENT | DIMP | 500 | - - - - | 0/20 | - - - 2 | 2/20 | 2/20 |
| TREATMENT | DIMP | 1000 | 1 4 - - | 5/20 | - - - 4 | 4/15 | 9/20 |
| TREATMENT | DIMP | 1500 | 3 4 - - | 7/20 | NOT TREATED | - | 7/20 |

TABLE I-F-45

LITTON BIONETICS, INC.
PROJECT NO. 20566

TABLE 2

CLINICAL SIGNS

INITIAL DOSING

| DOSE GROUP (MG/KG) | ANIMAL NUMBER | DAY OF STUDY | SIGN |
|---|---|---|---|
| CONTROL | 17 | 1[a] | QUIET; EYES SLIGHTLY CLOSED. |
| | 28 | 18 | DOWN IN CAGE AND UNABLE TO STAND; MORIBUND KILL. |
| TOCP 500 | 36 | 14-16 | UNSTEADY GAIT. |
| | | 17 | SLIGHTLY UNSTEADY GAIT. |
| | | 18-21 | UNSTEADY GAIT. |
| | 37 | 13-18 | UNSTEADY GAIT. |
| | | 19-21 | VERY UNSTEADY GAIT. |
| | 38 | 14, 15 | UNSTEADY GAIT. |
| | | 16-18 | VERY UNSTEADY GAIT. |
| | | 19-21 | SITTING, UNABLE TO STAND OR WALK. |
| | 39 | 13 | SLIGHTLY UNSTEADY GAIT. |
| | | 14-18 | UNSTEADY GAIT. |
| | | 19-21 | VERY UNSTEADY GAIT. |
| | 40 | 13 | SLIGHTLY UNSTEADY GAIT. |
| | | 14-19 | UNSTEADY GAIT. |
| | | 20, 21 | VERY UNSTEADY GAIT. |
| | 41 | 14-21 | UNSTEADY GAIT. |
| | 42 | 14, 16, 17 | SLIGHTLY UNSTEADY GAIT. |
| | | 15, 18-21 | UNSTEADY GAIT. |
| | 43 | 13-18 | UNSTEADY GAIT. |
| | | 19-21 | VERY UNSTEADY GAIT. |
| | 44 | 13-18 | UNSTEADY GAIT. |
| | | 19-21 | VERY UNSTEADY GAIT. |
| | 45 | 13 | SLIGHTLY UNSTEADY GAIT. |
| | | 14-19 | UNSTEADY GAIT. |
| | | 20, 21 | VERY UNSTEADY GAIT. |
| | 46 | 13 | SLIGHTLY UNSTEADY GAIT. |
| | | 14-18 | UNSTEADY GAIT. |
| | | 19-21 | VERY UNSTEADY GAIT. |
| | 47 | 13 | SLIGHTLY UNSTEADY GAIT. |
| | | 14-18 | UNSTEADY GAIT. |
| | | 19-21 | VERY UNSTEADY GAIT. |
| | 48 | 13-21 | UNSTEADY GAIT. |
| | 49 | 13 | SLIGHTLY UNSTEADY GAIT. |
| | | 14-19 | UNSTEADY GAIT. |
| | | 20, 21 | VERY UNSTEADY GAIT. |
| | 50 | 13 | SLIGHTLY UNSTEADY GAIT. |
| | | 14-21 | UNSTEADY GAIT. |

[a]Day 1 observations made one hour after treatment.

TABLE I-F-45 (Continued)

LITTON BIONETICS, INC.
PROJECT NO 20566

TABLE 2 (CONTINUED)

CLINICAL SIGNS

INITIAL DOSING

| DOSE GROUP (MG/KG) | ANIMAL NUMBER | DAY OF STUDY | SIGN |
|---|---|---|---|
| TOCP | 51 | 13-18 | SLIGHTLY UNSTEADY GAIT. |
| 500 | | 19-21 | UNSTEADY GAIT. |
| | 52 | 12, 13 | SLIGHTLY UNSTEADY GAIT. |
| | | 14-19 | UNSTEADY GAIT. |
| | | 20, 21 | VERY UNSTEADY GAIT. |
| | 54 | 12-18 | UNSTEADY GAIT. |
| | | 19 | VERY UNSTEADY GAIT. |
| | | 20, 21 | SITTING, UNABLE TO STAND OR WALK. |
| | 55 | 13-18 | SLIGHTLY UNSTEADY GAIT. |
| | | 19-21 | UNSTEADY GAIT. |
| DIMP | 56 | 1 | QUIET, UNABLE TO STAND. |
| 500 | 57 | 1 | UNSTEADY GAIT. |
| | 58 | 1 | UNSTEADY GAIT. |
| | 59 | 1 | SLIGHTLY UNSTEADY GAIT. |
| | 60 | 1 | UNSTEADY GAIT. |
| | 62 | 1 | UNSTEADY GAIT. |
| | 63 | 1 | UNSTEADY GAIT. |
| | 64 | 1 | UNSTEADY GAIT. |
| | 65 | 1 | UNSTEADY GAIT. |
| | 66 | 1 | UNSTEADY GAIT. |
| | 67 | 1 | UNSTEADY GAIT, VERY QUIET. |
| | 68 | 1 | UNSTEADY GAIT. |
| | 69 | 1 | UNSTEADY GAIT. |
| | 70 | 1 | UNSTEADY GAIT. |
| | 71 | 1 | UNSTEADY GAIT. |
| | 73 | 1 | UNSTEADY GAIT. |
| | 74 | 1 | UNSTEADY GAIT. |
| | 75 | 1 | SLIGHTLY UNSTEADY GAIT. |
| DIMP | 76 | 1 | PROSTRATE. |
| 1000 | | 2 | UNSTEADY GAIT. |
| | 77 | 1, 2 | UNSTEADY GAIT. |
| | 78 | 1 | PROSTRATE. |
| | | 2 | UNSTEADY GAIT. |
| | 79 | 1 | UNSTEADY GAIT. |
| | | 2 | FOUND DEAD. |
| | 80 | 1 | PROSTRATE. |
| | | 2 | VERY UNSTEADY GAIT. |
| | 81 | 1 | PROSTRATE. |
| | | 2 | UNSTEADY GAIT. |

TABLE I-F-45 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 20566

TABLE 2 (CONTINUED)

CLINICAL SIGNS

INITIAL DOSING

| DOSE GROUP (MG/KG) | ANIMAL NUMBER | DAY OF STUDY | SIGN |
|---|---|---|---|
| DIMP | 82 | 1 | PROSTRATE. |
| 1000 | | 2 | UNSTEADY GAIT. |
| | | 21 | SITTING, UNABLE TO STAND OR WALK; MORIBUND KILL. |
| | 83 | 1, 2 | UNSTEADY GAIT. |
| | 84 | 1, 2 | UNSTEADY GAIT. |
| | 85 | 1 | PROSTRATE. |
| | | 2 | FOUND DEAD. |
| | 86 | 1 | PROSTRATE. |
| | | 2 | UNSTEADY GAIT. |
| | 87 | 1 | PROSTRATE. |
| | | 2 | UNSTEADY GAIT. |
| | | 3 | SLIGHT UNSTEADY GAIT. |
| | 88 | 1 | PROSTRATE. |
| | | 2 | FOUND DEAD. |
| | 89 | 1 | PROSTRATE. |
| | | 2 | UNSTEADY GAIT. |
| | | 3 | SLIGHTLY UNSTEADY GAIT. |
| | 90 | 1 | PROSTRATE. |
| | | 2 | VERY UNSTEADY GAIT. |
| | | 3 | UNSTEADY GAIT. |
| | 91 | 1 | PROSTRATE. |
| | | 2 | SLIGHTLY UNSTEADY GAIT. |
| | 92 | 1 | UNSTEADY GAIT. |
| | | 2 | SLIGHTLY UNSTEADY GAIT. |
| | 93 | 1 | PROSTRATE. |
| | | 12-17 | SLIGHTLY UNSTEADY GAIT. |
| | 94 | 1 | UNSTEADY GAIT. |
| | | 2 | FOUND DEAD. |
| | 95 | 1, 2 | UNSTEADY GAIT. |
| | | 3 | SLIGHTLY UNSTEADY GAIT. |
| | | 12-14 | UNABLE TO STAND. |
| | | 15 | VERY UNSTEADY GAIT. |
| | | 16, 17 | UNSTEADY GAIT. |
| | | 18 | SLIGHTLY UNSTEADY GAIT. |
| | 96 | 1 | FOUND DEAD. |
| DIMP | 97 | 1 | UNSTEADY GAIT. |
| 1500 | | 2 | VERY UNSTEADY GAIT. |
| | | 3 | SLIGHTLY UNSTEADY GAIT. |
| | 98 | 1 | PROSTRATE. |
| | | 2 | FOUND DEAD. |

TABLE I-F-45 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 20566

TABLE 2 (CONTINUED)

CLINICAL SIGNS

INITIAL DOSING

| DOSE GROUP (MG/KG) | ANIMAL NUMBER | DAY OF STUDY | SIGN |
|---|---|---|---|
| DIMP | 99 | 1 | PROSTRATE. |
| 1500 | | 2 | FOUND DEAD. |
| | 100 | 1 | PROSTRATE. |
| | | 2 | UNSTEADY GAIT. |
| | | 19, 20 | SLIGHTLY UNSTEADY GAIT. |
| | 101 | 1 | PROSTRATE. |
| | | 2 | UNSTEADY GAIT. |
| | 102 | 1 | FOUND DEAD. |
| | 103 | 1 | PROSTRATE. |
| | | 2 | VERY UNSTEADY GAIT. |
| | | 3 | UNSTEADY GAIT. |
| | 104 | 1 | FOUND DEAD. |
| | 105 | 1 | PROSTRATE. |
| | | 2 | VERY UNSTEADY GAIT. |
| | | 3 | SLIGHTLY UNSTEADY GAIT. |
| | 106 | 1 | PROSTRATE. |
| | | 2 | VERY UNSTEADY GAIT. |
| | 107 | 1 | PROSTRATE. |
| | | 2, 3 | VERY UNSTEADY GAIT. |
| | 108 | 1 | FOUND DEAD. |
| | 109 | 1 | PROSTRATE. |
| | | 2 | UNSTEADY GAIT. |
| | 110 | 1, 2 | PROSTRATE. |
| | | 3 | SLIGHTLY UNSTEADY GAIT. |
| | 111 | 1, 2 | PROSTRATE. |
| | | 3 | SLIGHTLY UNSTEADY GAIT. |
| | 112 | 1 | PROSTRATE. |
| | | 2 | FOUND DEAD. |
| | 113 | 1, 2 | UNSTEADY GAIT. |
| | | 3 | SLIGHTLY UNSTEADY GAIT. |
| | 114 | 1 | PROSTRATE. |
| | | 2 | FOUND DEAD. |
| | 115 | 1, 2 | UNSTEADY GAIT. |

TABLE I-F-45 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 20566

TABLE 2 (CONTINUED)

CLINICAL SIGNS

SECOND DOSING

| DOSE GROUP (MG/KG) | ANIMAL NUMBER | DAY OF STUDY | SIGN |
|---|---|---|---|
| CONTROL | 35 | 41 | PROSTRATE, EYES CLOSED; MORIBUND KILL. |
| DIMP | 56 | 22 | SITTING, UNSTEADY GAIT WHEN TOUCHED. |
| 500 | 57 | 22 | QUIET, SLIGHTLY UNSTEADY GAIT. |
| | | 43 | SITTING, UNABLE TO STAND. |
| | | 44 | STANDS, BUT WALKS WITH GREAT DIFFICULTY. |
| | | 45 | WALKS, BUT UNSTEADY ON RIGHT LEG. |
| | 58 | 22 | UNSTEADY GAIT. |
| | | 34-45 | UNSTEADY ON RIGHT LEG, JOINT ENLARGED. |
| | 59 | 22 | SLIGHTLY UNSTEADY GAIT. |
| | 60 | 22 | SITTING, SLIGHTLY UNSTEADY GAIT WHEN TOUCHED. |
| | | 41-45 | SLIGHTLY UNSTEADY GAIT. |
| | 61 | 22 | STANDING, QUIET; UNSTEADY GAIT WHEN TOUCHED. |
| | 62 | 22 | SLIGHTLY UNSTEADY GAIT. |
| | 63 | 22 | SITTING, VERY UNSTEADY GAIT WHEN TOUCHED. |
| | 64 | 22 | STANDING WITH EYES CLOSED; UNSTEADY GAIT WHEN TOUCHED. |
| | 65 | 22 | SLIGHTLY UNSTEADY GAIT. |
| | | 35 | PROSTRATE. |
| | | 36 | PROSTRATE; NOT EATING OR DRINKING; MORIBUND KILL. |
| | 66 | 22 | STANDING, QUIET; UNSTEADY GAIT WHEN TOUCHED. |
| | 67 | 22 | SITTING, EYES CLOSED; SLIGHTLY REACTIVE WHEN TOUCHED. |
| | 68 | 22 | SLIGHTLY UNSTEADY GAIT. |
| | 70 | 22 | SLIGHTLY UNSTEADY GAIT. |
| | 71 | 22 | UNSTEADY GAIT. |
| | 72 | 22 | UNSTEADY GAIT. |
| | 73 | 22 | SITTING, EYES CLOSED; UNSTEADY GAIT WHEN TOUCHED. |
| | 75 | 22 | UNSTEADY GAIT. |
| DIMP | 76 | 22-24 | PROSTRATE. |
| 1000 | | 25 | SITTING, UNABLE TO STAND. |
| | | 26 | PROSTRATE; COMB LIMP, EDGES PURPLE. |
| | | 27 | FOUND DEAD. |

TABLE I-F-45 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 20566

TABLE 2 (CONTINUED)

CLINICAL SIGNS

SECOND DOSING

| DOSE GROUP (MG/KG) | ANIMAL NUMBER | DAY OF STUDY | SIGN |
|---|---|---|---|
| DIMP | 77 | 22 | PROSTRATE. |
| 1000 | 78 | 22 | PROSTRATE. |
| | 80 | 22 | PROSTRATE. |
| | | 23 | UNSTEADY GAIT. |
| | | 36-45 | UNABLE TO STAND ON LEFT LEG. |
| | 81 | 22 | PROSTRATE. |
| | | 23 | SLIGHTLY UNSTEADY GAIT. |
| | | 36, 37 | PROSTRATE. |
| | | 38, 39 | PROSTRATE; COMB LIMP, EDGES PURPLE. |
| | | 40 | PROSTRATE; COMB LIMP, COLOR NORMAL. |
| | | 41 | PROSTRATE; COMB LIMP; MORIBUND KILL. |
| | 83 | 22 | SITTING, SLIGHT MOVEMENT WHEN TOUCHED. |
| | | 36-41 | SLIGHTLY UNSTEADY GAIT. |
| | 84 | 22 | PROSTRATE. |
| | | 23 | SITTING/STANDING, UNSTEADY GAIT WHEN TOUCHED. |
| | | 42-44 | PROSTRATE. |
| | | 45 | STANDING, BUT UNABLE TO WALK. |
| | 86 | 22 | STANDING, QUIET; VERY UNSTEADY GAIT WHEN TOUCHED. |
| | | 36-40 | PROSTRATE. |
| | | 41 | PROSTRATE; MORIBUND KILL. |
| | 87 | 22 | PROSTRATE. |
| | | 23 | SLIGHTLY UNSTEADY GAIT. |
| | 89 | 22 | PROSTRATE. |
| | | 23 | SLIGHTLY UNSTEADY GAIT. |
| | 90 | 22 | SITTING, SLIGHT MOVEMENT WHEN TOUCHED. |
| | | 23 | SITTING/STANDING, VERY UNSTEADY GAIT WHEN TOUCHED. |
| | 91 | 22 | PROSTRATE. |
| | 92 | 22 | STANDING, QUIET; UNSTEADY GAIT WHEN TOUCHED. |
| | 93 | 22 | PROSTRATE. |
| | 95 | 22 | SITTING, SLIGHT MOVEMENT WHEN TOUCHED. |
| | | 23 | PROSTRATE. |
| | | 24-32 | SLIGHTLY UNSTEADY GAIT. |
| | | 36 | PROSTRATE. |
| | | 37 | PROSTRATE; COMB LIMP. |
| | | 38 | PROSTRATE; COMB LIMP, EDGES PURPLE; MORIBUND KILL. |

SUBJECT: FINAL PATHOLOGY REPORT
Demyelination Paralysis in Chickens
LBI Project No. 20566

## 1. OBJECTIVE

The objective was to determine the status of selected nerve tissue specimens with regard to the presence and degree of demyelination. Comparable nerve tissue specimens from chickens treated with Tri-O-Tolyl phosphate were provided as control material to serve as a basis for the microscopic evaluation.

## 2. METHODS

Specimens of sciatic, tibial and plantar nerve were fixed in buffered 10% formalin solution, pH 7.0, dehydrated with ascending concentrations of ethyl alcohol, cleared with xylene and embedded in Paraplast R. Sciatic nerve of each chicken was embedded in one block, while the tibial and plantar nerve segments were embedded together in a second block.

Duplicate sections were prepared at 6 microns; one was stained with hematoxylin and eosin and the other with Luxol-fast blue and counterstained with cresyl violet.

## 3. DEFINITIONS

Demyelination is the historical term applied to nerve fiber changes associated with the delayed neurotoxicity of Tri-O-cresyl phosphate (Tri-O-Tolyl phosphate is a synonym). In a recent discussion of the pathology of delayed neurotoxicity due to organo-phosphates the following statement was made, "Basically the lesion is a "dying back" process or Wallerian degeneration in the axons although earlier work tended to consider it a demyelinating disease."[1] The term "die back" is used in another report[2] and agreement is expressed with the concept that Wallerian degeneration of the axon represents the primary morphologic effect of organo-phosphates with delayed neurotoxicity. However, this author used the designation "nerve fiber degeneration" in general discussion of the subject. The designation nerve fiber degeneration is therefore appropriate for the purpose of this report.

* Also known as TOCP.

## 4. RESULTS

A tabulation of nerve fiber degeneration in the different groups of chickens (vehicle controls, positive controls, low dose, medium dose and high dose) is given in Table 1.

None of the 20 chickens in the vehicle control group (of which nine were redosed) had microscopic evidence of nerve fiber degeneration. A total of 13 of the 20 chickens in the positive control group had microscopic evidence of nerve fiber degeneration with an average degree of 1.8 (1=minimal, 2=slight). This compares with 19 that had clinical signs and indicates that the microscopic examination was a less sensitive indicator of delayed neurotoxicity than the clinical signs under the conditions of this test.

None of the 20 chickens in the low dose group (of which all were redosed) had microscopic evidence of nerve fiber degeneration. Two of the 16 chickens in the middle dose group (of which 15 were redosed) had trace nerve fiber degeneration consisting of one short segment of a single nerve fiber showing degenerative changes.

One of the 12 chickens in the high dose group (of which none were redosed) had slight nerve fiber degeneration.

## 5. DISCUSSION

The nerve fiber degeneration in two of the middle dose (DIMP) chickens and in one of the high dose has debatable validity in the interpretation of the test. Trace lesions similar to those in two of the middle dose chickens have been reported to occur in odd nerve fibers in normal hens.[1] The high dose chicken with slight nerve fiber degeneration had not shown any clinical signs.

## 6. CONCLUSIONS

Nerve fiber degeneration that can be attributed to delayed neurotoxicity was not recognized in the various groups of chickens dosed with DIMP.

SUBMITTED BY:

Herman R. Seibold, V.M.D.
Veterinary Pathologist

9-26-78
Date

REVIEWED BY:

Richard H. Cardy, D.V.M.
Director
Department of Pathology

29 Sept 78
Date

[1]Bradley, W.A.: The Pathology of Delayed Neurotoxicity Due to Organophosphates. In, Pesticide Induced Delayed Neurotoxicity, Proceedings of a Conference held in Washington, D.C., on February 19 and 20, 1976. US Department of Commerce, National Technical Information Service, PB-256 416. Prepared for National Institute of Environmental Health Sciences. pp 84-101, July 1, 1976.

[2]Cavanagh, J.B.: Peripheral Neuropathy Caused by Chemical Agents, CRC, Critical Reviews in Toxicology, 2:365-417, November, 1973.

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LEGEND TO TABLE OF MICROSCOPIC OBSERVATIONS

Column "A" = Animal number

Column "B" = Chicken disposition

TK = killed at termination of test.
MK = killed when moribund.
FD = found dead.
* = chicken did not survive for delayed neurotoxicity observation.

Column "C" = Nerve fiber degeneration

\- = microscopic lesions not recognized.
1 = present in minimal degree.
2 = present in slight degree.
3 = present in moderate degree.
T = trace (one short segment of a single nerve fiber showing degenerative changes).

TABLE I-F-46

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TABLE 1

MICROSCOPIC OBSERVATIONS

| Group #1 Vehicle Control | | | Group #2 Positive Control TOCP (500 mg/kg) | | | Group #3 Low Dose DIMP (500 mg/kg) | | | Group #4 Middle Dose DIMP (1000 mg/kg) | | | Group #5 High Dose DIMP (1500 mg/kg) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A | B | C | A | B | C | A | B | C | A | B | C | A | B | C |
| 16 | TK | - | 36 | TK | - | Redosed Chickens | | | 82 | MK | T | 97 | TK | - |
| 17 | TK | - | 37 | TK | 2 | | | | | | | 100 | TK | - |
| 18 | TK | - | 38 | TK | 3 | 56 | TK | - | Redosed Chickens | | | 101 | TK | - |
| 19 | TK | - | 39 | TK | 3 | 57 | TK | - | | | | 103 | TK | - |
| 20 | TK | - | 40 | TK | - | 58 | TK | - | 77 | TK | - | 105 | TK | - |
| 21 | TK | - | 41 | TK | 1 | 59 | TK | - | 78 | TK | - | 106 | TK | - |
| 22 | TK | - | 42 | TK | 1 | 60 | TK | - | 80 | TK | | 107 | TK | - |
| 23 | TK | - | 43 | TK | 1 | 61 | TK | - | 83 | TK | - | 109 | TK | - |
| 24 | TK | - | 44 | TK | 2 | 62 | TK | - | 84 | TK | T | 110 | TK | 2 |
| 25 | TK | - | 45 | TK | - | 63 | TK | - | 87 | TK | - | 111 | TK | - |
| 28 | MK | - | 46 | TK | 1 | 64 | TK | - | 89 | TK | - | 113 | TK | - |
| | | | 47 | TK | - | 66 | TK | - | 90 | TK | - | 115 | TK | - |
| Redosed Chickens | | | 48 | TK | 2 | 68 | TK | - | 91 | TK | - | 96 | * | |
| | | | 49 | TK | 2 | 69 | TK | - | 92 | TK | - | 98 | * | |
| 26 | TK | - | 50 | TK | - | 70 | TK | - | 93 | TK | - | 99 | * | |
| 27 | TK | - | 51 | TK | - | 71 | TK | - | 81 | MK | - | 102 | * | |
| 29 | TK | - | 52 | TK | 2 | 72 | TK | - | 86 | MK | - | 104 | * | |
| 30 | TK | - | 53 | TK | - | 73 | TK | - | 95 | MK | - | 108 | * | |
| 31 | TK | - | 54 | TK | 2 | 74 | TK | - | 76 | FD | - | 112 | * | |
| 32 | TK | - | 55 | TK | 1 | 75 | TK | - | 79 | * | | 114 | * | |
| 33 | TK | - | | | | 65 | MK | - | 85 | * | | | | |
| 34 | TK | - | | | | 67 | MK | - | 88 | * | | | | |
| 35 | MK | - | | | | | | | 94 | * | | | | |

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INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0016
DOSAGE: 0 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4660
GROUP NUMBER: 1
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
Tibial nerve, Plantar nerve - one lost in processing; other no lesion recognized.

ANIMAL NUMBER: 0017
DOSAGE: 0 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4661
GROUP NUMBER: 1
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

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INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0018
DOSAGE: 0 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4662
GROUP NUMBER: 1
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0019
DOSAGE: 0 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4663
GROUP NUMBER: 1
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

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INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0020 PM NUMBER: 78/4664
DOSAGE: 0 mg/kg GROUP NUMBER: 1
DATE OF DEATH: 3/3/78 SPECIES: Chicken
DEATH: Terminal kill SEX: Female
METHOD OF KILL: Cervical dislocation

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0021 PM NUMBER: 78/4665
DOSAGE: 0 mg/kg GROUP NUMBER: 1
DATE OF DEATH: 3/3/78 SPECIES: Chicken
DEATH: Terminal kill SEX: Female
METHOD OF KILL: Cervical dislocation

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

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INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0022
DOSAGE: 0 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4666
GROUP NUMBER: 1
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0023
DOSAGE: 0 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4667
GROUP NUMBER: 1
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

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INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0024
DOSAGE: 0 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4668
GROUP NUMBER: 1
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0025
DOSAGE: 0 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4669
GROUP NUMBER: 1
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

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INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0026 PM NUMBER: 78/4670
DOSAGE: 0 mg/kg GROUP NUMBER: 1
DATE OF DEATH: 3/27/78 SPECIES: Chicken
DEATH: Terminal kill SEX: Female
METHOD OF KILL: Cervical dislocation

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

MISSING TISSUES:
Sciatic nerve - lost in processing.
Tibial nerve - lost in processing.

ANIMAL NUMBER: 0027 PM NUMBER: 78/4671
DOSAGE: 0 mg/kg GROUP NUMBER: 1
DATE OF DEATH: 3/27/78 SPECIES: Chicken
DEATH: Terminal kill SEX: Female
METHOD OF KILL: Cervical dislocation

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

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INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0028 PM NUMBER: 78/4672
DOSAGE: 0 mg/kg GROUP NUMBER: 1
DATE OF DEATH: 2/27/78 SPECIES: Chicken
DEATH: Moribund sacrifice SEX: Female
METHOD OF KILL: Cervical dislocation

GROSS FINDINGS:
Animal sacrificed.

MICROSCOPIC FINDINGS:
No lesion recognized.

MISSING TISSUES:
Tibial nerve - one lost in processing.

ANIMAL NUMBER: 0029 PM NUMBER: 78/4673
DOSAGE: 0 mg/kg GROUP NUMBER: 1
DATE OF DEATH: 3/27/78 SPECIES: Chicken
DEATH: Terminal kill SEX: Female
METHOD OF KILL: Cervical dislocation

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

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INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0030
DOSAGE: 0 mg/kg
DATE OF DEATH: 3/27/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4674
GROUP NUMBER: 1
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0031
DOSAGE: 0 mg/kg
DATE OF DEATH: 3/27/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4675
GROUP NUMBER: 1
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

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INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0032
DOSAGE: 0 mg/kg
DATE OF DEATH: 3/27/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4676
GROUP NUMBER: 1
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0033
DOSAGE: 0 mg/kg
DATE OF DEATH: 3/27/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4677
GROUP NUMBER: 1
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

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INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0034
DOSAGE: 0 mg/kg
DATE OF DEATH: 3/27/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4678
GROUP NUMBER: 1
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0035
DOSAGE: 0 mg/kg
DATE OF DEATH: 3/22/78
DEATH: Moribund kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4679
GROUP NUMBER: 1
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

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INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0036
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 76/4680
GROUP NUMBER: 2
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0037
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4681
GROUP NUMBER: 2
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
Tibial nerve, Plantar nerve - slight nerve fiber degeneration.

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INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0038
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4682
GROUP NUMBER: 2
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
Sciatic nerve - minimal nerve fiber degeneration.
Tibial nerve, Plantar nerve - moderate nerve fiber degeneration.

ANIMAL NUMBER: 0039
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4683
GROUP NUMBER: 2
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
Tibial nerve, Plantar nerve - moderate nerve fiber degeneration.

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INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0040 PM NUMBER: 78/4684
DOSAGE: 500 mg/kg GROUP NUMBER: 2
DATE OF DEATH: 3/3/78 SPECIES: Chicken
DEATH: Terminal kill SEX: Female
METHOD OF KILL: Cervical dislocation

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0041 PM NUMBER: 78/4685
DOSAGE: 500 mg/kg GROUP NUMBER: 2
DATE OF DEATH: 3/3/78 SPECIES: Chicken
DEATH: Terminal kill SEX: Female
METHOD OF KILL: Cervical dislocation

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
Tibial nerve, Plantar nerve - minimal nerve fiber degeneration.

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INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0042 PM NUMBER: 78/4686
DOSAGE: 500 mg/kg GROUP NUMBER: 2
DATE OF DEATH: 3/3/78 SPECIES: Chicken
DEATH: Terminal kill SEX: Female
METHOD OF KILL: Cervical dislocation

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
Tibial nerve, Plantar nerve - minimal nerve fiber degeneration.

ANIMAL NUMBER: 0043 PM NUMBER: 78/4687
DOSAGE: 500 mg/kg GROUP NUMBER: 2
DATE OF DEATH: 3/3/78 SPECIES: Chicken
DEATH: Terminal kill SEX: Female
METHOD OF KILL: Cervical dislocation

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
Tibial nerve, Plantar nerve - minimal nerve fiber degeneration.

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INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0044
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4688
GROUP NUMBER: 2
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
Tibial nerve, Plantar nerve - one lost in processing, the other slight nerve fiber degeneration in tissue.

ANIMAL NUMBER: 0045
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4689
GROUP NUMBER: 2
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

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INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0046
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4690
GROUP NUMBER: 2
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
Tibial nerve, Plantar nerve - minimal nerve fiber degeneration.

ANIMAL NUMBER: 0047
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4691
GROUP NUMBER: 2
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

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INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0048 PM NUMBER: 78/4692
DOSAGE: 500 mg/kg GROUP NUMBER: 2
DATE OF DEATH: 3/3/78 SPECIES: Chicken
DEATH: Terminal kill SEX: Female
METHOD OF KILL: Cervical dislocation

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
Tibial nerve, Plantar nerve - slight nerve fiber degeneration.

ANIMAL NUMBER: 0049 PM NUMBER: 78/4693
DOSAGE: 500 mg/kg GROUP NUMBER: 2
DATE OF DEATH: 3/3/78 SPECIES: Chicken
DEATH: Terminal kill SEX: Female
METHOD OF KILL: Cervical dislocation

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
Tibial nerve, Plantar nerve - slight nerve fiber degeneration.

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INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0050
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4694
GROUP NUMBER: 2
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0051
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4695
GROUP NUMBER: 2
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

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INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0052
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4696
GROUP NUMBER: 2
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
Tibial nerve, Plantar nerve - slight nerve fiber degeneration.

ANIMAL NUMBER: 0053
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4697
GROUP NUMBER: 2
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
Tibial nerve, Plantar nerve - one lost in processing; the other no lesion recognized.

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INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0054
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4698
GROUP NUMBER: 2
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
Tibial nerve, Plantar nerve - slight nerve fiber degeneration.

ANIMAL NUMBER: 0055
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4699
GROUP NUMBER: 2
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
Tibial nerve, Plantar nerve - minimal nerve fiber degeneration.

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INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0056
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/27/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4700
GROUP NUMBER: 3
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0057
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/27/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4701
GROUP NUMBER: 3
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

LITTON BIONETICS, INC.
LBI PROJECT NO. 20566

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0058
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/27/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4702
GROUP NUMBER: 3
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0059
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/27/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4703
GROUP NUMBER: 3
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

LITTON BIONETICS, INC.
LBI PROJECT NO. 20566

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0060
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/27/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4704
GROUP NUMBER: 3
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0061
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/27/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4705
GROUP NUMBER: 3
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

LITTON BIONETICS, INC.
LBI PROJECT NO. 20566

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0062
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/27/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4706
GROUP NUMBER: 3
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0063
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/27/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4707
GROUP NUMBER: 3
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

LITTON BIONETICS, INC.
LBI PROJECT NO. 20566

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0064
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/27/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4708
GROUP NUMBER: 3
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

MISSING TISSUES:
Tibial nerve, Plantar nerve - both tissues lost in processing.

ANIMAL NUMBER: 0065
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/17/78
DEATH: Moribund sacrifice
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4709
GROUP NUMBER: 3
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

MISSING TISSUES:
Tibial nerve, Plantar nerve - lost in processing.

LITTON BIONETICS, INC.
LBI PROJECT NO. 20566

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0066 PM NUMBER: 78/4710
DOSAGE: 500 mg/kg GROUP NUMBER: 3
DATE OF DEATH: 3/27/78 SPECIES: Chicken
DEATH: Terminal kill SEX: Female
METHOD OF KILL: Cervical dislocation

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0067 PM NUMBER: 78/4711
DOSAGE: 500 mg/kg GROUP NUMBER: 3
DATE OF DEATH: 3/10/78 SPECIES: Chicken
DEATH: Moribund sacrifice SEX: Female
METHOD OF KILL: Cervical dislocation

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

LITTON BIONETICS, INC.
LBI PROJECT NO. 20566

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0068
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/27/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4712
GROUP NUMBER: 3
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0069
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/27/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4713
GROUP NUMBER: 3
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

LITTON BIONETICS, INC.
LBI PROJECT NO. 20566

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0070
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/27/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4714
GROUP NUMBER: 3
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0071
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/27/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4715
GROUP NUMBER: 3
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

LITTON BIONETICS, INC.
LBI PROJECT NO. 20566

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0072
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/27/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4716
GROUP NUMBER: 3
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0073
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/27/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4717
GROUP NUMBER: 3
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

LITTON BIONETICS, INC.
LBI PROJECT NO. 20566

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0074
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/27/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4718
GROUP NUMBER: 3
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0075
DOSAGE: 500 mg/kg
DATE OF DEATH: 3/27/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4719
GROUP NUMBER: 3
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

LITTON BIONETICS, INC.
LBI PROJECT NO. 20566

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0076
DOSAGE: 1000 mg/kg
DATE OF DEATH: 3/8/78
DEATH: Found dead
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4720
GROUP NUMBER: 4
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0077
DOSAGE: 1000 mg/kg
DATE OF DEATH: 3/27/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4721
GROUP NUMBER: 4
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

LITTON BIONETICS, INC.
LBI PROJECT NO. 20566

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0078
DOSAGE: 1000 mg/kg
DATE OF DEATH: 3/27/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4722
GROUP NUMBER: 4
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0080
DOSAGE: 1000 mg/kg
DATE OF DEATH: 3/27/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4723
GROUP NUMBER: 4
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:

Comment - Appears to be slight muscle wasting of left leg. Representative sections of muscle saved in 10% neutral buffered formalin. No other gross abnormalities noted.

MICROSCOPIC FINDINGS:
No lesion recognized.

LITTON BIONETICS, INC.
LBI PROJECT NO. 20566

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0081
DOSAGE: 1000 mg/kg
DATE OF DEATH: 3/22/78
DEATH: Moribund sacrifice
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4724
GROUP NUMBER: 4
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0082
DOSAGE: 1000 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Moribund sacrifice
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4725
GROUP NUMBER: 4
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDIGNS:
Tibial nerve, Plantar nerve - trace nerve fiber degeneration.

LITTON BIONETICS, INC.
LBI PROJECT NO. 20566

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0083 PM NUMBER: 78/4728
DOSAGE: 1000 mg/kg GROUP NUMBER: 4
DATE OF DEATH: 3/27/78 SPECIES: Chicken
DEATH: Terminal kill SEX: Female
METHOD OF KILL: Cervical dislocation

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0084 PM NUMBER: 78/4729
DOSAGE: 1000 mg/kg GROUP NUMBER: 4
DATE OF DEATH: 3/27/78 SPECIES: Chicken
DEATH: Terminal kill SEX: Female
METHOD OF KILL: Cervical dislocation

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
Sciatic nerve - trace nerve fiber degeneration.

LITTON BIONETICS, INC.
LBI PROJECT NO. 20566

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0086
DOSAGE: 1000 mg/kg
DATE OF DEATH: 3/22/78
DEATH: Moribund sacrifice
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4730
GROUP NUMBER: 4
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0087
DOSAGE: 1000 mg/kg
DATE OF DEATH: 3/27/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4731
GROUP NUMBER: 4
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

LITTON BIONETICS, INC.
LBI PROJECT NO. 20566

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0089 PM NUMBER: 78/4732
DOSAGE: 1000 mg/kg GROUP NUMBER: 4
DATE OF DEATH: 3/27/78 SPECIES: Chicken
DEATH: Terminal kill SEX: Female
METHOD OF KILL: Cervical dislocation

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0090 PM NUMBER: 78/4733
DOSAGE: 1000 mg/kg GROUP NUMBER: 4
DATE OF DEATH: 3/27/78 SPECIES: Chicken
DEATH: Terminal kill SEX: Female
METHOD OF KILL: Cervical dislocation

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

LITTON BIONETICS, INC.
LBI PROJECT NO. 20566

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0091 PM NUMBER: 78/4734
DOSAGE: 1000 mg/kg GROUP NUMBER: 4
DATE OF DEATH: 3/27/78 SPECIES: Chicken
DEATH: Terminal kill SEX: Female
METHOD OF KILL: Cervical dislocation

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0092 PM NUMBER: 78/4735
DOSAGE: 1000 mg/kg GROUP NUMBER: 4
DATE OF DEATH: 3/27/78 SPECIES: Chicken
DEATH: Terminal kill SEX: Female
METHOD OF KILL: Cervical dislocation

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
Tibial nerve, Plantar nerve - one lost in processing; the other
no lesion recognized.

LITTON BIONETICS, INC.
LBI PROJECT NO. 20566

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0093
DOSAGE: 1000 mg/kg
DATE OF DEATH: 3/27/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4736
GROUP NUMBER: 4
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0095
DOSAGE: 1000 mg/kg
DATE OF DEATH: 3/19/78
DEATH: Moribund sacrifice
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4737
GROUP NUMBER: 4
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
Tibial nerve, Plantar nerve - one lost in processing; the other no
no lesion recognized.

LITTON BIONETICS, INC.
LBI PROJECT NO. 2?506

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0097 PM NUMBER: 78/4738
DOSAGE: 1500 mg/kg GROUP NUMBER: 5
DATE OF DEATH: 3/3/78 SPECIES: Chicken
DEATH: Terminal kill SEX: Female
METHOD OF KILL: Cervical dislocation

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0100 PM NUMBER: 78/4739
DOSAGE: 1500 mg/kg GROUP NUMBER: 5
DATE OF DEATH: 3/3/78 SPECIES: Chicken
DEATH: Terminal kill SEX: Female
METHOD OF KILL: Cervical dislocation

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

LITTON BIONETICS, INC.
LBI PROJECT NO. 20566

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0101
DOSAGE: 1500 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4740
GROUP NUMBER: 5
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0103
DOSAGE: 1500 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4741
GROUP NUMBER: 5
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

LITTON BIONETICS, INC.
LBI PROJECT NO. 20566

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0105 PM NUMBER: 78/4742
DOSAGE: 1500 mg/kg GROUP NUMBER: 5
DATE OF DEATH: 3/3/78 SPECIES: Chicken
DEATH: Terminal kill SEX: Female
METHOD OF KILL: Cervical dislocation

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0106 PM NUMBER: 78/4743
DOSAGE: 1500 mg/kg GROUP NUMBER: 5
DATE OF DEATH: 3/3/78 SPECIES: Chicken
DEATH: Terminal kill SEX: Female
METHOD OF KILL: Cervical dislocation

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

LITTON BIONETICS, INC.
LBI PROJECT NO. 20566

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0107 PM NUMBER: 78/4744
DOSAGE: 1500 mg/kg GROUP NUMBER: 5
DATE OF DEATH: 3/3/78 SPECIES: Chicken
DEATH: Terminal kill SEX: Female
METHOD OF KILL: Cervical dislocation

GROSS FINDINGS:

Comment - Nerve at about midway.

MICROSCOPIC FINDINGS:
Tibial nerve, Plantar nerve - one tissue inadequate; the other no lesion recognized.

ANIMAL NUMBER: 0109 PM NUMBER: 78/4745
DOSAGE: 1500 mg/kg GROUP NUMBER: 5
DATE OF DEATH: 3/3/78 SPECIES: Chicken
DEATH: Terminal kill SEX: Female
METHOD OF KILL: Cervical dislocation

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

LITTON BIONETICS, INC.
LBI PROJECT NO. 20566

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0110
DOSAGE: 1500 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4746
GROUP NUMBER: 5
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
Sciatic nerve - slight nerve fiber degeneration.
Tibial nerve, Plantar nerve - minimal nerve fiber degeneration.

ANIMAL NUMBER: 0111
DOSAGE: 1500 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4747
GROUP NUMBER: 5
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

LITTON BIONETICS, INC.
LBI PROJECT NO. 20506

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 0113
DOSAGE: 1500 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4748
GROUP NUMBER: 5
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

ANIMAL NUMBER: 0115
DOSAGE: 1500 mg/kg
DATE OF DEATH: 3/3/78
DEATH: Terminal kill
METHOD OF KILL: Cervical dislocation

PM NUMBER: 78/4749
GROUP NUMBER: 5
SPECIES: Chicken
SEX: Female

GROSS FINDINGS:
No lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

PART I - SECTION G

THREE-MONTH SUBCHRONIC TOXICITY IN DOGS

DIMP

LBI PROJECT NO. 10734-08

## SUMMARY

Beagle dogs, four per sex per group, were given diisopropylmethylphosphate (DIMP) in the diet for 90 days. Dietary concentrations were 150, 1500 and 3000 ppm, and a control group was maintained in parallel. Initially and at 4, 8 and 13 weeks hemograms and clinical chemistry values were obtained on all dogs. The dogs were examined daily as to general condition, and weekly body weights and food consumption data were obtained. An ophthalmologic examination was conducted initially and at 13 weeks. At termination each dog was grossly necropsied and approximately 27 tissues were preserved. Eight organs were weighed. Tissues from the control and high-level groups were examined histologically. The dogs continued in good general health throughout the study. No clear or meaningful changes were seen in the data collected that could be ascribed to the ingestion of DIMP by these dogs, and it is concluded that this compound produced no toxic effects at a dietary concentration of 3000 ppm or below, over the 90-day period of study.

## 1. OBJECTIVE

The objective of this study was to evaluate and characterize the toxicity of the test material by feeding it in the diet to dogs for 90 days.

## 2. MATERIAL

Refer to Part I - Section A.

## 3. EXPERIMENTAL DESIGN

Purebred beagle dogs (five to six months old) were received from Hazleton Research Animals, Inc., Cumberland, Virginia, and acclimated to laboratory conditions for at least four weeks. The dogs had been immunized for hepatitis and rabies by the supplier and were further immunized against distemper and leptospirosis in this laboratory. The dogs were individually housed in stainless steel cages in temperature-controlled quarters with automated artificial lighting providing a 12-hr cycle of illumination. Water was provided ad libitum.

3. EXPERIMENTAL DESIGN (Continued)

The dogs were assigned LBI dog numbers and placed in the following treatment groups:

| Group Number | Animal Number | | Diet Concentrations (ppm) |
|---|---|---|---|
| | Males | Females | |
| 1 | 370-373 | 374-377 | 0 (Control) |
| 2 | 378-381 | 382-385 | 150 |
| 3 | 386-389 | 390-393 | 1500 |
| 4 | 394-397 | 398-401 | 3000 |

These dietary concentrations were selected by a representative of the sponsor. The dogs were identified by ear tattoo and cage cards.

DIMP was incorporated in the diet of the dogs (Purina Lab Canine Diet) at the stated concentrations using PEG 400 as a vehicle, and mixed with the feed in a twin-shell blender for 20-30 min. The proportion of PEG 400 to feed was 150 ml to 20 kg for all diet levels, including that of the control. Compound feeding began September 2, 1977.

The dogs were examined daily as to general condition, behavior, fecal consistency and signs of toxicity. Body weights were obtained initially and weekly during the experiment. Food consumption was estimated twice per week and recorded on a weekly basis. In addition, fecal examinations for parasites were made on all dogs, and after finding Giardia canis and Isospora canis in some animals, all were treated with sulfamethazine and quinacrine hydrochloride in sequence over a 12-day period.

Clinical pathology determinations were obtained initially and at 4, 8 and 13 weeks. These included:

| Hematology | Blood Chemistry | |
|---|---|---|
| erythrocyte count | glucose | uric acid |
| leukocyte count | blood urea nitrogen | bilirubin |
| differential leukocyte count | serum glutamic-pyruvic transaminase | cholesterol |
| hemoglobin | serum glutamic-oxaloacetic transaminase | lactic dehydrogenase |
| packed cell volume | serum alkaline phosphatase | acetyl cholinesterase** (RBC and plasma) |
| clotting time | total protein | CPK* |
| | albumin/globulin ratio* | total iron* |
| | creatinine* | triglycerides* |
| | sodium* | carbon dioxide* |
| | chloride* | phosphorus* |
| | calcium | albumin* |
| | | potassium* |

*Initially only except as noted
**Only on dogs receiving DIMP except as noted

Qualitative urinalyses were performed at Weeks 8 and 13.

3. EXPERIMENTAL DESIGN (Continued)

Detailed physical examinations were performed initially and ophthalmologic examinations were performed initially and at 13 weeks, using a solution of 1.0% Mydriacyl to dilate the pupils. (Note: Initial examinations were all made during the acclimation period.)

At 13 weeks the dogs were killed with an intravenous dose of a barbiturate and exsanguinated.

A gross necropsy was performed and the following organs from all dogs were removed and weighed:

liver
brain
thyroid
kidneys
adrenal glands
testes
ovaries
heart
spleen

The weighed organs as well as those listed below were fixed in 10% buffered formalin:

spinal cord
lungs
pancreas
stomach
small intestines
colon
urinary bladder
prostate
eyes (with optic nerve)
pituitary
bone marrow (femur)
rib junction
lymph node (mesenteric)
mammary tissue
skin
peripheral nerve (sciatic)
muscle
uterus
gallbladder
any gross lesions

The tissues from dogs of the control and high-level groups were examined histologically while those of the other two groups were stored in case of need.

Thirty days after transmittal of this report, all original data will be transferred to the LBI Archives, 1330 Piccard Drive, Rockville, Maryland.

A draft of this report and underlying data were reviewed by Litton Bionetics Quality Assurance Unit prior to submission.

TABLE I-G-47

LITTON BIONETICS, INC.
PROJECT NO. 10734-08

TABLE A

FREQUENCY[a] OF CLINICAL OBSERVATIONS IN DOGS

| WEEK | OBSERVATION | DIET CONCENTRATION - PPM | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 0 | | 150 | | 1500 | | 3000 | |
| | | M | F | M | F | M | F | M | F |
| -1 | Soft Feces | 2 | 1 | | 2 | 2 | 2 | 2 | 1 |
| | Vomiting | | | | | | | | 1 |
| 1 | Soft Feces | 1 | | | 1 | | 1 | 1 | |
| | Diarrhea | 1 | | | 1 | | | | |
| 2 | Soft Feces | 3 | | 1 | 1 | | | 3 | |
| | Diarrhea | | | | | | 1 | | |
| | Vomiting | | | | | | | | 1 |
| 3 | Soft Feces | 3 | 1 | 2 | 1 | 2 | 2 | 2 | |
| | Vomiting | | | | 1 | | | | |
| | Hair Loss on Foreleg | | | | | 1 | | | |
| 4 | Soft Feces | 3 | 2 | 1 | | 1 | 3 | 2 | 4 |
| | Vomiting | | 1 | | | | | | |
| 5 | Soft Feces | 3 | 1 | 2 | 2 | 2 | 1 | 3 | 3 |
| | Estrus | | | | 1 | | | | |
| | Hair Loss on Foreleg | | | | | 1 | | | |
| | Vomiting | | | | | | 1 | | |
| 6 | Soft Feces | 4 | 4 | 1 | 3 | 2 | 2 | 3 | 4 |
| | Watery Feces | | 1 | | 1 | 1 | 2 | 1 | |
| | Decreased Activity | | | | | | 1 | | |
| 7 | Soft Feces | 4 | 1 | 3 | 2 | 1 | 2 | 2 | 1 |
| | Watery Feces | 1 | 1 | | 1 | 1 | | | |
| | Hair Loss on Foreleg | | | | | 1 | | | |
| 8 | Soft Feces | 2 | | | | 1 | 2 | 1 | 2 |
| | Hair Loss on Foreleg | | | | | 2 | | | 1 |
| | Hair Loss on Ear | | | | | | 1 | | 1 |
| | Estrus | | | | | | | | 1 |
| 9 | Soft Feces | 2 | 2 | | 2 | 2 | 1 | 1 | 1 |
| | Watery Feces | | | 1 | 2 | 1 | | 1 | |
| | Hair Loss, Sores on Forepaws | | | 1 | | | | | |
| | Estrus | | | | | | 1 | | 1 |
| | Hair Loss on Foreleg | | | | | 2 | | | 1 |
| | Hair Loss on Ear | | | | | | 1 | | |
| 10 | Soft Feces | 2 | 1 | | 4 | 3 | 2 | 2 | 3 |
| | Watery Feces | 3 | | | | | 2 | | |
| | Hair Loss on Foreleg(s) | | | 1 | | 2 | | | 1 |
| | Vomiting | | | | | | 1 | | |
| | Hair Loss on Ear | | | | | | 1 | | |
| 11 | Soft Feces | 3 | 1 | 1 | 1 | 2 | 3 | 3 | 3 |
| | Watery Feces | 1 | | | 1 | 2 | | 1 | |
| | Hair Loss on Foreleg(s) | | | 1 | | 2 | | | |
| | Hair Loss on Ear | | | | | | 1 | | 1 |

[a]Number of dogs showing indicated signs at least once during the week.

TABLE I-G-47 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-08

TABLE A (CONTINUED)

FREQUENCY[a] OF CLINICAL OBSERVATIONS IN DOGS

| WEEK | OBSERVATION | DIET CONCENTRATION - PPM | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 0 | | 150 | | 1500 | | 3000 | |
| | | M | F | M | F | M | F | M | F |
| 12 | Soft Feces | 3 | 2 | 1 | | | 1 | 1 | 1 |
| | Watery Feces | 1 | 1 | | | | | 1 | |
| | Hair Loss on Foreleg(s) | | | 1 | | 2 | 1 | | 1 |
| | Hair Loss on Ear | | | | | | 1 | | |
| 13 | Soft Feces | 2 | | | 1 | 3 | 2 | 2 | 2 |
| | Watery Feces | 1 | | | | 2 | 1 | 1 | |
| | Hair Loss on Foreleg(s) | | | | | 3 | | | 1 |
| | Hair Loss on Ear | | | | | | 1 | | |
| | Hair Loss and Sores on Forelegs | | | 1 | | | | | |
| | Hair Loss on Abdomen | | | | | 1 | | | |

4. RESULTS (Continued)

No changes in the eyes of any dogs were reported following the ophthalmologic examinations. The only notations given at the terminal examination were for amelanotic chorioid in both eyes of female dog No. 383 (150-ppm group) and in male dog No. 388 (1500-ppm group), both notations accompanied by the comment, "normal variation". Male dog No. 386 (1500-ppm group) was thought to have larger-than-normal optic discs at the terminal examination.

Hematologic data are presented in Appendix Table 4 and group means for the hematocrits, hemoglobin concentrations, erythrocyte counts and leukocyte counts are given in Text Tables B and C for males and females, respectively. No dose-related changes were seen in these measurements throughout the 13 weeks of study.

Clinical chemistry data are given in Appendix Table 5, with summaries for those tests which were followed throughout the study also being given in Text Tables B and C. (Some tests not specified in the protocol were done initially as part of routine screening procedures and are shown in Table 5. Since these tests were not repeated, their means are not summarized in Text Tables B and C.)

No dose- or time-related changes were apparent with respect to glucose, blood urea nitrogen, SGOT, SGPT, alkaline phosphatase, lactic dehydrogenase, calcium, phosphorus, total protein, albumin, bilirubin, uric acid or cholesterol. Values for some of these tests varied markedly, but statistical evaluations failed to show significance in any consistent or meaningful way.

Clotting time means (Appendix Table 6, Text Tables B and C) likewise showed no pattern indicative of compound effect. Only one of these means was statistically significantly different from control mean, that of the 1500-ppm males at 4 weeks.

Plasma and RBC cholinesterase data are given in Appendix Table 5, with summaries of group means in Text Tables B and C. As preface to discussion of these data, it may be noted that a misinterpretation of the wording of the experimental protocol led to the omission of cholinesterase assays for the control dogs at Weeks 4 and 8, and while the enzyme was determined in all eight controls initially, technical difficulties with the RBC samples at Week 0 make all values for RBC invalid for that time interval. (Plasma values were not affected.) Moreover, at Week 13 cholinesterase for only two control dogs was assayed. Thus, attempts to perceive a pattern in RBC and plasma cholinesterases are somewhat complicated.

TABLE I-G-48

LITTON BIONETICS, INC.
PROJECT NO. 10734-08

TABLE B

MEAN HEMATOLOGICAL AND CLINICAL CHEMISTRY VALUES IN MALE DOGS

| | DIET CONCENTRATIONS (PPM) | INTERVAL (WEEKS) 0 | 4 | 8 | 13 |
|---|---|---|---|---|---|
| PCV (%) | 0 | 48 | 48 | 48 | 49 |
| | 150 | 44 | 50 | 48 | 47 |
| | 1500 | 42* | 48 | 48 | 47 |
| | 3000 | 44 | 46 | 48 | 49 |
| HGB (g %) | 0 | 15.7 | 16.9 | 16.9 | 16.6 |
| | 150 | 14.8 | 17.2 | 16.9 | 15.8 |
| | 1500 | 14.2 | 17.1 | 17.1 | 15.6 |
| | 3000 | 15.0 | 15.9 | 17.6 | 16.4 |
| RBC/ $MM^3 \times 10^6$ | 0 | 7.54 | 6.91 | 8.46 | 7.21 |
| | 150 | 6.57 | 7.00 | 8.07 | 7.11 |
| | 1500 | 6.49 | 6.95 | 7.88 | 7.23 |
| | 3000 | 6.63 | 6.82 | 7.71 | 7.60 |
| WBC/ $MM^3 \times 10^3$ | 0 | 7.7 | 9.1 | 12.3 | 11.0 |
| | 150 | 7.9 | 10.3 | 14.5 | 10.6 |
| | 1500 | 6.5 | 10.9 | 13.5 | 10.7 |
| | 3000 | 7.6 | 9.9 | 11.2 | 9.4 |
| CLOTTING TIME (SEC) | 0 | 353 | 405 | 488 | 458 |
| | 150 | 375 | 555 | 488 | 570 |
| | 1500 | 465 | 675* | 533 | 518 |
| | 3000 | 435 | 578 | 488 | 480 |
| GLUCOSE (MG/DL) | 0 | 99 | 97 | 88 | 89 |
| | 150 | 120 | 109 | 93 | 99 |
| | 1500 | 94 | 109 | 93 | 104 |
| | 3000 | 111 | 106 | 101 | 105 |
| BUN (MG/DL) | 0 | 12 | 15 | 18 | 14 |
| | 150 | 10 | 14 | 15 | 14 |
| | 1500 | 14 | 14 | 14 | 14 |
| | 3000 | 10 | 12 | 13 | 13 |
| SGOT (MIU/ML) | 0 | 40 | 37 | 35 | 45 |
| | 150 | 40 | 41 | 46 | 52 |
| | 1500 | 36 | 37 | 45 | 50 |
| | 3000 | 31 | 32 | 40 | 49 |

*$p<0.05$ as compared to controls: Dunnett's t-test.

LITTON BIONETICS, INC.
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TABLE B (CONTINUED)

MEAN HEMATOLOGICAL AND CLINICAL CHEMISTRY VALUES IN MALE DOGS

| | DIET CONCENTRATIONS (PPM) | INTERVAL (WEEKS) 0 | 4 | 8 | 13 |
|---|---|---|---|---|---|
| SGPT (MIU/ML) | 0 | 32 | 41 | 38 | 44 |
| | 150 | 37 | 36 | 35 | 44 |
| | 1500 | 29 | 35 | 36 | 36 |
| | 3000 | 32 | 42 | 42 | 44 |
| ALK. PHOS. (MIU/ML) | 0 | 152 | 127 | 124 | 82 |
| | 150 | 112 | 87 | 77 | 53 |
| | 1500 | 113 | 84 | 74 | 51 |
| | 3000 | 106 | 72 | 71 | 48 |
| LDH (MIU/ML) | 0 | 225 | 87 | 183 | 231 |
| | 150 | 238 | 98 | 287 | 518 |
| | 1500 | 213 | 83 | 269 | 499 |
| | 3000 | 158 | 53 | 201 | 332 |
| CALCIUM (MG/DL) | 0 | 11.9 | 11.3 | 10.8 | 11.2 |
| | 150 | 11.6 | 11.4 | 10.8 | 10.9 |
| | 1500 | 11.8 | 11.4 | 10.6 | 11.2 |
| | 3000 | 11.4 | 11.3 | 10.5 | 11.0 |
| PHOSPHORUS (MG/DL) | 0 | 6.8 | 4.9 | 5.4 | 5.1 |
| | 150 | 6.0 | 4.6 | 4.8* | 4.5 |
| | 1500 | 6.3 | 4.5 | 4.7* | 4.6 |
| | 3000 | 6.4 | 4.4 | 4.7* | 4.6 |
| TOTAL PROTEIN (G/DL) | 0 | 6.3 | 6.3 | 6.9 | 6.6 |
| | 150 | 5.8 | 5.9 | 6.6 | 6.3 |
| | 1500 | 6.0 | 6.1 | 6.6 | 6.6 |
| | 3000 | 5.8 | 6.0 | 6.5 | 6.4 |
| ALBUMIN (G/DL) | 0 | 3.5 | 3.5 | 3.2 | 3.3 |
| | 150 | 3.2 | 3.5 | 3.1 | 3.3 |
| | 1500 | 2.9 | 3.7 | 3.1 | 3.4 |
| | 3000 | 2.9 | 3.5 | 3.1 | 3.3 |
| BILIRUBIN (MG/DL) | 0 | 0.2 | 0.1 | 0.4 | 0.1 |
| | 150 | 0.3 | 0.1 | 0.4 | 0.1 |
| | 1500 | 0.3 | 0.1 | 0.1 | 0.4 |
| | 3000 | 0.3 | 0.1 | 0.1 | 0.2 |

*$p<0.05$ as compared to controls: Dunnett's t-test.

LITTON BIONETICS, INC.
PROJECT NO. 10734-08

TABLE B (CONTINUED)

MEAN HEMATOLOGICAL AND CLINICAL CHEMISTRY VALUES IN MALE DOGS

| | DIET CONCENTRATIONS (PPM) | INTERVAL (WEEKS) 0 | 4 | 8 | 13 |
|---|---|---|---|---|---|
| URIC ACID (MG/DL) | 0 | 0.4 | 0.4 | 0.4 | 0.6 |
| | 150 | 0.3 | 0.8 | 0.6 | 1.1 |
| | 1500 | 0.2 | 0.3 | 0.5 | 0.9 |
| | 3000 | 0.3 | 0.3 | 0.5 | 0.6 |
| CHOLESTEROL (MG/DL) | 0 | 182 | 164 | 176 | 156 |
| | 150 | 163 | 141 | 152 | 145 |
| | 1500 | 167 | 167 | 166 | 170 |
| | 3000 | 169 | 153 | 152 | 142 |
| PLASMA CHOLIN - ESTERASE (MU/ML) | 0 | 2359 | -- | -- | 2704[a] |
| | 150 | 2062 | 1862 | 2176 | 1888 |
| | 1500 | 1775 | 1571 | 1692 | 1687 |
| | 3000 | 2087 | 1750 | 1798 | 1839 |
| RBC CHOLIN - ESTERASE (MU/ML) | 0 | 685 | -- | -- | 2688[a] |
| | 150 | 798 | 2667 | 2688 | 2302 |
| | 1500 | 815 | 4804 | 3181 | 1982 |
| | 3000 | 523 | 4889 | 2709 | 3392 |

[a]Mean of 2 dogs.

[illegible] Labs, Inc.
PROJECT NO. 10734-08

TABLE C

MEAN HEMATOLOGICAL AND CLINICAL CHEMISTRY VALUES IN FEMALE DOGS

| | DIET CONCENTRATION (PPM) | INTERVAL (WEEKS) 0 | 4 | 8 | 13 |
|---|---|---|---|---|---|
| PCV (%) | 0 | 45 | 49 | 49 | 50 |
| | 150 | 46 | 48 | 48 | 46 |
| | 1500 | 48 | 50 | 50 | 49 |
| | 3000 | 45 | 49 | 49 | 48 |
| HGB (G %) | 0 | 15.2 | 17.2 | 17.8 | 16.9 |
| | 150 | 15.1 | 16.9 | 17.0 | 15.5 |
| | 1500 | 16.4 | 17.3 | 17.7 | 16.6 |
| | 3000 | 15.1 | 17.3 | 17.7 | 16.5 |
| RBC/ $MM^3 \times 10^6$ | 0 | 6.84 | 7.04 | 8.14 | 7.38 |
| | 150 | 6.58 | 6.84 | 7.87 | 7.02 |
| | 1500 | 7.09 | 6.90 | 8.05 | 7.43 |
| | 3000 | 6.84 | 7.07 | 8.10 | 7.32 |
| WBC/ $MM^3 \times 10^3$ | 0 | 5.7 | 9.8 | 11.7 | 9.8 |
| | 150 | 6.4 | 9.8 | 12.4 | 10.2 |
| | 1500 | 6.7 | 9.5 | 10.8 | 11.3 |
| | 3000 | 7.6 | 7.7 | 14.1 | 9.8 |
| CLOTTING TIME (SEC) | 0 | 338 | 465 | 413 | 458 |
| | 150 | 443 | 555 | 495 | 638 |
| | 1500 | 443 | 668 | 570 | 540 |
| | 3000 | 465 | 600 | 480 | 600 |
| GLUCOSE (MG/DL) | 0 | 108 | 109 | 92 | 88 |
| | 150 | 109 | 105 | 91 | 101 |
| | 1500 | 113 | 118 | 103 | 103 |
| | 3000 | 122 | 112 | 102 | 104 |
| BUN (MG/DL) | 0 | 11 | 13 | 15 | 13 |
| | 150 | 11 | 14 | 15 | 14 |
| | 1500 | 12 | 15 | 16 | 15 |
| | 3000 | 13 | 14 | 15 | 15 |
| SGOT (MIU/ML) | 0 | 36 | 37 | 39 | 42 |
| | 150 | 32 | 37 | 34 | 54 |
| | 1500 | 30 | 39 | 42 | 51 |
| | 3000 | 33 | 30 | 44 | 46 |

TABLE C (CONTINUED)

MEAN HEMATOLOGICAL AND CLINICAL CHEMISTRY VALUES IN FEMALE DOGS

| | DIET CONCENTRATION (PPM) | INTERVAL (WEEKS) 0 | 4 | 8 | 13 |
|---|---|---|---|---|---|
| SGPT (MIU/ML) | 0 | 27 | 31 | 34 | 35 |
| | 150 | 32 | 38 | 41 | 38 |
| | 1500 | 33 | 37 | 40 | 41 |
| | 3000 | 37 | 38 | 46 | 43 |
| ALK. PHOS. (MIU/ML) | 0 | 110 | 95 | 96 | 63 |
| | 150 | 107 | 92 | 96 | 69 |
| | 1500 | 99 | 81 | 74 | 60 |
| | 3000 | 103 | 73 | 76 | 50 |
| LDH (MIU/ML) | 0 | 269 | 83 | 175 | 232 |
| | 150 | 160 | 105 | 175 | 620 |
| | 1500 | 156 | 54 | 234 | 422 |
| | 3000 | 182 | 46 | 256 | 362 |
| CALCIUM (MG/DL) | 0 | 11.9 | 11.4 | 11.0 | 11.1 |
| | 150 | 11.8 | 11.5 | 10.8 | 11.1 |
| | 1500 | 11.8 | 11.7 | 11.1 | 11.4 |
| | 3000 | 11.6 | 11.3 | 10.6 | 10.9 |
| PHOSPHORUS (MG/DL) | 0 | 6.2 | 4.3 | 4.6 | 4.4 |
| | 150 | 6.5 | 4.5 | 4.8 | 4.5 |
| | 1500 | 6.1 | 4.7 | 4.5 | 4.5 |
| | 3000 | 6.2 | 4.5 | 4.5 | 4.6 |
| TOTAL PROTEIN (G/DL) | 0 | 6.1 | 6.2 | 6.7 | 6.4 |
| | 150 | 5.8 | 6.1 | 6.4 | 6.3 |
| | 1500 | 6.0 | 6.0 | 6.8 | 6.5 |
| | 3000 | 5.8 | 5.7 | 6.6 | 6.4 |
| ALBUMIN (G/DL) | 0 | 3.4 | 3.7 | 3.3 | 3.4 |
| | 150 | 3.1 | 3.7 | 3.2 | 3.4 |
| | 1500 | 3.1 | 3.7 | 3.3 | 3.1 |
| | 3000 | 2.9 | 3.5 | 3.2 | 3.3 |
| BILIRUBIN (MG/DL) | 0 | 0.4 | 0.1 | 0.4 | 0.1 |
| | 150 | 0.3 | 0.1 | 0.4 | 0.1 |
| | 1500 | 0.2 | 0.1 | 0.1 | 0.3 |
| | 3000 | 0.2 | 0.1 | 0.1 | 0.2 |

LITTON BIONETICS, INC.
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TABLE C (CONTINUED)

MEAN HEMATOLOGICAL AND CLINICAL CHEMISTRY VALUES IN FEMALE DOGS

| | DIET CONCENTRATION (PPM) | INTERVAL (WEEKS) 0 | 4 | 8 | 13 |
|---|---|---|---|---|---|
| URIC ACID (MG/DL) | 0 | 0.3 | 0.5 | 1.2 | 0.5 |
| | 150 | 0.2 | 0.5 | 0.5 | 0.8 |
| | 1500 | 0.3 | 0.7 | 0.4 | 0.6 |
| | 3000 | 0.2 | 0.3 | 0.4 | 0.5 |
| CHOLESTEROL (MG/DL) | 0 | 188 | 165 | 175 | 158 |
| | 150 | 177 | 180 | 191 | 215 |
| | 1500 | 176 | 162 | 173 | 186 |
| | 3000 | 174 | 151 | 166 | 173 |
| PLASMA CHOLIN-ESTERASE (MU/ML) | 0 | 2324 | -- | -- | 1779[a] |
| | 150 | 1820 | 1739 | 1890 | 1919 |
| | 1500 | 2296 | 2003 | 2257 | 2284 |
| | 3000 | 2016 | 1603 | 1846 | 1779 |
| RBC CHOLIN-ESTERASE (MU/ML) | 0 | 1075 | -- | -- | 2431[a] |
| | 150 | 865 | 3772 | 2919 | 2302 |
| | 1500 | 1018 | 4576 | 2478 | 2045 |
| | 3000 | 735 | 4016 | 2281 | 2045 |

[a]Mean of 2 dogs.

4. RESULTS (Continued)

For plasma, if one considers each group mean at Week 0 for the DIMP-dosed dogs as the index of enzyme activity (100%), there seemed to be a tendency toward slight inhibition in the 3000-ppm group (16-20% at Week 4, but only 8-14% at Week 13), while dogs of the other two groups showed at most only 13% inhibition at 4 weeks. Or, to take the 13-week values alone (with the two controls of each sex that were assayed as 100%), the males were inhibited to about the same extent (30-38%) in all three groups, while the females were not inhibited at all. For the RBC enzyme the situation is complicated by the invalid Week 0 values, but if the Week 4 mean of each group is used as the index, there appears to be as much as 45% inhibition for both sexes in the high-dose dogs. If the 13-week means are considered alone, with only two control dogs per sex as 100% activity, there was no clear dose-related effect.

All in all, it is believed that no valid effect on cholinesterase in these dogs was induced by DIMP ingestion.

Appendix Table 7 shows results of qualitative urinalyses. These data are unexceptional and indicate no compound-induced effects.

Absolute organ weights and relative organ weights (organ-to-body weight percentages) are given in Appendix Tables 8 and 9, respectively. Group means of organ weights and relative organ weights are collected in Text Table D. None of the mean values of the 3000-ppm group were statistically significantly different from control mean values. Only the mean relative ovary weight in the group that received 1500-ppm of DIMP in the diet was statistically significantly different from the control mean ($p<0.05$). The mean absolute ovary weight in this group was not statistically different from control value, however. Since the mean ovary weights, absolute and relative, of the other dose groups were not statistically significantly different from control figures, the difference noted for the 1500-ppm group is not believed to be meaningful.

The report of the histopathologist is appended. Most of the changes seen were such as are commonly encountered in dogs and the only one thought to be possibly associated with compound administration was the occurrence of cystic crypts of Lieberkühn in the small intestines of male dogs No. 395 and No. 397 (both in the 3000-ppm group). Such crypts are thought to be indicative of intestinal hypermotility, and review of daily observations shows these two dogs did have soft or watery feces one or more times per week during much of the study. However, control male No. 370 also had cystic crypts of Lieberkühn and soft feces during the study, and various other dogs had soft feces but no histological intestinal changes. The cystic crypt observations may therefore be regarded as suggestive at most.

TABLE I-G-50

LITTON BIONETICS, INC.
PROJECT NO. 10734-08

TABLE D

MEAN ORGAN WEIGHTS

MEAN ABSOLUTE ORGAN WEIGHTS (G)

| DOSE (PPM) | BODY WEIGHT (KG) | BRAIN | HEART | LIVER | SPLEEN | KIDNEYS | THYROIDS | ADRENALS | TESTES/ OVARIES |
|---|---|---|---|---|---|---|---|---|---|
| MALES | | | | | | | | | |
| 0 | 11.5 | 75.45 | 90.44 | 296.2 | 61.89 | 57.49 | 0.88 | 0.93 | 22.09 |
| 150 | 12.4 | 78.87 | 88.10 | 314.6 | 63.54 | 59.18 | 0.95 | 0.96 | 23.78 |
| 1500 | 11.9 | 80.40 | 86.79 | 314.6 | 63.49 | 60.06 | 1.00 | 1.05 | 22.59 |
| 3000 | 10.6 | 79.65 | 85.77 | 296.4 | 56.38 | 62.04 | 0.86 | 0.97 | 18.40 |
| FEMALES | | | | | | | | | |
| 0 | 10.5 | 73.32 | 81.58 | 262.4 | 58.06 | 50.14 | 0.84 | 0.97 | 0.73 |
| 150 | 10.1 | 75.19 | 74.88 | 283.8 | 50.06 | 50.39 | 0.89 | 1.03 | 1.04 |
| 1500 | 10.5 | 70.43 | 78.85 | 283.2 | 55.76 | 46.13 | 0.77 | 1.10 | 1.96 |
| 3000 | 10.1 | 73.58 | 74.69 | 276.0 | 69.12 | 45.29 | 0.83 | 0.88 | 1.46 |

TABLE I-G-50 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-08

TABLE D (CONTINUED)

MEAN ORGAN WEIGHTS

MEAN RELATIVE ORGAN WEIGHTS (G OR MG/100 G OF BODY WEIGHT)

| DOSE (PPM) | BRAIN | HEART | LIVER | SPLEEN | KIDNEYS | THYROIDS | ADRENALS | TESTES/ OVARIES |
|---|---|---|---|---|---|---|---|---|
| MALES | | | | | | | | |
| 0 | 0.657 | 0.783 | 2.575 | 0.549 | 0.492 | 7.77 | 8.18 | 0.192 |
| 150 | 0.643 | 0.713 | 2.560 | 0.511 | 0.480 | 7.71 | 7.80 | 0.193 |
| 1500 | 0.679 | 0.731 | 2.661 | 0.536 | 0.509 | 8.48 | 8.83 | 0.191 |
| 3000 | 0.733 | 0.785 | 2.721 | 0.517 | 0.570 | 8.06 | 8.79 | 0.168 |
| FEMALES | | | | | | | | |
| 0 | 0.713 | 0.786 | 2.514 | 0.549 | 0.485 | 8.08 | 9.36 | 7.12 |
| 150 | 0.752 | 0.743 | 2.829 | 0.496 | 0.505 | 8.75 | 10.24 | 9.96 |
| 1500 | 0.674 | 0.751 | 2.689 | 0.527 | 0.439 | 7.27 | 10.38 | 18.27* |
| 3000 | 0.744 | 0.746 | 2.776 | 0.692 | 0.449 | 8.34 | 8.86 | 14.58 |

*$p<0.05$ compared to controls: Student's t-test.

5. CONCLUSION

Based on the results presented it is concluded that no dose- or time-related toxic effects were produced in dogs given DIMP in the diet at concentrations of 150, 1500 and 3000 ppm daily for 90 days.

Submitted by:

Carter D. Johnston, Ph.D. — Date 7/6/78
Senior Toxicologist

Reviewed by:

Robert J. Weir, Ph.D. — Date 7/20/79
Vice President

# TABLE I-G-51

LITTON BIONETICS, INC.
PROJECT NO. 10734-08

TABLE 1

BODY WEIGHT (KG)

GROUP 1 - 0 PPM

| ANIMAL NO. | WEEK 1 | 2 | 3 | 4[a] | 5 | 6 | 7 | 8[a] | 9 | 10 | 11 | 12 | 13[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MALES | | | | | | | | | | | | | |
| 370 | 8.6 | 8.6 | 8.8 | 9.4 | 9.2 | 9.4 | 9.4 | 9.6 | 9.8 | 10.8 | 9.8 | 9.8 | 10.2 |
| 371 | 9.8 | 9.8 | 10.0 | 10.0 | 10.2 | 10.2 | 10.6 | 11.2 | 10.8 | 11.6 | 10.8 | 10.9 | 11.5 |
| 372 | 10.6 | 10.6 | 11.2 | 10.6 | 10.8 | 10.6 | 11.2 | 12.0 | 11.8 | 12.0 | 11.6 | 11.6 | 11.0 |
| 373 | 11.8 | 12.0 | 11.2 | 12.4 | 12.2 | 12.4 | 12.2 | 12.8 | 12.8 | 13.2 | 12.8 | 12.8 | 13.4 |
| MEAN | 10.2 | 10.1 | 10.3 | 10.6 | 10.6 | 10.7 | 10.9 | 11.4 | 11.3 | 11.9 | 11.3 | 11.3 | 11.5 |
| SD | 1.35 | 1.12 | 1.15 | 1.30 | 1.25 | 1.27 | 1.17 | 1.37 | 1.29 | 1.00 | 1.27 | 1.26 | 1.36 |
| SE | 0.67 | 0.56 | 0.57 | 0.65 | 0.63 | 0.63 | 0.59 | 0.68 | 0.65 | 0.50 | 0.63 | 0.63 | 0.68 |
| FEMALES | | | | | | | | | | | | | |
| 374 | 7.2 | 7.3 | 7.4 | 7.8 | 7.6 | 7.6 | 7.8 | 8.2 | 8.0 | 8.8 | 8.2 | 8.2 | 8.2 |
| 375 | 8.6 | 8.6 | 8.8 | 8.8 | 8.8 | 9.0 | 9.2 | 9.2 | 9.2 | 10.0 | 9.8 | 9.8 | 9.3 |
| 376 | 10.2 | 10.2 | 9.8 | 9.8 | 10.2 | 10.4 | 10.4 | 11.0 | 10.6 | 11.2 | 11.2 | 11.4 | 10.8 |
| 377 | 10.0 | 10.2 | 10.4 | 10.6 | 10.8 | 11.0 | - | 11.2 | 11.2 | 11.8 | 11.8 | 12.1 | 12.0 |
| MEAN | 9.0 | 9.1 | 9.1 | 9.3 | 9.4 | 9.5 | 9.1 | 9.9 | 9.8 | 10.5 | 10.3 | 10.4 | 10.1 |
| SD | 1.40 | 1.40 | 1.31 | 1.22 | 1.44 | 1.52 | 1.30 | 1.45 | 1.44 | 1.33 | 1.60 | 1.74 | 1.67 |
| SE | 0.70 | 0.70 | 0.66 | 0.61 | 0.72 | 0.76 | 0.75 | 0.72 | 0.72 | 0.67 | 0.80 | 0.87 | 0.83 |

[a]Fasted 1 night for bloods.

TABLE I-G-51 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-08

TABLE 1 (CONTINUED)

BODY WEIGHT (KG)

GROUP 2 - 150 PPM

| ANIMAL NO. | WEEK 1 | 2 | 3 | 4[a] | 5 | 6 | 7 | 8[a] | 9 | 10 | 11 | 12 | 13[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MALES | | | | | | | | | | | | | |
| 378 | 10.6 | 10.6 | 10.4 | 10.4 | 10.6 | 10.6 | 10.6 | 11.0 | 10.8 | 11.8 | 11.6 | 11.4 | 11.5 |
| 379 | 10.6 | 10.8 | 10.2 | 10.8 | 11.0 | 11.0 | 11.2 | 12.2 | 11.4 | 11.8 | 11.4 | 11.6 | 11.9 |
| 380 | 11.2 | 11.3 | 11.4 | 11.4 | 11.8 | 11.8 | 12.4 | 12.6 | 12.8 | 13.8 | 13.0 | 13.1 | 13.2 |
| 381 | 11.8 | 11.8 | 11.8 | 11.4 | 11.2 | 11.4 | 11.2 | 11.8 | 12.4 | 13.2 | 12.2 | 12.2 | 12.8 |
| MEAN | 11.1 | 11.1 | 11.0 | 11.0 | 11.2 | 11.2 | 11.4 | 11.9 | 11.9 | 12.7 | 12.1 | 12.1 | 12.4 |
| SD | 0.57 | 0.54 | 0.77 | 0.49 | 0.50 | 0.52 | 0.75 | 0.68 | 0.91 | 1.01 | 0.72 | 0.76 | 0.79 |
| SE | 0.29 | 0.27 | 0.39 | 0.24 | 0.25 | 0.26 | 0.38 | 0.34 | 0.46 | 0.51 | 0.36 | 0.38 | 0.39 |
| FEMALES | | | | | | | | | | | | | |
| 382 | 8.2 | 8.0 | 8.4 | 8.6 | 8.8 | 8.6 | 8.8 | 8.2 | 8.8 | 10.2 | 9.2 | 9.5 | 9.0 |
| 383 | 8.2 | 8.1 | 8.2 | 8.2 | 8.4 | 8.4 | 8.6 | 8.8 | 9.2 | 9.4 | 8.6 | 8.6 | 8.8 |
| 384 | 9.8 | 9.8 | 9.8 | 10.6 | 10.2 | 10.6 | 11.4 | 11.2 | 11.2 | 12.0 | 11.4 | 11.4 | 11.1 |
| 385 | 10.6 | 10.8 | 10.8 | 11.0 | 11.2 | 11.4 | 11.8 | 12.2 | 11.8 | 12.2 | 11.2 | 11.2 | 11.5 |
| MEAN | 9.2 | 9.2 | 9.3 | 9.6 | 9.7 | 9.8 | 10.2 | 10.1 | 10.3 | 11.0 | 10.1 | 10.2 | 10.1 |
| SD | 1.20 | 1.36 | 1.23 | 1.40 | 1.29 | 1.48 | 1.68 | 1.91 | 1.47 | 1.37 | 1.41 | 1.35 | 1.40 |
| SE | 0.60 | 0.68 | 0.61 | 0.70 | 0.64 | 0.74 | 0.84 | 0.95 | 0.74 | 0.68 | 0.70 | 0.68 | 0.70 |

[a]Fasted 1 night for bloods.

TABLE I-G-51 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-08

TABLE 1 (CONTINUED)

BODY WEIGHT (KG)

GROUP 3 - 1500 PPM

| ANIMAL NO. | WEEK 1 | 2 | 3 | 4[a] | 5 | 6 | 7 | 8[a] | 9 | 10 | 11 | 12 | 13[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MALES | | | | | | | | | | | | | |
| 386 | 9.6 | 10.6 | 10.2 | 8.4 | 10.4 | 10.6 | 11.6 | 10.2 | 10.8 | 11.8 | 11.2 | 11.3 | 11.0 |
| 387 | 10.4 | 10.3 | 10.4 | 10.6 | 10.6 | 11.2 | 11.4 | 11.2 | 11.6 | 11.8 | 11.6 | 11.7 | 11.6 |
| 388 | 11.2 | 11.2 | 11.4 | 11.8 | 11.6 | 11.8 | 11.8 | 12.4 | 12.2 | 12.8 | 12.8 | 13.0 | 12.5 |
| 389 | 11.6 | 11.8 | 11.6 | 11.8 | 12.2 | 12.2 | 11.8 | 12.2 | 11.6 | 12.8 | 12.2 | 12.1 | 12.3 |
| MEAN | 10.7 | 11.0 | 10.9 | 10.7 | 11.2 | 11.5 | 11.7 | 11.5 | 11.6 | 12.3 | 12.0 | 12.0 | 11.9 |
| SD | 0.89 | 0.67 | 0.70 | 1.60 | 0.85 | 0.70 | 0.19 | 1.01 | 0.57 | 0.58 | 0.70 | 0.73 | 0.69 |
| SE | 0.44 | 0.33 | 0.35 | 0.80 | 0.42 | 0.35 | 0.10 | 0.51 | 0.29 | 0.29 | 0.35 | 0.36 | 0.34 |
| FEMALES | | | | | | | | | | | | | |
| 390 | 8.4 | 8.2 | 8.6 | 8.8 | 9.0 | 9.2 | 9.2 | 9.6 | 9.8 | 10.2 | 10.2 | 10.2 | 10.2 |
| 391 | 8.4 | 8.6 | 8.8 | 9.0 | 9.4 | 9.2 | 9.0 | 9.8 | 9.4 | 10.0 | 10.0 | 10.1 | 9.6 |
| 392 | 8.6 | 8.8 | 8.6 | 9.0 | 9.2 | 9.6 | 9.8 | 10.2 | 10.2 | 10.8 | 10.2 | 10.4 | 10.2 |
| 393 | 10.2 | 10.3 | 10.8 | 10.8 | 10.8 | 10.8 | 11.4 | 11.4 | 11.4 | 12.2 | 11.6 | 11.7 | 12.1 |
| MEAN | 8.9 | 9.0 | 9.2 | 9.4 | 9.6 | 9.7 | 9.9 | 10.3 | 10.2 | 10.8 | 10.5 | 10.6 | 10.5 |
| SD | 0.87 | 0.92 | 1.07 | 0.94 | 0.82 | 0.76 | 1.09 | 0.81 | 0.86 | 0.99 | 0.74 | 0.74 | 1.09 |
| SE | 0.44 | 0.46 | 0.54 | 0.47 | 0.41 | 0.38 | 0.54 | 0.40 | 0.43 | 0.50 | 0.37 | 0.37 | 0.54 |

[a]Fasted 1 night for bloods.

# TABLE I-G-51 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-08

TABLE 1 (CONTINUED)

BODY WEIGHT (KG)

GROUP 4 - 3000 PPM

| ANIMAL NO. | WEEK 1 | 2 | 3 | 4[a] | 5 | 6 | 7 | 8[a] | 9 | 10 | 11 | 12 | 13[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MALES | | | | | | | | | | | | | |
| 394 | 9.8 | 10.1 | 9.6 | 10.2 | 9.8 | 10.2 | 10.2 | 10.4 | 10.6 | 11.2 | 10.6 | 10.9 | 10.9 |
| 395 | 9.2 | 9.3 | 9.4 | 9.6 | 9.8 | 9.6 | 9.8 | 9.8 | 10.2 | 10.4 | 9.8 | 10.0 | 9.4 |
| 396 | 11.0 | 11.1 | 11.2 | 11.0 | 11.2 | 11.2 | 11.2 | 11.4 | 11.6 | 12.4 | 11.6 | 11.6 | 11.2 |
| 397 | 11.2 | 11.2 | 11.8 | 12.0 | 11.8 | 11.8 | 12.2 | 12.2 | 12.2 | 13.2 | 12.8 | 12.8 | 12.3 |
| MEAN | 10.3 | 10.4 | 10.5 | 10.7 | 10.7 | 10.7 | 10.9 | 11.0 | 11.2 | 11.8 | 11.2 | 11.3 | 11.0 |
| SD | 0.96 | 0.90 | 1.18 | 1.04 | 1.01 | 0.99 | 1.10 | 1.06 | 0.91 | 1.24 | 1.30 | 1.18 | 1.20 |
| SE | 0.48 | 0.45 | 0.59 | 0.52 | 0.51 | 0.49 | 0.55 | 0.53 | 0.46 | 0.62 | 0.65 | 0.59 | 0.60 |
| FEMALES | | | | | | | | | | | | | |
| 398 | 7.0 | 7.2 | 7.4 | 7.6 | 7.8 | 7.8 | 8.2 | 8.2 | 8.2 | 9.2 | 8.2 | 8.3 | 8.6 |
| 399 | 8.8 | 8.8 | 8.8 | 8.8 | 8.6 | 8.8 | 9.2 | 9.4 | 9.2 | 9.4 | 9.8 | 9.8 | 9.2 |
| 400 | 9.8 | 9.7 | 9.8 | 10.2 | 10.2 | 10.2 | 10.4 | 8.8 | 10.4 | 11.6 | 11.2 | 11.2 | 11.1 |
| 401 | 10.6 | 10.8 | 10.8 | 11.0 | 10.8 | 11.0 | 11.2 | 11.4 | 11.0 | 11.8 | 11.6 | 11.6 | 11.3 |
| MEAN | 9.1 | 9.1 | 9.2 | 9.4 | 9.4 | 9.5 | 9.8 | 9.5 | 9.7 | 10.5 | 10.2 | 10.2 | 10.1 |
| SD | 1.55 | 1.52 | 1.45 | 1.51 | 1.39 | 1.43 | 1.32 | 1.39 | 1.25 | 1.39 | 1.54 | 1.50 | 1.35 |
| SE | 0.78 | 0.76 | 0.73 | 0.75 | 0.69 | 0.71 | 0.66 | 0.69 | 0.62 | 0.69 | 0.77 | 0.75 | 0.68 |

[a]Fasted 1 night for bloods.

# TABLE I-G-52

LITTON BIONETICS, INC.
PROJECT NO. 10734-08

TABLE 2

FOOD CONSUMPTION (KG)

GROUP 1 - 0 PPM

| ANIMAL NO. | WEEK 1 | 2 | 3[a] | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MALES | | | | | | | | | | | | | |
| 370 | 3.4 | 2.4 | - | 2.1 | 2.7 | 3.0 | 3.3 | 3.0 | 3.8 | 2.8 | 2.5 | 2.5 | 2.9 |
| 371 | 2.5 | 2.3 | - | 1.9 | 2.4 | 2.7 | 3.2 | 2.8 | 2.6 | 2.9 | 2.5 | 2.7 | 3.1 |
| 372 | 3.2 | S.F. | - | 2.8 | S.F. | 2.2 | 2.8 | 2.4 | 3.0 | 2.5 | 1.8 | 2.2 | 2.0 |
| 373 | 2.3 | 2.3 | - | 2.0 | 2.3 | 2.9 | 2.2 | 2.4 | 2.4 | 2.6 | 2.9 | 2.7 | 2.4 |
| MEAN | 2.9 | 2.3 | | 2.2 | 2.5 | 2.7 | 2.9 | 2.7 | 3.0 | 2.7 | 2.4 | 2.5 | 2.6 |
| SD | 0.53 | 0.06 | | 0.41 | 0.21 | 0.36 | 0.50 | 0.30 | 0.62 | 0.18 | 0.46 | 0.24 | 0.50 |
| SE | 0.27 | 0.03 | | 0.20 | 0.12 | 0.18 | 0.25 | 0.15 | 0.31 | 0.09 | 0.23 | 0.12 | 0.25 |
| FEMALES | | | | | | | | | | | | | |
| 374 | 1.8 | 2.0 | - | 1.6 | 1.9 | 2.1 | 2.0 | 2.7 | 2.0 | 2.1 | S.F. | 1.9 | 2.1 |
| 375 | 1.6 | 1.7 | - | 1.5 | S.F. | 2.3 | 2.1 | 2.1 | 2.4 | 2.4 | 1.8 | 2.4 | 1.9 |
| 376 | 2.2 | 2.1 | - | 1.6 | 1.6 | 2.6 | 2.4 | 2.5 | 2.7 | 2.5 | 2.5 | 2.3 | 2.4 |
| 377 | 1.8 | 1.2 | - | 2.0 | 2.3 | 3.0 | 2.4 | 2.4 | 2.3 | 2.2 | 2.4 | 2.4 | 2.3 |
| MEAN | 1.9 | 1.8 | | 1.7 | 1.9 | 2.5 | 2.2 | 2.4 | 2.4 | 2.3 | 2.2 | 2.3 | 2.2 |
| SD | 0.25 | 0.40 | | 0.22 | 0.35 | 0.39 | 0.21 | 0.25 | 0.29 | 0.18 | 0.38 | 0.24 | 0.22 |
| SE | 0.13 | 0.20 | | 0.11 | 0.20 | 0.20 | 0.10 | 0.13 | 0.14 | 0.09 | 0.22 | 0.12 | 0.11 |

[a]Not measured Week 3; see text.

## TABLE I-G-52 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-08

TABLE 2 (CONTINUED)

FOOD CONSUMPTION (KG)

GROUP 2 - 150 PPM

| ANIMAL NO. | WEEK 1 | 2 | 3[a] | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MALES | | | | | | | | | | | | | |
| 378 | 2.4 | - | - | S.F. | S.F. | 2.4 | 2.3 | 1.9 | 2.4 | 2.7 | 2.4 | 2.0 | 2.2 |
| 379 | S.F. | S.F. | - | S.F. | S.F. | 3.3 | 3.6 | 2.6 | 3.0 | 2.4 | 2.6 | 3.1 | S.F. |
| 380 | S.F. | S.F. | - | S.F. | S.F. | 3.4 | 4.1 | 3.9 | S.F. | 3.5 | 3.4 | S.F. | 3.9 |
| 381 | S.F. | S.F. | - | 1.7 | 2.0 | 2.3 | 2.5 | 2.5 | 2.9 | 2.5 | 2.2 | 2.6 | 2.7 |
| MEAN | | | | | | 2.9 | 3.1 | 2.7 | 2.8 | 2.8 | 2.7 | 2.5 | 2.9 |
| SD | | | | | | 0.58 | 0.87 | 0.84 | 0.32 | 0.50 | 0.53 | 0.57 | 0.87 |
| SE | | | | | | 0.29 | 0.43 | 0.42 | 0.19 | 0.25 | 0.26 | 0.33 | 0.50 |
| FEMALES | | | | | | | | | | | | | |
| 382 | 2.0 | 2.1 | - | 1.6 | 2.1 | [illegible] | 2.3 | 1.9 | 2.5 | 2.4 | 2.1 | 2.2 | 2.7 |
| 383 | 1.5 | 1.4 | - | 1.1 | 1.[illegible] | | 1.4 | 1.5 | 2.0 | 1.8 | 1.6 | 1.7 | 2.2 |
| 384 | S.F. | 2.2 | - | 1.9 | S | | S.F. | 2.3 | 2.7 | 2.8 | 2.4 | 2.6 | 2.4 |
| 385 | 2.2 | 2.4 | - | 2.0 | 2 | | 2.5 | 2.6 | 2.6 | 1.9 | 2.1 | 2.3 | 1.9 |
| MEAN | 1.9 | 2.0 | | 1.7 | 2.. | [illegible] | 2.1 | 2.1 | 2.5 | 2.2 | 2.1 | 2.2 | 2.3 |
| SD | 0.51 | 0.75 | | 0.70 | 0.85 | [illegible] | 0.59 | 0.48 | 0.31 | 0.46 | 0.33 | 0.37 | 0.34 |
| SE | 0.29 | 0.38 | | 0.35 | 0.49 | [illegible] | 0.34 | 0.24 | 0.16 | 0.23 | 0.17 | 0.19 | 0.17 |

[a]Not measured Week 3: see text.

## TABLE I-G-52 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-08

TABLE 2 (CONTINUED)

FOOD CONSUMPTION (KG)

GROUP 3 - 1500 PPM

| ANIMAL NO. | WEEK 1 | 2 | 3[a] | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MALES | | | | | | | | | | | | | |
| 386 | 2.7 | 2.7 | - | 2.6 | S.F. | 2.2 | 2.2 | 1.6 | 2.1 | 2.5 | 2.1 | 2.1 | 2.2 |
| 387 | 2.4 | 2.3 | - | 1.9 | S.F. | 1.9 | 2.1 | 2.3 | 2.6 | 2.3 | 2.5 | 2.0 | 2.1 |
| 388 | S.F. | 1.9 | - | 1.8 | S.F. | 2.5 | 1.8 | 2.3 | 2.4 | 2.1 | 2.2 | 2.4 | 2.5 |
| 389 | 2.5 | 2.4 | - | 1.7 | 2.2 | 2.2 | 1.7 | 1.4 | 2.0 | 2.1 | 2.2 | 2.3 | 2.1 |
| MEAN | 2.5 | 2.3 | - | 2.0 | - | 2.2 | 2.0 | 1.9 | 2.3 | 2.3 | 2.3 | 2.2 | 2.2 |
| SD | 0.15 | 0.33 | - | 0.41 | - | 0.24 | 0.24 | 0.47 | 0.28 | 0.19 | 0.17 | 0.18 | 0.19 |
| SE | 0.09 | 0.17 | - | 0.20 | - | 0.12 | 0.12 | 0.23 | 0.14 | 0.10 | 0.09 | 0.09 | 0.09 |
| FEMALES | | | | | | | | | | | | | |
| 390 | 1.9 | 1.5 | - | 2.0 | 2.2 | [illegible] | 2.0 | 1.9 | 2.7 | 2.4 | 2.5 | 2.5 | [illegible] |
| 391 | S.F. | 1.8 | - | 1.7 | 2.0 | [illegible] | 1.9 | 1.8 | 2.2 | 2.1 | 1.9 | 2.1 | 1.9 |
| 392 | 3.1 | S.F. | - | S.F. | S.F. | [illegible] | 2.3 | 2.1 | 2.4 | 2.3 | 3.2 | 2.4 | 2.2 |
| 393 | S.F. | 2.0 | - | 1.7 | 2.1 | [illegible] | 2.4 | 2.0 | 2.2 | 2.0 | 2.1 | 2.6 | 1.9 |
| MEAN | 2.5 | 1.8 | - | 1.8 | 2.1 | 2.2 | 2.2 | 2.0 | 2.4 | 2.2 | 2.4 | 2.4 | 2.1 |
| SD | 0.85 | 0.25 | - | 0.17 | 0.10 | 0.26 | 0.24 | 0.13 | 0.24 | 0.18 | 0.57 | 0.22 | 0.29 |
| SE | 0.60 | 0.15 | - | 0.10 | 0.06 | 0.13 | 0.12 | 0.06 | 0.12 | 0.09 | 0.29 | 0.11 | 0.14 |

[a]Not measured Week 3: see text.

## TABLE I-G-52 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-08

TABLE 2 (CONTINUED)

FOOD CONSUMPTION (KG)

GROUP 4 - 3000 PPM

| ANIMAL NO. | WEEK 1 | 2 | 3[a] | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MALES | | | | | | | | | | | | | |
| 394 | 2.2 | - | - | 2.0 | 2.4 | 2.4 | 2.4 | 2.4 | 2.7 | 2.2 | 2.6 | S.F. | 2.0 |
| 395 | 1.6 | 1.6 | - | 1.4 | 1.8 | 1.7 | 1.9 | 1.6 | 1.7 | 1.7 | 1.5 | 1.9 | 2.2 |
| 396 | 2.7 | 2.2 | - | S.F. | S.F. | 2.2 | 2.3 | 2.2 | 2.6 | 2.5 | S.F. | 2.4 | 2.2 |
| 397 | 1.8 | 2.2 | - | 2.3 | 2.4 | 2.4 | 2.1 | 2.0 | 2.6 | 3.1 | 2.5 | 2.8 | S.F. |
| MEAN | 2.1 | 2.0 | - | 1.9 | 2.2 | 2.2 | 2.2 | 2.1 | 2.4 | 2.4 | 2.2 | 2.4 | 2.1 |
| SD | 0.49 | 0.35 | - | 0.46 | 0.35 | 0.33 | 0.22 | 0.34 | 0.47 | 0.59 | 0.61 | 0.45 | 0.12 |
| SE | 0.24 | 0.20 | - | 0.26 | 0.20 | 0.17 | 0.11 | 0.17 | 0.23 | 0.29 | 0.35 | 0.26 | 0.07 |
| FEMALES | | | | | | | | | | | | | |
| 398 | 1.4 | 1.9 | - | 1.6 | 2.1 | 2.1 | 2.1 | 1.9 | 1.8 | 2.2 | 2.1 | 2.4 | 2.0 |
| 399 | 1.5 | 2.3 | - | 1.3 | 1.4 | 1.9 | 1.8 | 1.8 | 1.6 | 2.1 | 1.7 | 2.1 | 2.0 |
| 400 | 2.1 | 1.9 | - | 1.8 | 1.9 | 2.3 | 1.7 | 2.2 | 2.3 | 2.2 | 2.7 | 2.9 | 2.2 |
| 401 | 3.1 | 2.4 | - | 2.2 | 2.6 | 2.5 | 2.7 | 1.8 | 2.7 | 2.2 | 2.5 | 2.7 | 2.1 |
| MEAN. | 2.0 | 2.1 | - | 1.7 | 2.0 | 2.2 | 2.1 | 1.9 | 2.1 | 2.2 | 2.3 | 2.5 | 2.1 |
| SD | 0.78 | 0.26 | - | 0.38 | 0.50 | 0.26 | 0.45 | 0.19 | 0.50 | 0.05 | 0.44 | 0.35 | 0.10 |
| SE | 0.39 | 0.13 | - | 0.19 | 0.25 | 0.13 | 0.23 | 0.09 | 0.25 | 0.03 | 0.22 | 0.18 | 0.05 |

[a]Not measured Week 3: see text.

THREE MONTH TOXICITY STUDY IN DOGS

LBI PROJECT NO. 10730-08

HISTOPATHOLOGIC SUMMARY

A summary of the significant histologic observations in this group of eight high-dose and eight control dogs is appended.

The cystic crypts of Lieberkuhn noted in #395 (3000 ppm) and #397 (3000 ppm) may have been related to oral dosing with this compound. Such changes were not noted in the controls. Cystic crypts are considered to be an indication of intestinal hypermotility, which may have been manifested clinically as diarrhea prior to death. Cystic crypts are a result of diarrhea, not the cause of diarrhea. The cysts were filled with cell debris and none had progressed to the "crypt abscess" stage, therefore the lesion was considered to be mild and of short duration.

The observed hypospermatogenesis was more pronounced in #397 (3000 ppm) than in #373 (0 ppm), but the changes were rather mild in both dogs. Lack of spermatogenesis in a few seminiferous tubules is commonly observed in dogs and is not considered to be particularly significant. Examination of a very large number of dogs would be required to determine whether there was a significant increase in the incidence or severity of this change in dosed dogs. Results from the present group of sixteen dogs do not suggest such an effect.

The remaining lesions are relatively common incidental findings or spontaneous diseases of dogs. The most significant of these was the nonsuppurative thyroiditis noted in #400 (3000 ppm). The lesion was very pronounced in one thyroid lobe and milder in the other lobe. There were multiple nodular aggregations of lymphocytes among the moderate diffuse infiltration of lymphocytes and plasma cells. A few thyroid follicles were compromised by the disease process. This spontaneous lesion occurs primarily in beagles and is presently considered to be an immune-mediated disease.

The focal ulcerative dermatitis in #401 (3000 ppm) probably resulted from minor trauma sustained in the kennel or during handling. An etiologic agent was not observed in the H&E stained sections; contamination by multiple bacterial species is suspected.

Cystic Rathke's pouch remnants in the pituitary and cystic ultimobranchial remnants in the parathyroid/thyroid are common incidental findings in dogs. Such small cysts as were observed in these animals are not considered to be of pathologic significance.

Chronic inflammation of the interstitium of the kidney is commonly seen in dogs and often becomes clinically significant in older dogs. The etiology is speculative. The mild changes seen in the kidney of #374 (0 ppm) were considered to be an early manifestation of that disease process.

Cystic glandular hyperplasia of the prostate is nearly ubiquitous in old dogs. The changes noted in the prostate of #396 (3000 ppm) were very mild.

Phagocytosis of erythrocytes by cells of the fixed reticuloendothelial system in the lymph nodes is commonly observed in dogs. The phagocytized erythrocytes in the lymph nodes of #394 (3000 ppm) and #371 (0 ppm) were well preserved and there was no accumulation of hemosiderin. The peracute erythrophagocytosis observed in these two dogs was considered to be an insignificant agonal event.

The genesis of the intra-alveolar hyaline bodies such as were noted in #399 (3000 ppm) is not known. Very large accumulations of such material cause little or no signs of respiratory distress, therefore the minimal accumulation in #399 was considered to be an incidental finding of no pathologic significance.

A number of very minor histologic observations are recorded on the histopathologic records.

In summary, the only histologic change which could reasonably be related to the dosing was the occurrance of cystic crypts in the small intestine. This findings suggests a very mild gastrointestinal disturbance, which may have been clinically manifested as diarrhea. The lesions were very mild and would be expected to resolve within 4-7 days following the termination of the gastrointestinal disturbance.

3 March 1978
Date

George A. Parker
George A. Parker, D.V.M.
Veterinary Pathologist

THREE MONTH TOXICITY STUDY IN DOGS

LBI PROJECT NO. 10734-08

SUMMARY OF SIGNIFICANT HISTOLOGIC FINDINGS

A. Thyroid - nonsuppurative thyroiditis, #400 (3000 ppm).

B. Small intestine - cystic crypts, #395 (3000 ppm) and #397 (3000 ppm).

C. Skin - focal ulcerative dermatitis, #401 (3000 ppm).

D. Parathyroid/thyroid - cystic ultimobranchial remnants, #372 (0 ppm), #395 (3000 ppm) and #397 (3000 ppm).

E. Kidneys - mild nonsuppurative pyelitis - #374 (0 ppm).

F. Mesenteric lymph node - erythrophagocytosis, #394 (3000 ppm) and #371 (0 ppm).

G. Prostate - mild cystic glandular hyperplasia, #396 (3000 ppm).

H. Pituitary - cystic Rathke's pouch remnant, #394 (3000 ppm) and #371 (0 ppm).

I. Testis - hypospermatogenesis, #397 (3000 ppm) and #373 (0 ppm).

J. Lungs - intra-alveolar hyaline bodies - #399 (3000 ppm).

LITTON BIONETICS, INC.

PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 370 | PROJECT NUMBER: | 10734 |
| DOSAGE: | 0 ppm | PM NUMBER: | 77/11148 |
| DATE OF DEATH: | 12/5/77 | | |
| DEATH: | Terminal kill | GROUP NUMBER: | 1 |
| METHOD OF KILL: | OD Somlethol | SEX: | Male |
| MORIBUND KILL: | | WEEK OF STUDY: | |

GROSS FINDINGS:
No gross lesion recognized.

MICROSCOPIC FINDINGS:
Mesenteric lymph node - active appearing node.
Small intestine - cystic crypt, duodenum.

23 Feb 1978
Date

George A. Parker per
George A. Parker, D.V.M.
Veterinary Pathologist

LITTON BIONETICS, INC.
PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 371 | PROJECT NUMBER: | 10734-08 |
| DOSAGE: | 0 ppm | PM NUMBER: | 77/11156 |
| DATE OF DEATH: | 12/6/77 | | |
| DEATH: | Terminal kill | GROUP NUMBER: | 1 |
| METHOD OF KILL: | OD Somlethal | SEX: | Male |
| MORIBUND KILL: | | WEEK OF STUDY: | |

GROSS FINDINGS:
No gross lesions recognized.

MICROSCOPIC FINDINGS:
Thyroid/parathyroid - C-cell hyperplasia, mild.
Spleen - inactive lymphoid component.
Lung - mild multifocal nonsuppurative perivasculitis.
Adrenal - cytoplasmic vacuolization, zona glomerulosa.
Mesenteric lymph node - erythrophagocytosis, active appearing node.
Prostate - minimal cystic dilatation of glands; mild epithelial vacuolization.
Pituitary - cystic Rathke's pouch remnant.
Brain - focal capillary ectasia.
Comment - all lesions considered to be incidental findings.

23 Feb 1978
Date

George A. Parker DVM
George A. Parker, D.V.M.
Veterinary Pathologist

LITTON BIONETICS, INC.
PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 372 | PROJECT NUMBER: | 10734 |
| DOSAGE: | 0 ppm | PM NUMBER: | 77/11164 |
| DATE OF DEATH: | 12/7/77 | | |
| DEATH: | Terminal kill | GROUP NUMBER: | 1. |
| METHOD OF KILL: | OD Somlethol | SEX: | Male |
| MORIBUND KILL: | | WEEK OF STUDY: | |

GROSS FINDINGS:
No gross lesion recognized.

MICROSCOPIC FINDINGS:
Thyroid/parathyroid - abundant C-cells; cystic ultimobranchial remnant, parathyroid.
Kidneys - microlithiasis, papilla.
Prostate - minimal cystic dilatation.
Brain - minimal focal neuronal swelling and degeneration, probably presection artefact.

23 Feb 1978
Date

George A. Parker
George A. Parker, D.V.M.
Veterinary Pathologist

LITTON BIONETICS, INC.

PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 373 | PROJECT NUMBER: | 10734 |
| DOSAGE: | 0 ppm | PM NUMBER: | 77/11172 |
| DATE OF DEATH: | 12/8/77 | | |
| DEATH: | Terminal kill | GROUP NUMBER: | 1 |
| METHOD OF KILL: | OD Somlethol | SEX: | Male |
| MORIBUND KILL: | | WEEK OF STUDY: | |

GROSS FINDINGS:

No gross lesion recognized.

MICROSCOPIC FINDINGS:

Kidneys - microlithiasis, papilla.
Small intestine - focal mineralization, mucosa.
Testis - minimal giant cell degeneration and focal hypospermatogenesis.
Muscle - minimal focal chronic myositis.
Brain - occasional swollen axon, medulla oblongata.

23 Feb 1978
Date

George A. Parker per
George A. Parker, D.V.M.
Veterinary Pathologist

LITTON BIONETICS, INC.
PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 374 | PROJECT NUMBER: | 10734 |
| DOSAGE: | 0 ppm | PM NUMBER: | 77/11149 |
| DATE OF DEATH: | 12/5/77 | | |
| DEATH: | Terminal kill | GROUP NUMBER: | 1 |
| METHOD OF KILL: | OD Somlethol | SEX: | Female |
| MORIBUND KILL: | | WEEK OF STUDY: | |

GROSS FINDINGS:
No gross lesions recognized.

MICROSCOPIC FINDINGS:
Thyroid/parathyroid - mild C-cell hyperplasia.
Spleen - inactive lymphoid component.
Kidneys - mild nonsuppurative pyelitis.
Comment - all changes are common incidental findings.

23 Feb 1978
Date

George A. Parker DVM
George A. Parker, D.V.M.
Veterinary Pathologist

LITTON BIONETICS, INC.
PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 375 | PROJECT NUMBER: | 10734 |
| DOSAGE: | 0 ppm | PM NUMBER: | 77/11157 |
| DATE OF DEATH: | 12/6/77 | | |
| DEATH: | Terminal kill | GROUP NUMBER: | 1 |
| METHOD OF KILL: | OD Somlethol | SEX: | Female |
| MORIBUND KILL: | | WEEK OF STUDY: | |

GROSS FINDINGS:
No gross lesion recognized.

MICROSCOPIC FINDINGS:
No lesion recognized.

23 Feb 1978
Date

George A. Parker
George A. Parker, D.V.M.
Veterinary Pathologist

LITTON BIONETICS, INC.
PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 376 | PROJECT NUMBER: | 10734 |
| DOSAGE: | 0 ppm | PM NUMBER: | 77/11165 |
| DATE OF DEATH: | 12/7/77 | | |
| DEATH: | Terminal kill | GROUP NUMBER: | 1 |
| METHOD OF KILL: | OD Somlethol | SEX: | Female |
| MORIBUND KILL: | | WEEK OF STUDY: | |

GROSS FINDINGS:
No gross lesion recognized.

MICROSCOPIC FINDINGS:
Kidneys - microlithiasis, papilla.

23 Feb 1978
Date

George A. Parker DVM
George A. Parker, D.V.M.
Veterinary Pathologist

LITTON BIONETICS, INC.
PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 377 | PROJECT NUMBER: | 10734 |
| DOSAGE: | 0 ppm | PM NUMBER: | 77/11173 |
| DATE OF DEATH: | 12/8/77 | | |
| DEATH: | Terminal kill | GROUP NUMBER: | 1 |
| METHOD OF KILL: | OD Somlethol | SEX: | Female |
| MORIBUND KILL: | | WEEK OF STUDY: | |

GROSS FINDINGS:
No gross lesion recognized.

MICROSCOPIC FINDINGS:
Thyroid/parathyroid - abundant C-cells.
Kidneys - microlithiasis, pelvis.
Urinary bladder - perivascular hyaline material, serosa; congestion.

23 Feb 1978
Date

George A. Parker per
George A. Parker, D.V.M.
Veterinary Pathologist

LITTON BIONETICS, INC.
PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 394 | PROJECT NUMBER: | 10734 |
| DOSAGE: | 3000 ppm | PM NUMBER: | 77/11154 |
| DATE OF DEATH: | 12/5/77 | | |
| DEATH: | Terminal kill | GROUP NUMBER: | 4 |
| METHOD OF KILL: | OD Somlethol | SEX: | Male |
| MORIBUND KILL: | | WEEK OF STUDY: | |

GROSS FINDINGS:
No gross lesion recognized.

MICROSCOPIC FINDINGS:
Spleen - very mild lymphoid depletion.
Lungs - substantial number of circulating neutrophils.
Liver - minimal vacuolar change.
Adrenal - vacuolization of zona glomerulosa cells.
Mesenteric lymph node - erythrophagocytosis.
Prostate - perinuclear vacuoles in a moderate number of prostatic epithelial cells.
Pituitary - cystic Rathke's pouch remnant.

23 Feb 1978
Date

George A. Parker, D.V.M.
Veterinary Pathologist

LITTON BIONETICS, INC.
PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 395 | PROJECT NUMBER: | 10734 |
| DOSAGE: | 3000 ppm | PM NUMBER: | 77/11162 |
| DATE OF DEATH: | 12/6/77 | | |
| DEATH: | Terminal kill | GROUP NUMBER: | 4 |
| METHOD OF KILL: | OD Somlethol | SEX: | Male |
| MORIBUND KILL: | | WEEK OF STUDY: | |

GROSS FINDINGS:
No gross lesion recognized.

MICROSCOPIC FINDINGS:
Thyroid/parathyroid - cystic ultimobranchial remnant, thyroid.
Kidneys - mild multifocal mineralization, papilla.
Adrenal - vacuolization of zona glomerulosa.
Small intestine - cystic crypts.
Colon - mild multifocal mucosal congestion.
Pituitary - pronounced aggregation of pars intermedia cells. No expansion.

23 Feb 1978
Date

George A. Parker, D.V.M.
Veterinary Pathologist

LITTON BIONETICS, INC.
PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 396 | PROJECT NUMBER: | 10734 |
| DOSAGE: | 3000 ppm | PM NUMBER: | 77/11170 |
| DATE OF DEATH: | 12/7/77 | | |
| DEATH: | Terminal kill | GROUP NUMBER: | 4 |
| METHOD OF KILL: | OD Somlethol | SEX: | Male |
| MORIBUND KILL: | | WEEK OF STUDY: | |

GROSS FINDINGS:
Heart - small (3mm) hard white nodule in aorta beneath one cusp of semilunar valve.
Kidneys - rim of cortex dark brown.

MICROSCOPIC FINDINGS:
Lungs - minimal multifocal perivasculitis; pleuritis; interstitial pneumonia.
Kidneys - mild mineralization, papilla.
Prostate - mild cystic glandular hyperplasia.
Heart - no lesion recognized.

23 Feb 1978
Date

George A. Parker, D.V.M.
Veterinary Pathologist

LITTON BIONETICS, INC.
PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 397 | PROJECT NUMBER: | 10734 |
| DOSAGE: | 3000 ppm | PM NUMBER: | 77/11178 |
| DATE OF DEATH: | 12/8/77 | | |
| DEATH: | Terminal kill | GROUP NUMBER: | 4 |
| METHOD OF KILL: | OD Somlethol | SEX: | Male |
| MORIBUND KILL: | | WEEK OF STUDY: | |

GROSS FINDINGS:
No gross lesion recognized.

MICROSCOPIC FINDINGS:
Thyroid/parathyroid - cystic ultimobranchial remnants, parathyroid.
Liver - minimal vacuolar change.
Kidneys - microlithiasis, papilla. Several small (immature) glomeruli.
Small intestine - multifocal cystic crypts, mild.
Testis - mild multifocal hypospermatogenesis.
Urinary bladder - perivascular hyalinosis, serosa.

23 Feb 1978
Date

George A. Parker
George A. Parker, D.V.M.
Veterinary Pathologist

LITTON BIONETICS, INC.
PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 398 | PROJECT NUMBER: | 10734 |
| DOSAGE: | 3000 ppm | PM NUMBER: | 77/11155 |
| DATE OF DEATH: | 12/5/77 | | |
| DEATH: | Termina' kill | GROUP NUMBER: | 4 |
| METHOD OF KILL: | OD Somlethol | SEX: | Female |
| MORIBUND KILL: | | WEEK OF STUDY: | |

GROSS FINDINGS:
No gross lesion recognized.

MICROSCOPIC FINDINGS:
Kidneys - mild mineralization, papilla.
Adrenal - mild vacuolization of zona glomerulosa cells.

23 Feb 1978
Date

George A. Parker, DVM
George A. Parker, D.V.M.
Veterinary Pathologist

LITTON BIONETICS, INC.
PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 399 | PROJECT NUMBER: | 10734 |
| DOSAGE: | 3000 ppm | PM NUMBER: | 77/11163 |
| DATE OF DEATH: | 12/6/77 | | |
| DEATH: | Terminal kill | GROUP NUMBER: | 4 |
| METHOD OF KILL: | OD Somlethol | SEX: | Female |
| MORIBUND KILL: | | WEEK OF STUDY: | |

GROSS FINDINGS:
No gross lesion recognized.

MICROSCOPIC FINDINGS:
Ovary - several large corpora lutea.
Lungs - focal alveolar proteinosis; intra-alveolar hyaline bodies.
Kidneys - microlithiasis, papilla.
Uterus - secretory; no lesion recognized.
Urinary bladder - perivascular hyalinosis, serosa.
Mammary gland - active, not secretory, no lesion recognized.

23 Feb 1978
Date

George A. Parker DVM
George A. Parker, D.V.M.
Veterinary Pathologist

LITTON BIONETICS, INC.
PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 400 | PROJECT NUMBER: | 10734 |
| DOSAGE: | 3000 ppm | PM NUMBER: | 77/11171 |
| DATE OF DEATH: | 12/7/77 | | |
| DEATH: | Terminal kill | GROUP NUMBER: | 4 |
| METHOD OF KILL: | OD Somlethol | SEX: | Female |
| MORIBUND KILL: | | WEEK OF STUDY: | |

GROSS FINDINGS:
No gross lesion recognized.

MICROSCOPIC FINDINGS:
Thyroid/parathyroid - moderate nonsuppurative thyroiditis.
Ovary - has several large corpora lutea.
Lung - mineralith.
Liver - mottled due to glycogen in centrilobular areas.
Gallbladder - segments of epithelial cells have clear cytoplasm.
Kidneys - microliths, papilla; minimal multifocal glomerulosclerosis.
Uterus - secretory; no lesion recognized.
Urinary bladder - perivascular hyaline material, serosa.
Mammary gland - active, but not secretory.

23 Feb 1978
Date

George A. Parker DVM
George A. Parker, D.V.M.
Veterinary Pathologist

LITTON BIONETICS, INC.
PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 401 | PROJECT NUMBER: | 10734 |
| DOSAGE: | 3000 ppm | PM NUMBER: | 77/11179 |
| DATE OF DEATH: | 12/8/77 | | |
| DEATH: | Terminal kill | GROUP NUMBER: | 4 |
| METHOD OF KILL: | OD Somlethol | SEX: | Female |
| MORIBUND KILL: | | WEEK OF STUDY: | |

GROSS FINDINGS:
Skin - two small (8mm) denuded areas in skin of left carpal and metacarpal areas.
Kidneys - very slight dark brownish coloration at periphery of cortex.

MICROSCOPIC FINDINGS:
Kidneys - minimal microlithiasis, papilla. Minimal focal nonsuppurative nephritis.
Skin - focal ulcerative dermatitis with scab formation. No obvious etiologic agent.

23 Feb 1978
Date

George A. Parker dvm
George A. Parker, D.V.M.
Veterinary Pathologist

THREE MONTH TOXICITY STUDY IN DOGS

LBI PROJECT NO. 10734-08

LEGEND FOR TABLE OF HISTOLOGIC FINDINGS

+ = Positive finding (ungraded lesion) encountered in a designated tissue or organ.

- = Negative finding in a designated tissue or organ; tissue examined.

1 = Positive finding graded "minimal".

2 = Positive finding graded "mild".

3 = Positive finding graded "moderate".

# TABLE I-G-53

THREE-MONTH TOXICITY STUDY IN DOGS

LBI PROJECT NO. 10734-08

TABLE OF HISTOLOGIC FINDINGS

| GROUP NUMBER | #1 | | | | #1 | | | | #4 | | | | #4 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SEX | Males | | | | Females | | | | Males | | | | Females | | | |
| ANIMAL NUMBER | 370 | 371 | 372 | 373 | 374 | 375 | 376 | 377 | 394 | 395 | 396 | 397 | 398 | 399 | 400 | 401 |
| SPINAL CORD | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| THYROID/PARATHYROID | - | | | - | | - | - | | - | | - | | - | - | | - |
| C-cell hyperplasia | | 2 | | | 2 | | | | | | | | | | | |
| Abundant C-cells | | | + | | | | | + | | | | | | | | |
| Cystic ultimobranchial remnant | | | + | | | | | | | + | | + | | | | |
| Non-suppurative thyroiditis | | | | | | | | | | | | | | | 3 | |
| SCIATIC NERVE | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| SPLEEN | - | | - | - | | - | - | - | | - | - | - | - | - | - | - |
| Inactive lymphoid component | | + | | | + | | | | | | | | | | | |
| Lymphoid depletion | | | | | | | | | 2 | | | | | | | |
| PANCREAS | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| LUNG | - | | - | - | - | - | - | - | | - | | - | - | | | - |
| Intraalveolar hyaline bodies | | | | | | | | | | | | | | + | | |
| Mineralith | | | | | | | | | | | | | | | + | |
| Multifocal non-suppurative perivasculitis | | 2 | | | | | | | | | | | | | | |
| Substantial number of circulating neutrophils | | | | | | | | | + | | | | | | | |
| Multifocal perivasculitis | | | | | | | | | | | 1 | | | | | |
| Interstitial pneumonia | | | | | | | | | | | + | | | | | |
| Pleuritis | | | | | | | | | | | + | | | | | |
| HEART | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| LIVER | - | - | - | - | - | - | - | - | | - | - | | - | - | | - |
| Vacuolar change | | | | | | | | | 1 | | | 1 | | | | |
| Glycogen in centrilobular areas | | | | | | | | | | | | | | | + | |

# TABLE I-G-53 (Continued)

THREE-MONTH TOXICITY STUDY IN DOGS

LBI PROJECT NO. 10734-08

TABLE OF HISTOLOGIC FINDINGS

| GROUP NUMBER | #1 Males | | | | #1 Females | | | | #4 Males | | | | #4 Females | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SEX / ANIMAL NUMBER | 370 | 371 | 372 | 373 | 374 | 375 | 376 | 377 | 394 | 395 | 396 | 397 | 398 | 399 | 400 | 401 |
| GALLBLADDER | - | - | - | - | - | - | - | - | - | - | - | - | - | - | | - |
| Clear cytoplasm, epithelial cells | | | | | | | | | | | | | | | + | |
| KIDNEY | - | - | | | | - | | | - | | | | | | | |
| Bicrolithiasis | | | + | + | | | + | + | | | | + | | + | + | 1 |
| Non-suppurative pyelitis | | | | | 2 | | | | | | | | | | | |
| Multifocal mineralization - papilla | | | | | | | | | | 2 | 2 | | 2 | | | |
| Multifocal glomerulosclerosis | | | | | | | | | | | | | | | 1 | |
| Non-suppurative nephritis | | | | | | | | | | | | | | | | 1 |
| ADRENAL | - | | - | - | - | - | - | - | | | - | - | | - | - | - |
| Vacuolization | | + | | | | | | | + | + | | | 2 | | | |
| STOMACH | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| MESENTERIC LYMPH NODE | | | - | - | - | - | - | - | | - | - | - | - | - | - | - |
| Active-appearing node | + | + | | | | | | | | | | | | | | |
| Erythrophagocytosis | | + | | | | | | | + | | | | | | | |
| SMALL INTESTINE | | - | - | | - | - | - | - | - | | - | | - | - | - | - |
| Cystic crypt | + | | | | | | | | | + | | 2 | | | | |
| Focal mineralization, mucosa | | | | + | | | | | | | | | | | | |
| COLON | - | - | - | - | - | - | - | - | - | | - | - | - | - | - | - |
| Multifocal mucosal congestion | | | | | | | | | | 2 | | | | | | |
| CECUM | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |

# TABLE I-G-53 (Continued)

THREE-MONTH TOXICITY STUDY IN DOGS

LBI PROJECT NO. 10734-08

TABLE OF HISTOLOGIC FINDINGS

| GROUP NUMBER | #1 | | | | #1 | | | | #4 | | | | #4 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SEX | Males | | | | Females | | | | Males | | | | Females | | | |
| ANIMAL NUMBER | 370 | 371 | 372 | 373 | 374 | 375 | 376 | 377 | 394 | 395 | 396 | 397 | 398 | 399 | 400 | 401 |
| TESTIS | - | - | - | | | | | | - | - | - | | | | | |
| Giant cell degeneration | | | | 1 | | | | | | | | | | | | |
| Focal hypospermatogenesis | | | | 1 | | | | | | | | 2 | | | | |
| EPIDIDYMUS | - | - | - | - | | | | | - | - | - | - | | | | |
| PROSTATE | - | | | - | | | | | | - | | - | | | | |
| Cystic dilatation | | 1 | 1 | | | | | | | | | | | | | |
| Epithelial vacuolization | | 2 | | | | | | | 3 | | | | | | | |
| Cystic glandular hyperplasia | | | | | | | | | | | 2 | | | | | |
| MUSCLE | - | - | - | | - | - | - | - | - | - | - | - | - | - | - | - |
| Focal chronic myositis | | | | 1 | | | | | | | | | | | | |
| URINARY BLADDER | - | - | - | - | - | - | - | | - | - | - | | - | | | - |
| Perivascular hyaline material, serosa | | | | | | | | + | | | | + | | + | + | |
| Congestion | | | | | | | | + | | | | | | | | |
| MAMMARY GLAND | - | - | - | - | - | - | - | - | - | - | - | - | - | | | - |
| Active | | | | | | | | | | | | | | + | + | |
| PITUITARY | - | | - | - | - | - | - | - | | | - | - | - | - | - | - |
| Cystic Rathke's pouch remnant | | + | | | | | | | + | | | | | | | |
| Pronounced aggregation of pars intermedia cells | | | | | | | | | | + | | | | | | |
| RIB JUNCTION | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |

## TABLE I-G-53 (Continued)

THREE-MONTH TOXICITY STUDY IN DOGS

LBI PROJECT NO. 10734-08

TABLE OF HISTOLOGIC FINDINGS

| GROUP NUMBER | #1 | | | | #1 | | | | #4 | | | | #4 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SEX | Males | | | | Females | | | | Males | | | | Females | | | |
| ANIMAL NUMBER | 370 | 371 | 372 | 373 | 374 | 375 | 376 | 377 | 394 | 395 | 396 | 397 | 398 | 399 | 400 | 401 |
| STERNUM | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| BRAIN | - | | | | - | - | - | - | - | - | - | - | - | - | - | - |
| Focal capillary ectasia | | + | | | | | | | | | | | | | | |
| Focal neuronal swelling | | | 1 | | | | | | | | | | | | | |
| Swollen axon medulla oblongata | | | | + | | | | | | | | | | | | |
| Degeneration | | | 1 | | | | | | | | | | | | | |
| EYE | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| SKIN | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | |
| Dermatitis | | | | | | | | | | | | | | | | + |
| Scabs | | | | | | | | | | | | | | | | + |
| OVARIES | | | | | - | - | - | - | | | | | - | | | - |
| Large corpora lutea | | | | | | | | | | | | | | + | + | |
| UTERUS | | | | | - | - | - | - | | | | | - | | | - |
| Secretory | | | | | | | | | | | | | | + | + | |

TABLE I-G-54

THREE MONTH TOXICITY STUDY IN DOGS

LBI PROJECT NO. 10734-08

INCIDENCE TABLE

| GROUP NUMBER | 1 | 1 | 4 | 4 |
|---|---|---|---|---|
| SEX | Males | Females | Males | Females |
| NUMBER OF ANIMALS EXAMINED | 4 | 4 | 4 | 4 |
| THYROID/PARATHYROID | | | | |
| C-cell hyperplasia | 1 | 1 | 0 | 0 |
| Abundant C-cells | 1 | 1 | 0 | 0 |
| Cystic ultimobranchial remnant | 1 | 0 | 2 | 0 |
| Non-suppurative thyroiditis | 0 | 0 | 0 | 1 |
| SPLEEN | | | | |
| Inactive lymphoid component | 1 | 1 | 0 | 0 |
| Lymphoid depletion | 0 | 0 | 1 | 0 |
| LUNG | | | | |
| Intraalveolar hyaline bodies | 0 | 0 | 0 | 1 |
| Mineralith | 0 | 0 | 0 | 1 |
| Multifocal non-suppurative perivasculitis | 1 | 0 | 0 | 0 |
| Substantial number of circulating neutrophils | 0 | 0 | 1 | 0 |
| Multifocal perivasculitis | 0 | 0 | 1 | 0 |
| Interstitial pneumonia | 0 | 0 | 1 | 0 |
| Pleuritis | 0 | 0 | 1 | 0 |
| LIVER | | | | |
| Vacuolar change | 0 | 0 | 2 | 0 |
| Glycogen in centrilobular areas | 0 | 0 | 0 | 1 |
| GALLBLADDER | | | | |
| Clear cytoplasm, epithelial cells | 0 | 0 | 0 | 1 |

TABLE I-G-54 (Continued)

LBI PROJECT NO. 10734-08
INCIDENCE TABLE (Continued)

| GROUP NUMBER | 1 | 1 | 4 | 4 |
|---|---|---|---|---|
| SEX | Males | Females | Males | Females |
| NUMBER OF ANIMALS EXAMINED | 4 | 4 | 4 | 4 |
| KIDNEYS | | | | |
| Microlithiasis | 2 | 2 | 1 | 3 |
| Non-suppurative pyelitis | 0 | 1 | 0 | 0 |
| Multifocal mineralization | 0 | 0 | 2 | 1 |
| Multifocal glomerulosclerosis | 0 | 0 | 0 | 1 |
| Non-suppurative nephritis | 0 | 0 | 0 | 1 |
| ADRENALS | | | | |
| Vacuolization | 1 | 0 | 2 | 1 |
| MESENTERIC LYMPH NODES | | | | |
| Active appearing node | 2 | 0 | 0 | 0 |
| Erythrophagocytosis | 1 | 0 | 1 | 0 |
| SMALL INTESTINE | | | | |
| Cystic crypt | 1 | 0 | 2 | 0 |
| Focal mineralization | 1 | 0 | 0 | 0 |
| COLON | | | | |
| Multifocal mucosal congestion | 0 | 0 | 1 | 0 |
| TESTIS | | | | |
| Giant cell degeneration | 1 | | 0 | |
| PROSTATE | | | | |
| Cystic dilatation | 2 | | 0 | |
| Epithelial vacuolization | 1 | | 1 | |
| Cystic glandular hyperplasia | 0 | | 1 | |

TABLE I-G-54 (Continued)

LBI PROJECT NO. 10734-08
INCIDENCE TABLE (Continued)

| GROUP NUMBER | 1 | 1 | 4 | 4 |
|---|---|---|---|---|
| SEX | Males | Females | Males | Females |
| NUMBER OF ANIMALS EXAMINED | 4 | 4 | 4 | 4 |
| MUSCLE | | | | |
| Focal chronic myositis | 1 | 0 | 0 | 0 |
| URINARY BLADDER | | | | |
| Perivascular hyaline material | 0 | 1 | 1 | 2 |
| Congestion | 0 | 1 | 0 | 0 |
| MAMMARY GLAND | | | | |
| Active | 0 | 0 | 0 | 2 |
| PITUITARY | | | | |
| Cystic Rathke's pouch remnant | 1 | 0 | 1 | 0 |
| Pronounced aggregation of pars intermedia cells | 0 | 0 | 1 | 0 |
| BRAIN | | | | |
| Focal capillary ectasia | 1 | 0 | 0 | 0 |
| Focal neuronal swelling | 1 | 0 | 0 | 0 |
| Swollen axon, medulla oblongata | 1 | 0 | 0 | 0 |
| Degeneration | 1 | 0 | 0 | 0 |
| SKIN | | | | |
| Dermatitis | 0 | 0 | 0 | 1 |
| Scabs | 0 | 0 | 0 | 1 |
| OVARIES | | | | |
| Large corpora lutea | | 0 | | 2 |
| UTERUS | | | | |
| Secretory | | 0 | | 2 |

PART II - SECTION A

INTRODUCTION AND MATERIAL

DCPD

In a continuation of an evaluation of the mammalian toxicity of DCPD, this compound has been studied by subchronic (90 day) administration to dogs, for reproductive and teratologic effects in rats, for mutagenic effects in certain tester strains of salmonella and additional aspects of its metabolic fate.

Earlier parts of the evaluation were reported in November 1976 under Contract No. DAMD 17-75-C-5068.

## 2. MATERIAL

DCPD (Dicyclopentadiene) also known as 3a,4,7,7a-Tetrahydro-4,7-methanoindene, was purchased from MC/B, 2909 Highland Avenue, Norwood, Ohio 45212, under catalog number TX 310. A single batch of 650 g was received on August 18, 1976, and assigned LBI No. 763A.

Analysis of DCPD was performed with a UC-W98 column. The retention time of the compound was 1.9 minutes. Trace impurities were noted at approximately 1.5 minutes and 2.1 minutes. The purity of DCPD appeared to be 98 to 99%, which is consistent with the MC/B assay of 99.79%. It cannot now be determined if one of these impurities may be the cis form.

Because of poor water solubility, DCPD was prepared for administration to animals by dissolving it in corn oil (Mazola) at concentrations appropriate to the various studies. The handling of DCPD itself was facilitated by slight warming, which converted the waxy solid to an easily measured liqud.

PART II - SECTION B

MICROBIAL MUTAGENESIS

DCPD

LBI PROJECT NO. 10734-01

## SUMMARY

The test compound, DCPD Lot No. 040667, did not demonstrate mutagenic activity in any of the assays conducted in this evaluation and was considered not mutagenic under these test conditions.

The test compound, DCPD W-761226, did not demonstrate mutagenic activity in any of the assays conducted in this evaluation and was considered not mutagenic under these test conditions.

1. OBJECTIVE

The objective of this study was to evaluate the test compound for genetic activity in microbial assays with and without the addition of mammalian metabolic activation preparations.

2. MATERIALS

A. Test Compound

1. Date Received: January 17, 1977

2. Description: Colorless liquid; DCPD Lot No. 04066

B. Indicator Microorganisms

Salmonella typhimurium, strains: TA-1535 TA-98
TA-1537 TA-100
TA-1538

Saccharomyces cerevisiae, strain: D4

C. Activation System (Ames et al., Mutation Research 31:347, 1975)

1. Reaction Mixture

| Component | Final Concentration/ml |
|---|---|
| TPN | 4 µmoles |
| Glucose-6-phosphate | 5 µmoles |
| Sodium phosphate (diabasic) | 100 µmoles |
| $MgCl_2$ | 8 µmoles |
| KCl | 33 µmoles |
| Homogenate fraction equivalent to 25 mg of wet tissue | 0.1-0.15 ml 9,000 x g supernatant of rat liver |

2. S-9 Homogenate

A 9,000 x g supernatant was prepared from Sprague-Dawley adult male rat liver induced by Aroclor 1254 five days prior to kill.

2. MATERIALS (Continued)

D. Positive Control Chemicals

Table 1 below lists the chemicals used for positive controls in the nonactivation and activation assays.

TABLE 1

| ASSAY | CHEMICAL[a] | SOLVENT | PROBABLE MUTAGENIC SPECIFICITY |
|---|---|---|---|
| Nonactivation | Methylnitrosoguanidine (MNNG) | Water or Saline | BPS[b] |
| | 2-Nitrofluorene (NF) | Dimethylsulfoxide[c] | FS[b] |
| | Quinacrine mustard (QM) | Water or saline | FS[b] |
| Activation | 2-Anthramine (ANTH) | Dimethylsulfoxide[c] | BPS[b] |
| | 2-Acetylaminofluorene (AAF) | Dimethylsulfoxide[c] | FS[b] |
| | 8-Aminoquinoline (AMQ) | Dimethylsulfoxide[c] | FS[b] |

[a]Concentrations given in Results Section

[b]BPS = Base-pair substi tion

FS = Frameshift

[c]Previcusly shown to be nonmutagenic

E. Solvent

Either deionized water or dimethylsulfoxide (DMSO) was used to prepare stock solutions of solid materials. All dilutions of test materials were made in ei.. - deionized water or DMSO. The solvent employed and its concentr.. ion are recorded in the Results Section.

3. EXPERIMENTAL DESIGN

A. Plate Test (Overlay Method*)

Approximately $10^8$ cells from an overnight culture of each indicator strain were added to separate test tubes containing 2.0 ml of molten agar supplemented with biotin and a trace of histidine. For non-activation tests, at least four dose levels of the test compound were added to the contents of the appropriate tubes and poured over the surfaces of selective agar plates. In activation tests, a minimum of four different concentrations of the test chemical were added to the appropriate tubes with cells. Just prior to pouring, an aliquot of reaction mixture (0.5 ml containing the 9,000 x g liver homogenate) was added to each of the activation overlay tubes, which were then mixed, and the contents poured over the surface of a minimal agar plate and allowed to solidify. The plates were incubated for 48 hours at 37C, and scored for the number of colonies growing on each plate. The concentrations of all chemicals are given in the Results Section. Positive and solvent controls using both directly active positive chemicals and those that require metabolic activation were run with each assay.

B. Recording and Presenting Data

The numbers of colonies on each plate were counted and recorded on printed forms. These raw data were analyzed in a computer program and reported on a printout. The results are presented as revertants per plate for each indicator strain employed in the assay. The positive and the solvent controls are provided as reference points. Other relevant data are provided on the computer printout.

*Certain classes of chemicals known to be mutagens and carcinogens do not produce detectable responses using the standard Ames overlay method. Some dialkyl nitrosamines and certain substituted hydrazines are mutagenic in suspension assays, but not in the plate assay. Chemicals of these classes should be screened in a suspension assay.

# TABLE II-B-1

4. SUMMARY OF PLATE TEST RESULTS — LITTON BIONETICS, INC.

A. NAME OR CODE DESIGNATION OF THE TEST COMPOUND: DCPD LOT #040667
B. SOLVENT: DMSO
C. TEST DATE: FEB. 7, 1977
NOTE: CONCENTRATIONS ARE GIVEN IN MICROLITERS (UL) OR MICROGRAMS (UG) PER PLATE.

| TEST | SPECIES | TISSUE | REVERTANTS PER PLATE TA-1535 1 | TA-1535 2 | TA-1537 1 | TA-1537 2 | TA-1538 1 | TA-1538 2 | TA-98 1 | TA-98 2 | TA-100 1 | TA-100 2 | D4* 1 | D4* 2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NONACTIVATION | | | | | | | | | | | | | | |
| SOLVENT CONTROL | --- | --- | 20 | | 15 | | 14 | | 24 | | 182 | | 12 | |
| POSITIVE CONTROL** | --- | --- | >1000 | | 1000 | | >1000 | | >1000 | | >1000 | | 262 | |
| TEST COMPOUND | | | | | | | | | | | | | | |
| 0.00100 UL | --- | --- | 13 | | 6 | | 16 | | 25 | | 147 | | 11 | |
| 0.01000 UL | --- | --- | 15 | | 13 | | 19 | | 32 | | 133 | | 17 | |
| 0.10000 UL | --- | --- | 10 | | 15 | | 24 | | 34 | | 156 | | 17 | |
| 1.00000 UL | --- | --- | 8 | | 10 | | 15 | | 15 | | 159 | | 3 | |
| 5.00000 UL | --- | --- | 0 | | 6 | | 4 | | 8 | | 76 | | 0 | |
| ACTIVATION | | | | | | | | | | | | | | |
| SOLVENT CONTROL | RAT | LIVER | 42 | | 21 | | 26 | | 35 | 47 | 194 | | 47 | |
| POSITIVE CONTROL*** | RAT | LIVER | >1000 | | 297 | | >1000 | | >1000 | | >1000 | | 398 | |
| TEST COMPOUND | | | | | | | | | | | | | | |
| 0.00100 UL | RAT | LIVER | 45 | | 17 | | 19 | | 42 | - | 182 | | 36 | |
| 0.01000 UL | RAT | LIVER | 38 | | 24 | | 13 | | 47 | - | 191 | | 56 | |
| 0.10000 UL | RAT | LIVER | 34 | | 15 | | 18 | | 26 | - | 181 | | 67 | |
| 1.00000 UL | RAT | LIVER | 26 | | 15 | | 11 | | 23 | - | 186 | | 61 | |
| 5.00000 UL | RAT | LIVER | 23 | | 17 | | 2 | | 132 | 15 | 15 | | 15 | |
| 10.00000 UL | RAT | LIVER | - | | - | | - | | - | 19 | - | | - | |

* IBY. CONVERTANTS PER PLATE

| | | | |
|---|---|---|---|
| ** | TA-1535 | MNNG | 10 UG/PLATE |
| | TA-1537 | QM | 10 UG/PLATE |
| | TA-1538 | NF | 100 UG/PLATE |
| | TA-98 | NF | 100 UG/PLATE |
| | TA-100 | MNNG | 10 UG/PLATE |
| | D4 | MNNG | 10 UG/PLATE |
| | SOLVENT | DMSO | 2.5 %/PLATE |

| | | | |
|---|---|---|---|
| *** | TA-1535 | ANTH | 100 UG/PLATE |
| | TA-1537 | AMQ | 100 UG/PLATE |
| | TA-1538 | AAF | 100 UG/PLATE |
| | TA-98 | AAF | 100 UG/PLATE |
| | TA-100 | ANTH | 100 UG/PLATE |
| | D4 | DMNA | 100 MICROMOLES/PLATE |
| | SOLVENT | DMSO | 2.5 %/PLATE |

5. INTERPRETATION OF RESULTS AND CONCLUSIONS

The test compound was examined for mutagenic activity in a series of *in vitro* microbial assays employing *Salmonella* and *Saccharomyces* indicator organisms. The compound was tested directly and in the presence of liver microsomal enzyme preparations from Aroclor-induced rats. The following results were obtained:

A. Toxicity

The compound was tested over a series of concentrations such that there was either quantitative or qualitative evidence of some chemically-induced physiological effects at the high dose level. The low dose in all cases was below a concentration that demonstrated any toxic effect. The dose range employed for the evaluation of this compound was from 0.001 µl to 5 µl per plate. The compound was toxic to the strains TA-1535, TA-1537, TA-1538, TA-98, and the yeast strain D4 at 5 µl per plate in the nonactivation assays.

B. Nonactivation Test Results

The results of the tests conducted on the compound in the absence of a metabolic system were all negative.

C. Activation Test Results

The results of the tests conducted on the compound in the presence of the rat liver activation system were all negative.

D. Conclusions

The test compound, DCPD Lot No. 040667, did not demonstrate mutagenic activity in any of the assays conducted in this evaluation and was considered not mutagenic under these test conditions.

Submitted by:

David J. Brusick, Ph.D. — 2/27/77
Director — Date
Department of Genetics

Reviewed by:

Robert J. Weir, Ph.D. — 2/27/77
Vice President — Date

## 6. EXPLANATION OF EVALUATION PROCEDURES FOR PLATE ASSAYS

Plate test data consist of direct revertant colony counts obtained from a set of selective agar plates seeded with populations of mutant cells suspended in a semisolid overlay. Because the test chemical and the cells are incubated in the overlay for 2 to 3 days, and a few cell divisions occur during the incubation period, the test is semi-quantitative in nature. Although these features of the assay reduce the quantitation of results, they provide certain advantages not contained in a quantitative suspension test:

- The small number of cell divisions permits potential mutagens to act on replicating DNA, which is often more sensitive than nonreplicating DNA.
- The combined incubation of the compound and the cells in the overlay permits constant exposure of the indicator cells for 2 to 3 days.

### A. Surviving Populations

Plate test procedures do not permit exact quantitation of the number of cells surviving chemical treatment. At low concentrations of the test chemical, the surviving population on the treatment plates is essentially the same as that on the negative control plate. At high concentrations, the surviving population is usually reduced by some fraction. Our protocol normally employs several doses ranging over two or three log concentrations, the highest of these doses being selected to show slight toxicity as determined by subjective criteria.

### B. Dose Response Phenomena

The demonstration of dose-related increases in mutant counts is an important criterion in establishing mutagenicity. A factor that might modify dose-response results for a mutagen would be the selection of doses that are too low (usually mutagenicity and toxicity are related). If the highest dose is far lower than a toxic concentration, no increases may be observed over the dose range selected. Conversely, if the lowest dose employed is highly cytotoxic, the test chemical may kill any mutants that are induced, and the compound will not appear to be mutagenic.

6. EXPLANATION OF EVALUATION PROCEDURES FOR PLATE ASSAYS (Continued)

C. Control Tests

Positive and negative control assays are conducted with each experiment and consist of direct-acting mutagens for nonactivation assays and mutagens that require metabolic biotransformation in activation assays. Negative controls consist of the test compound solvent in the overlay agar together with the other essential components. The negative control plate for each strain gives a reference point to which the test data are compared. The positive control assay is conducted to demonstrate that the test systems are functional with known mutagens.

D. Evaluation Criteria for Ames Assay

Because the procedures used to evaluate the mutagenicity of the test chemical are semiquantitative, the criteria used to determine positive effects are inherently subjective and are based primarily on a historical data base. Most data sets are evaluated using the following criteria:

1. Strains TA-1535, TA-1537, and TA-1538

If the solvent control value is within the normal range, a chemical that produces a positive dose response over three concentrations with the lowest increase equal to twice the solvent control value is considered to be mutagenic.

2. Strains TA-98, TA-100, and D4

If the solvent control value is within the normal range, a chemical that produces a positive dose response over three concentrations with the highest increase equal to twice the solvent control value for TA-100 and two to three times the solvent control value for strains TA-98 and D4 is considered to be mutagenic. For these strains, the dose response increase should start at approximately the solvent control value.

3. Pattern

Because TA-1535 and TA-100 were both derived from the same parental strain (G-46) and because TA-1538 and TA-98 were both derived from the same parental strain (D3052), there is a built-in redundancy in the microbial assay. In general the two strains of a set respond to the same mutagen and such a pattern is sought. It is also anticipated that if a

6. EVALUATION OF EVALUATION PROCEDURES FOR PLATE ASSAYS (Continued)

D. Evaluation Criteria for Ames Assay

3. Pattern

given strain, e.g. TA-1537, responds to a mutagen in nonactivation tests it will generally do so in activation tests. (The converse of this relationship is not expected.) While similar response patterns are not required for all mutagens, they can be used to enhance the reliability of an evaluation decision.

4. Reproducibility

If a chemical produces a response in a single test that cannot be reproduced in one or more additional runs, the initial positive test data loses significance.

The preceding criteria are not absolute and other extenuating factors may enter into a final evaluation decision. However, these criteria are applied to the majority of situations and are presented to aid those individuals not familiar with this procedure. As the data base is increased, the criteria for evaluation can be more firmly established.

E. Relationship Between Mutagenicity and Carcinogenicity

It must be emphasized that the Ames Salmonella/microsome test is not a definitive test for chemical carcinogens. It is recognized, however, that correlative and functional relationships have been demonstrated between these two end points. The results of comparative tests on 300 chemicals by McCann et al. (Proc. Nat. Acad. Sci. USA, 72:5135-5139, 1975) show an extremely good correlation between results of microbial mutagenesis tests and in vivo rodent carcinogenesis assays.

All evaluation and interpretation of the data presented in this report are based only on the demonstration of or lack of mutagenic activity.

## STANDARD OPERATING PROCEDURES

To ensure an accurate and reliable mutagenicity testing program, LBI instituted the following procedures:

- The test compound was registered in a bound log book recording the date of receipt, complete client identification, physical description and LBI code number.

- Complete records of weights and dilutions associated with the testing of the submitted material were entered into a bound notebook.

- Raw data information was recorded on special printed forms that were dated and initialed by the individual performing the data collection at the time the observations were made. These forms were filed as permanent records.

- All animal tissue S-9 preparations used in the activation tests were taken from dated and pretested frozen lots identified by a unique number. The S-9 preparations were monitored for uniformity and the information recorded.

1. OBJECTIVE

The objective of this study was to evaluate the test compound for genetic activity in microbial assays with and without the addition of mammalian metabolic activation preparations.

2. MATERIALS

A. Test Compound

1. Date Received: January 17, 1977

2. Description: Colorless liquid; DCPD W-761226

B. Indicator Microorganisms

Salmonella typhimurium, strains: TA-1535 TA-98
TA-1537 TA-100
TA-1538

Saccharomyces cerevisiae, strain: D4

C. Activation System (Ames et al., Mutation Research 31:347, 1975)

1. Reaction Mixture

| Component | Final Concentration/ml |
|---|---|
| TPN | 4 µmoles |
| Glucose-6-phosphate | 5 µmoles |
| Sodium phosphate (diabasic) | 100 µmoles |
| $MgCl_2$ | 8 µmoles |
| KCl | 33 µmoles |
| Homogenate fraction equivalent to 25 mg of wet tissue | 0.1-0.15 ml 9,000 x g supernatant of rat liver |

2. S-9 Homogenate

A 9,000 x g supernatant was prepared from Sprague-Dawley adult male rat liver induced by Aroclor 1254 five days prior to kill.

2. MATERIALS (Continued)

D. Positive Control Chemicals

Table 1 below lists the chemicals used for positive controls in the nonactivation and activation assays.

TABLE 1

| ASSAY | CHEMICAL[a] | SOLVENT | PROBABLE MUTAGENIC SPECIFICITY |
|---|---|---|---|
| Nonactivation | Methylnitrosoguanidine (MNNG) | Water or Saline | BPS[b] |
| | 2-Nitrofluorene (NF) | Dimethylsulfoxide[c] | FS[b] |
| | Quinacrine mustard (QM) | Water or saline | FS[b] |
| Activation | 2-Anthramine (ANTH) | Dimethylsulfoxide[c] | BPS[b] |
| | 2-Acetylaminofluorene (AAF) | Dimethylsulfoxide[c] | FS[b] |
| | 8-Aminoquinoline (AMQ) | Dimethylsulfoxide[c] | FS[b] |

[a]Concentrations given in Results Section

[b]BPS = Base-pair substitution

FS = Frameshift

[c]Previously shown to be nonmutagenic

E. Solvent

Either deionized water or dimethylsulfoxide (DMSO) was used to prepare stock solutions of solid materials. All dilutions of test materials were made in either deionized water or DMSO. The solvent employed and its concentration are recorded in the Results Section.

## 3. EXPERIMENTAL DESIGN

### A. Plate Test (Overlay Method*)

Approximately $10^8$ cells from an overnight culture of each indicator strain were added to separate test tubes containing 2.0 ml of molten agar supplemented with biotin and a trace of histidine. For non-activation tests, at least four dose levels of the test compound were added to the contents of the appropriate tubes and poured over the surfaces of selective agar plates. In activation tests, a minimum of four different concentrations of the test chemical were added to the appropriate tubes with cells. Just prior to pouring, an aliquot of reaction mixture (0.5 ml containing the 9,000 x g liver homogenate) was added to each of the activation overlay tubes, which were then mixed, and the contents poured over the surface of a minimal agar plate and allowed to solidify. The plates were incubated for 48 hours at 37C, and scored for the number of colonies growing on each plate. The concentrations of all chemicals are given in the Results Section. Positive and solvent controls using both directly active positive chemicals and those that require metabolic activation were run with each assay.

### B. Recording and Presenting Data

The numbers of colonies on each plate were counted and recorded on printed forms. These raw data were analyzed in a computer program and reported on a printout. The results are presented as revertants per plate for each indicator strain employed in the assay. The positive and the solvent controls are provided as reference points. Other relevant data are provided on the computer printout.

*Certain classes of chemicals known to be mutagens and carcinogens do not produce detectable responses using the standard Ames overlay method. Some dialkyl nitrosamines and certain substituted hydrazines are mutagenic in suspension assays, but not in the plate assay. Chemicals of these classes should be screened in a suspension assay.

# TABLE II-B-2

4. SUMMARY OF PLATE TEST RESULTS — LITTON BIONETICS, INC.

a. NAME OR CODE DESIGNATION OF THE TEST COMPOUND: DCPDW-761226
b. SOLVENT: DMSO
c. TEST DATE: FEB. 7, 1977
NOTE: CONCENTRATIONS ARE GIVEN IN MICROLITERS (UL) OR MICROGRAMS (UG) PER PLATE.

| TEST | SPECIES | TISSUE | REVERTANTS PER PLATE | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | TA-1535 | | TA-1537 | | TA-1538 | | TA-98 | | TA-100 | | D4* | |
| | | | 1 | 2 | 1 | 2 | 1 | 2 | 1 | 2 | 1 | 2 | 1 | 2 |
| **NONACTIVATION** | | | | | | | | | | | | | | |
| SOLVENT CONTROL | --- | --- | 20 | | 15 | | 14 | | 24 | | 182 | | 12 | |
| POSITIVE CONTROL** | --- | --- | >1000 | | >1000 | | >1000 | | >1000 | | >1000 | | 262 | |
| TEST COMPOUND | | | | | | | | | | | | | | |
| 0.00100 UL | --- | --- | 14 | | 10 | | 14 | | 87 | | 183 | | 15 | |
| 0.01000 UL | --- | --- | 12 | | 16 | | 12 | | 25 | | 140 | | 4 | |
| 0.10000 UL | --- | --- | 9 | | 14 | | 18 | | 26 | | 145 | | 8 | |
| 1.00000 UL | --- | --- | 9 | | 19 | | 5 | | 14 | | 133 | | 4 | |
| 5.00000 UL | --- | --- | 0 | | 5 | | 4 | | 0 | | 43 | | 1 | |
| **ACTIVATION** | | | | | | | | | | | | | | |
| SOLVENT CONTROL | RAT | LIVER | 42 | | 23 | | 26 | | 22 | | 201 | | 47 | |
| POSITIVE CONTROL*** | RAT | LIVER | >1000 | | 297 | | >1000 | | >1000 | | >1000 | | 398 | |
| TEST COMPOUND | | | | | | | | | | | | | | |
| 0.00100 UL | RAT | LIVER | 47 | | 13 | | 18 | | 30 | | 169 | | 43 | |
| 0.01000 UL | RAT | LIVER | 37 | | 26 | | 20 | | 24 | | 159 | | 56 | |
| 0.10000 UL | RAT | LIVER | 41 | | 20 | | 13 | | 25 | | 159 | | 56 | |
| 1.00000 UL | RAT | LIVER | 23 | | 23 | | 5 | | 26 | | 276 | | 84 | |
| 5.00000 UL | RAT | LIVER | 16 | | 14 | | 0 | | 4 | | 35 | | 89 | |
| 10.00000 UL | RAT | LIVER | - | | - | | - | | - | | - | | 21 | |

* IBY+ CONVERTANTS PER PLATE

** TA-1535 MNNG 10 UG/PLATE
TA-1537 QM 10 UG/PLATE
TA-1538 NF 100 UG/PLATE
TA-98 NF 100 UG/PLATE
TA-100 MNNG 10 UG/PLATE
D4 MNNG 10 UG/PLATE
SOLVENT DMSO 2.5 %/PLATE

*** TA-1535 ANTH 100 UG/PLATE
TA-1537 AMQ 100 UG/PLATE
TA-1538 AAF 100 UG/PLATE
TA-98 AAF 100 UG/PLATE
TA-100 ANTH 100 UG/PLATE
D4 DMNA 100 MICROMOLES/PLATE
SOLVENT DMSO 2.5 %/PLATE

5. INTERPRETATION OF RESULTS AND CONCLUSIONS

The test compound was examined for mutagenic activity in a series of *in vitro* microbial assays employing *Salmonella* and *Saccharomyces* indicator organisms. The compound was tested directly and in the presence of liver microsomal enzyme preparations from Aroclor-induced rats. The following results were obtained:

A. Toxicity

The compound was tested over a series of concentrations such that there was either quantitative or qualitative evidence of some chemically-induced physiological effects at the high dose level. The low dose in all cases was below a concentration that demonstrated any toxic effect. The dose range employed for the evaluation of this compound was from 0.001 µl to 5 µl per plate. The compound was toxic to all the strains at 5 µl per plate.

B. Nonactivation Test Results

The results of the tests conducted on the compound in the absence of a metabolic system were all negative.

C. Activation Test Results

The results of the tests conducted on the compound in the presence of the rat liver activation system were all negative.

D. Conclusions

The test compound, DCPD W-761226, did not demonstrate mutagenic activity in any of the assays conducted in this evaluation and was considered not mutagenic under these test conditions.

Submitted by:

David J. Brusick, Ph.D.
Director
Department of Genetics

2/24/77
Date

Reviewed by:

Robert J. Weir, Ph.D.
Vice President

2/25/77
Date

## 6. EXPLANATION OF EVALUATION PROCEDURES FOR PLATE ASSAYS

Plate test data consist of direct revertant colony counts obtained from a set of selective agar plates seeded with populations of mutant cells suspended in a semisolid overlay. Because the test chemical and the cells are incubated in the overlay for 2 to 3 days, and a few cell divisions occur during the incubation period, the test is semi-quantitative in nature. Although these features of the assay reduce the quantitation of results, they provide certain advantages not contained in a quantitative suspension test:

- The small number of cell divisions permits potential mutagens to act on replicating DNA, which is often more sensitive than nonreplicating DNA.
- The combined incubation of the compound and the cells in the overlay permits constant exposure of the indicator cells for 2 to 3 days.

### A. Surviving Populations

Plate test procedures do not permit exact quantitation of the number of cells surviving chemical treatment. At low concentrations of the test chemical, the surviving population on the treatment plates is essentially the same as that on the negative control plate. At high concentrations, the surviving population is usually reduced by some fraction. Our protocol normally employs several doses ranging over two or three log concentrations, the highest of these doses being selected to show slight toxicity as determined by subjective criteria.

### B. Dose Response Phenomena

The demonstration of dose-related increases in mutant counts is an important criterion in establishing mutagenicity. A factor that might modify dose-response results for a mutagen would be the selection of doses that are too low (usually mutagenicity and toxicity are related). If the highest dose is far lower than a toxic concentration, no increases may be observed over the dose range selected. Conversely, if the lowest dose employed is highly cytotoxic, the test chemical may kill any mutants that are induced, and the compound will not appear to be mutagenic.

6. EXPLANATION OF EVALUATION PROCEDURES FOR PLATE ASSAYS (Continued)

C. Control Tests

Positive and negative control assays are conducted with each experiment and consist of direct-acting mutagens for nonactivation assays and mutagens that require metabolic biotransformation in activation assays. Negative controls consist of the test compound solvent in the overlay agar together with the other essential components. The negative control plate for each strain gives a reference point to which the test data are compared. The positive control assay is conducted to demonstrate that the test systems are functional with known mutagens.

D. Evaluation Criteria for Ames Assay

Because the procedures used to evaluate the mutagenicity of the test chemical are semiquantitative, the criteria used to determine positive effects are inherently subjective and are based primarily on a historical data base. Most data sets are evaluated using the following criteria:

1. Strains TA-1535, TA-1537, and TA-1538

If the solvent control value is within the normal range, a chemical that produces a positive dose response over three concentrations with the lowest increase equal to twice the solvent control value is considered to be mutagenic.

2. Strains TA-98, TA-100, and D4

If the solvent control value is within the normal range, a chemical that produces a positive dose response over three concentrations with the highest increase equal to twice the solvent control value for TA-100 and two to three times the solvent control value for strains TA-98 and D4 is considered to be mutagenic. For these strains, the dose response increase should start at approximately the solvent control value.

3. Pattern

Because TA-1535 and TA-100 were both derived from the same parental strain (G-46) and because TA-1538 and TA-98 were both derived from the same parental strain (D3052), there is a built-in redundancy in the microbial assay. In general the two strains of a set respond to the same mutagen and such a pattern is sought. It is also anticipated that if a

6. EVALUATION OF EVALUATION PROCEDURES FOR PLATE ASSAYS (Continued)

D. Evaluation Criteria for Ames Assay

3. Pattern

given strain, e.g. TA-1537, responds to a mutagen in nonactivation tests it will generally do so in activation tests. (The converse of this relationship is not expected.) While similar response patterns are not required for all mutagens, they can be used to enhance the reliability of an evaluation decision.

4. Reproducibility

If a chemical produces a response in a single test that cannot be reproduced in one or more additional runs, the initial positive test data loses significance.

The preceding criteria are not absolute and other extenuating factors may enter into a final evaluation decision. However, these criteria are applied to the majority of situations and are presented to aid those individuals not familiar with this procedure. As the data base is increased, the criteria for evaluation can be more firmly established.

E. Relationship Between Mutagenicity and Carcinogenicity

It must be emphasized that the Ames Salmonella/microsome test is not a definitive test for chemical carcinogens. It is recognized, however, that correlative and functional relationships have been demonstrated between these two end points. The results of comparative tests on 300 chemicals by McCann et al. (Proc. Nat. Acad. Sci. USA, 72:5135-5139, 1975) show an extremely good correlation between results of microbial mutagenesis tests and in vivo rodent carcinogenesis assays.

All evaluation and interpretation of the data presented in this report are based only on the demonstration of or lack of mutagenic activity.

## STANDARD OPERATING PROCEDURES

To ensure an accurate and reliable mutagenicity testing program, LBI instituted the following procedures:

- The test compound was registered in a bound log book recording the date of receipt, complete client identification, physical description and LBI code number.

- Complete records of weights and dilutions associated with the testing of the submitted material were entered into a bound notebook.

- Raw data information was recorded on special printed forms that were dated and initialed by the individual performing the data collection at the time the observations were made. These forms were filed as permanent records.

- All animal tissue S-9 preparations used in the activation tests were taken from dated and pretested frozen lots identified by a unique number. The S-9 preparations were monitored for uniformity and the information recorded.

PART II - SECTION C

PHARMACOKINETICS AND METABOLISM

DCPD

LBI PROJECT NO. 10734-02

## SUMMARY

With the concurrence of the Project Officer, emphasis was placed on DIMP rather than DCPD with the result that no additional significant information was developed regarding DCPD. Previous findings are summarized below:

DCPD was absorbed after oral administration to mice, rats, and dogs. Peak plasma levels occurred in 2 hours in mice and dogs, and in 6 hours in rats. DCPD was widely distributed in all three species at 1 to 2 hours with the highest levels in urinary bladder, gall bladder and body fat in mice, in gall bladder and bile in dogs, and in body fat, adrenals and urinary bladder in rats. Excretion appeared to be primarily via the urine in all three species. About 85% of the administered radioactivity was accounted for in urine and feces within 24 hours. Urine from mice and dogs showed two radioactive components while rat urine also contained a third. All of these seemed to differ from DCPD on TLC, but none has yet been identified.

PART II - SECTION D

TERATOLOGY IN RATS

DCPD

LBI PROJECT NO. 10734-05

## SUMMARY

The test material was administered in the diet at doses of 80, 250 and 750 ppm to pregnant female rats on Days 6 through 15 of gestation. There were no changes in the dams or among the fetuses that indicated an adverse compound-related effect.

## 1. OBJECTIVE

The objective of this study was to investigate the effect of the test material on fetuses during the period of organogenesis when administered to the pregnant rat.

## 2. MATERIAL

Refer to Part II - Section A.

## 3. EXPERIMENTAL DESIGN

Female [CRL:COBS CD (SD) BR] rats were obtained from Charles River Breeding Laboratories, Inc., Portage, Michigan, and acclimated to laboratory conditions for 12 days. At that time, each female was paired with a sexually mature male of the same strain and from the same supplier. The females were examined daily for the presence of a copulatory plug. The presence of such a plug was taken as evidence of mating and designated as Day 0 of gestation. The female rats were 11 weeks of age at the time of the first dose (June 13, 1977). Mated female rats were assigned sequentially to treatment groups and identified by cage cards as indicated below.

| Group Number | Female Rat Numbers | Dose (ppm) |
|---|---|---|
| 1 | 6615-6635 | 0 (Control) |
| 2 | 6640-6659 | 80 |
| 3 | 6665-6684 | 250 |
| 4 | 6690-6709 | 750 |

3. EXPERIMENTAL DESIGN (Continued)

The female rats were individually housed in wire cages in a temperature-controlled animal room with artificial illumination automatically controlled to provide a 12 hour light cycle. No other species were housed in this animal room during the course of the study. No other test materials were under concurrent investigation in this animal room. The appropriate diets and fresh water (acidified pH 2.5) were provided ad libitum.

The test material was incorporated into the basal diet (Purina Laboratory Chow) on gestation Days 6 through 15 so as to provide the dose levels indicated previously. The test material (0.8, 2.5 or 7.5 g) was suspended in 300 ml of corn oil and blended with 10 kg of the basal diet in a twin shell blender for 15 minutes. The control diet contained 300 ml of corn oil per 10 kg of meal. The dose levels used in this study were approved by Dr. E. Ross Hart of LBI based on previous studies.

Although the revised protocol for this study indicated that the female rats be killed on Day 20 of gestation, the original protocol which called for termination on Day 19 of gestation was inadvertently followed. This was not judged to affect the integrity of the study.

The mated female rats were weighed on Days 0, 6, 16 and 19 of gestation. Food consumption was measured during the period 0-6, 6-16 and 16-19 days of gestation. The female rats were observed daily for changes in general appearance, behavior and condition.

On Day 19 of gestation, the adult female rats were anesthetized with chloroform, and the visceral and thoracic organs examined. The uterus was removed and opened. The number of implantation sites and their placement in the uterine horns, live and dead fetuses, and resorption sites were recorded. The fetuses were removed, examined externally for abnormalities and weighed.

One third of the fetuses of each litter were fixed in Bouin's fluid. These were later examined for changes in the soft tissues of the head, thoracic and visceral organs. The remaining fetuses of each litter were examined for skeletal abnormalities following staining with Alizarin Red S.

The uterus and ovaries from the adult females were preserved in 10% formalin for possible future examination. No further examination was judged to be necessary.

3. EXPERIMENTAL DESIGN (Continued)

Statistical analysis of the data was performed using the litter as a basic sampling unit. This concept has been widely supported with regard to teratology [1,2]. Dunnett's t-test [3] was used to determine statistical significance ($p<0.05$) with regard to difference between means with near normal distribution (body weights and food consumption of dams, mean pup weight based on litter averages). Ratios, for example sex ratio and pregnancy ratio, were analyzed with a 2x2 contingency table with Yates' correction [4]. With regard to discontinuous parameters as measured by the number of abnormal fetuses within a litter, Wilcoxon Rank Sum [5] was used.

4. RESULTS

No deaths occurred among the adult female rats, and except for Group 2 female rat no. 6654, these animals were normal in appearance throughout the study. Female rat no. 6654 was emaciated and had an arched back and a red crust around the nose and mouth on Day 19 of gestation.

Examination of the females at necropsy revealed a dark red area in the lungs of female rat no. 6650 (Group 2) and a liver mottled with small white spots in female no. 6698 (Group 4). These changes were not considered to be related to dose.

Mean body weight and food consumption, as shown in the Appendix Table 1, indicated no significant difference between control and treated pregnant rats [3].

Based on the observations of the uterine contents obtained on Day 19 of gestation, the test material did not produce any effect. These data have been summarized in Text Table A, and the details have been tabulated in Table 2 included in the Appendix.

Examination of the offspring at delivery revealed subcutaneous hematomas in fetuses from litters at all dose levels as tabulated below.

| Dose (ppm) | Number of Fetuses with Subcutaneous Hematomas (litters) |
|---|---|
| 0 (Control) | 41 (10) |
| 80 | 15 ( 7) |
| 250 | 29 (11) |
| 750 | 34 (14) |

TABLE II-D-3

LITTON BIONETICS, INC.
PROJECT NO. 0734-05

TABLE A

SUMMARY OF REPRODUCTIVE PERFORMANCE

| | DOSE (PPM) | | | | STATISTICAL METHOD |
|---|---|---|---|---|---|
| | 0 | 80 | 250 | 750 | |
| PREGNANCY RATIO (PREGNANT/BRED) | 19/21 | 20/20 | 19/20 | 19/20 | |
| LIVE LITTERS | 19/19 (100%) | 20/20 (100%) | 19/19 (100%) | 19/19 (100%) | [4] |
| IMPLANTATION SITES (LEFT HORN/RIGHT HORN) | 154/159 | 132/168 | 132/160 | 134/158 | [4] |
| RESORPTIONS | 18 | 22 | 19 | 13 | [5] |
| LITTERS WITH RESORPTIONS | 14 (74%) | 8 (40%) | 11 (58%) | 8 (42%) | [4] |
| DEAD FETUSES | 0 | 0 | 0 | 0 | [5] |
| LITTERS WITH DEAD FETUSES | 0 | 0 | 0 | 0 | [4] |
| LIVE FETUSES/IMPLANTATION SITE | 295/313 (94%) | 278/300 (93%) | 273/292 (93%) | 279/292 (96%) | [4] |
| MEAN LIVE LITTER SIZE (FETUSES) | 15.5 | 13.9 | 14.4 | 14.7 | [3] |
| AVERAGE FETAL WEIGHT (G) | 2.3 | 2.3 | 2.4 | 2.4 | [3] |
| AVERAGE FETAL LENGTH (CM) | 2.7 | 2.6 | 2.7 | 2.7 | [3] |

4. RESULTS (Continued)

Although there was a significant decrease in the number of fetuses with subcutaneous hematomas in Group 2 [4], this was not judged to be a dose-related response. Other observations on fetuses at delivery included one fetus of female no. 6622 (Group 1) with swelling of the right hind limb and one fetus of female no. 6617 (Group 1) with intestines protruding at the umbilicus.

Examination of the Bouin's fixed specimens revealed (in addition to the previously mentioned protruding intestines in the fetus of litter no. 6617) the absence of the left kidney in one fetus of litter no. 6620 (Group 1), enlarged kidneys in one fetus of litter no. 6645 (Group 2), and unilateral anophthalmia in one fetus of litter no. 6709 (Group 4). These changes did not indicate a dose-related response. The sex and number of fetuses examined for soft tissue changes were as follows.

| Dose (ppm) | Males | Females |
|---|---|---|
| 0 (Control) | 48 | 46 |
| 80 | 40 | 46 |
| 250 | 47 | 39 |
| 750 | 40 | 47 |

The sex ratio did not differ significantly between treated and control groups [4].

The results of the skeletal examination of the cleared and stained fetuses have been detailed in Appendix Table 3. Most of the changes noted, while not strictly normal, are frequently observed in 19 day old rat fetuses of this strain and source in our laboratory. These changes have been summarized below.

| Dose (ppm) | Number Fetuses Examined | Number Fetuses Normal | Fetuses With Commonly Encountered Changes Only | Fetuses With Unusual Skeletal Variations |
|---|---|---|---|---|
| 0 (Control) | 199[a] (19)[b] | 106 | 91 (17) | 2 (2) |
| 80 | 192 (20) | 85 | 103 (19) | 4 (3) |
| 250 | 187 (19) | 92 | 95 (13) | 0 (0) |
| 750 | 192 (19) | 91 | 98 (17) | 3 (2) |

[a]Two specimens of litter no. 6634 lost during processing and handling, not examined.

[b]Number of litters in parentheses.

4. RESULTS (Continued)

The unusual changes for the most part were related to retarded bone ossification and were not malformations as such. Neither the frequency nor the character of these changes indicated an adverse effect on fetal growth and development, or a teratogenic potential [4,5].

Thirty days after transmittal of this report, original data from the Department of Toxicology will be transferred to the LBI Archives, 5516 Nicholson Lane, Kensington, Maryland. A copy of this report was reviewed by the LBI Quality Assurance Unit.

5. CONCLUSION

Administration of the test material to female rats by incorporation into the diet at 80, 250 and 750 ppm produced no effect on the pregnant dams. There was no evidence of compound-induced terata, variation in sex ratio, embryo toxicity or inhibition of fetal growth and development.

Submitted by:

Robert P. Beliles 6/6/78

Robert P. Beliles, Ph.D. Date
Director
Department of Toxicology

Susan L. Makris

Susan L. Makris, B.S.
Toxicology Technician

Reviewed by:

Robert J. Weir 6/6/78

Robert J. Weir, Ph.D. Date
Vice President

## LITERATURE CITED


[1] Palmer, A.K. Statistical analysis and choice sampling units. Teratology, 10:301-302, 1974.

[2] Weil, C.S. Selection of the valid number of sampling units and a consideration of their combination in toxicological studies involving reproduction, teratogenesis or carcinogens. Fd. Cosmet. Toxicol. 8:172-182, 1970.

[3] Dunnett, C.W. Multiple comparison procedure for comparing several treatments with a control. J. Amer. Statistical Assn., 50:1096-1121, 1955.

[4] Snedecor, G. and Cochran, W. Statistical Methods, Iowa State University Press, Ames, Iowa, (Sixth Ed.), pp.215-223, 1974.

[5] Hollander, M. and Wolfe, D. Nonparametric Statistical Methods, John Wiley and Sons, New York, pp. 67-82, 1973.

# APPENDIX

TABLE 1 BODY WEIGHTS AND FOOD CONSUMPTION OF PREGNANT RATS

TABLE 2 OBSERVATIONS AT CAESAREAN SECTION

TABLE 3 OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

TABLE II-D-4

LITTON BIONETICS, INC.
PROJECT NO. 10734-05

TABLE 1

BODY WEIGHTS AND FOOD CONSUMPTION OF PREGNANT RATS

| DOSE (PPM). | | MEAN BODY WEIGHTS IN GRAMS[a] | | | | MEAN DAILY FOOD CONSUMPTION IN GRAMS[a] | | |
|---|---|---|---|---|---|---|---|---|
| | | DAY 0 | DAY 6 | DAY 15 | DAY 19 | DAY 0-6 | DAY 6-15 | DAY 16-19 |
| 0 (CONTROL) | MEAN | 218 | 244 | 296 | 350 | 19 | 20 | 26 |
| | SD | 13 | 13 | 18 | 20 | 4 | 4 | 3 |
| | SE | 3.1 | 3.0 | 4.1 | 4.7 | 1.0 | 1.1 | 0.8 |
| | N | 19 | 19 | 19 | 19 | 17 | 11 | 19 |
| 80 | MEAN | 214 | 244 | 289 | 334 | 20 | 19 | 23 |
| | SD | 18 | 13 | 34 | 45 | 4 | 3 | 5 |
| | SE | 4.1 | 2.9 | 7.5 | 10.0 | 1.0 | 0.8 | 1.2 |
| | N | 20 | 20 | 20 | 20 | 15 | 18 | 20 |
| 250 | MEAN | 223 | 247 | 295 | 346 | 22 | 20 | 26 |
| | SD | 12 | 18 | 15 | 17 | 5 | 1 | 4 |
| | SE | 2.8 | 4.2 | 3.4 | 3.8 | 1.2 | 0.3 | 0.9 |
| | N | 19 | 19 | 19 | 19 | 15 | 11 | 18 |
| 750 | MEAN | 213 | 243 | 291 | 342 | 22 | 20 | 26 |
| | SD | 18 | 14 | 19 | 27 | 4 | 1 | 3 |
| | SE | 4.1 | 3.1 | 4.4 | 6.3 | 1.0 | 0.3 | 0.6 |
| | N | 19 | 19 | 19 | 19 | 16 | 11 | 19 |

[a]Calculations do not include non-pregnant females.

TABLE II-D-5

LITTON BIONETICS, INC.
PROJECT NO. 10734-05

TABLE 2

OBSERVATIONS AT CAESAREAN SECTION

DOSE - 0 PPM

| FEMALE NUMBER | IMPLANTATION SITES | | RESORPTION SITES | DEAD FETUSES | VIABLE FETUSES | | |
|---|---|---|---|---|---|---|---|
| | LEFT HORN | RIGHT HORN | | | NUMBER | MEAN WEIGHT (G) | MEAN LENGTH (CM) |
| 6615 | 7 | 8 | 1 | 0 | 14 | 2.9 | 3.1 |
| 6616 | 6 | 11 | 1 | 0 | 16 | 2.8 | 2.9 |
| 6617 | 11 | 6 | 0 | 0 | 17 | 1.8 | 2.3 |
| 6618 | 0 | 0 | 0 | 0 | 0 | ---- | ---- |
| 6619 | 9 | 8 | 1 | 0 | 16 | 2.5 | 2.7 |
| 6620 | 6 | 8 | 0 | 0 | 14 | 2.5 | 2.8 |
| 6621 | 7 | 10 | 0 | 0 | 17 | 2.2 | 2.4 |
| 6622 | 10 | 5 | 0 | 0 | 15 | 2.2 | 2.5 |
| 6623 | 9 | 10 | 1 | 0 | 18 | 2.4 | 2.7 |
| 6624 | 7 | 8 | 1 | 0 | 14 | 2.2 | 2.5 |
| 6625 | 9 | 8 | 2 | 0 | 15 | 2.4 | 2.8 |
| 6626 | 0 | 0 | 0 | 0 | 0 | ---- | ---- |
| 6627 | 6 | 7 | 1 | 0 | 12 | 2.3 | 2.9 |
| 6628 | 10 | 6 | 1 | 0 | 15 | 2.4 | 2.9 |
| 6629 | 10 | 10 | 1 | 0 | 19 | 2.2 | 2.7 |
| 6630 | 4 | 12 | 1 | 0 | 15 | 2.2 | 2.8 |
| 6631 | 5 | 7 | 0 | 0 | 12 | 2.2 | 2.5 |
| 6632 | 9 | 11 | 1 | 0 | 19 | 2.1 | 2.4 |
| 6633 | 8 | 6 | 1 | 0 | 13 | 2.0 | 2.6 |
| 6634 | 12 | 6 | 1 | 0 | 17 | 1.8 | 2.5 |
| 6635 | 9 | 12 | 4 | 0 | 17 | 1.9 | 2.5 |
| TOTAL | 154 | 159 | 18 | 0 | 295 | | |
| MEAN* | | | | | 15.5 | 2.3 | 2.7 |
| SD | | | | | 2.09 | 0.29 | 0.21 |
| SE | | | | | 0.480 | 0.067 | 0.049 |
| N | 19 | 19 | 19 | 19 | 19 | 19 | 19 |

*Mean, SD and SE do not include non-pregnant females.

TABLE II-D-5 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-05

TABLE 2 (CONTINUED)

OBSERVATIONS AT CAESAREAN SECTION

DOSE - 80 PPM

| FEMALE NUMBER | IMPLANTATION SITES | | RESORPTION SITES | DEAD FETUSES | VIABLE FETUSES | | |
|---|---|---|---|---|---|---|---|
| | LEFT HORN | RIGHT HORN | | | NUMBER | MEAN WEIGHT (G) | MEAN LENGTH (CM) |
| 6640 | 3 | 10 | 9 | 0 | 4 | 3.0 | 3.2 |
| 6641 | 8 | 11 | 0 | 0 | 19 | 2.3 | 2.6 |
| 6642 | 0 | 6 | 1 | 0 | 5 | 3.0 | 3.0 |
| 6643 | 7 | 8 | 0 | 0 | 15 | 2.7 | 2.9 |
| 6644 | 9 | 8 | 0 | 0 | 17 | 2.7 | 2.8 |
| 6645 | 6 | 13 | 0 | 0 | 19 | 2.4 | 2.6 |
| 6646 | 7 | 7 | 0 | 0 | 14 | 1.9 | 2.3 |
| 6647 | 8 | 10 | 0 | 0 | 18 | 2.0 | 2.3 |
| 6648 | 3 | 12 | 5 | 0 | 10 | 2.5 | 2.7 |
| 6649 | 9 | 1 | 1 | 0 | 9 | 1.7 | 2.3 |
| 6650 | 7 | 9 | 0 | 0 | 16 | 2.3 | 2.6 |
| 6651 | 7 | 8 | 1 | 0 | 14 | 2.2 | 2.5 |
| 6652 | 9 | 7 | 0 | 0 | 16 | 2.7 | 2.9 |
| 6653 | 8 | 7 | 0 | 0 | 15 | 2.2 | 2.5 |
| 6654 | 7 | 7 | 1 | 0 | 13 | 1.6 | 2.3 |
| 6655 | 7 | 7 | 0 | 0 | 14 | 2.4 | 2.7 |
| 6656 | 6 | 12 | 2 | 0 | 16 | 2.1 | 2.5 |
| 6657 | 10 | 6 | 0 | 0 | 16 | 2.1 | 2.5 |
| 6658 | 6 | 9 | 0 | 0 | 15 | 2.7 | 2.8 |
| 6659 | 5 | 10 | 2 | 0 | 13 | 1.9 | 2.4 |
| TOTAL | 132 | 168 | 22 | 0 | 278 | | |
| MEAN | | | | | 13.9 | 2.3 | 2.6 |
| SD | | | | | 4.09 | 0.40 | 0.25 |
| SE | | | | | 0.915 | 0.089 | 0.057 |
| N | 20 | 20 | 20 | 20 | 20 | 20 | 20 |

LITTON BIONETICS, INC.
PROJECT NO. 10734-05

TABLE 2 (CONTINUED)

OBSERVATIONS AT CAESAREAN SECTION

DOSE - 250 PPM

| FEMALE NUMBER | IMPLANTATION SITES | | RESORPTION SITES | DEAD FETUSES | VIABLE FETUSES | | |
|---|---|---|---|---|---|---|---|
| | LEFT HORN | RIGHT HORN | | | NUMBER | MEAN WEIGHT (G) | MEAN LENGTH (CM) |
| 6665 | 9 | 5 | 0 | 0 | 14 | 2.9 | 3.1 |
| 6666 | 9 | 9 | 2 | 0 | 16 | 2.9 | 3.1 |
| 6667 | 8 | 4 | 1 | 0 | 11 | 2.0 | 2.3 |
| 6668 | 7 | 7 | 0 | 0 | 14 | 2.8 | 3.0 |
| 6669 | 6 | 9 | 0 | 0 | 15 | 2.6 | 2.9 |
| 6670 | 7 | 7 | 0 | 0 | 14 | 2.7 | 2.9 |
| 6671 | 5 | 10 | 2 | 0 | 13 | 2.1 | 2.3 |
| 6672 | 5 | 9 | 3 | 0 | 11 | 2.7 | 2.9 |
| 6673 | 6 | 10 | 0 | 0 | 16 | 2.4 | 2.7 |
| 6674 | 0 | 0 | 0 | 0 | 0 | ---- | ---- |
| 6675 | 6 | 12 | 2 | 0 | 16 | 2.1 | 2.4 |
| 6676 | 8 | 10 | 2 | 0 | 16 | 2.5 | 2.7 |
| 6677 | 4 | 12 | 2 | 0 | 14 | 2.2 | 2.5 |
| 6678 | 5 | 8 | 1 | 0 | 12 | 2.2 | 2.5 |
| 6679 | 5 | 5 | 2 | 0 | 8 | 2.7 | 3.1 |
| 6680 | 9 | 9 | 0 | 0 | 18 | 2.3 | 2.6 |
| 6681 | 11 | 6 | 0 | 0 | 17 | 1.8 | 2.3 |
| 6682 | 8 | 7 | 0 | 0 | 15 | 2.1 | 2.6 |
| 6683 | 8 | 10 | 1 | 0 | 17 | 2.0 | 2.3 |
| 6684 | 6 | 11 | 1 | 0 | 16 | 3.5 | 3.4 |
| TOTAL | 132 | 160 | 19 | 0 | 273 | | |
| MEAN* | | | | | 14.4 | 2.4 | 2.7 |
| SD | | | | | 2.50 | 0.42 | 0.33 |
| SE | | | | | 0.573 | 0.097 | 0.077 |
| N | 19 | 19 | 19 | 19 | 19 | 19 | 19 |

*Mean, SD and SE do not include non-pregnant female.

TABLE II-D-5 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-05

TABLE 2 (CONTINUED)

OBSERVATIONS AT CAESAREAN SECTION

DOSE - 750 PPM

| FEMALE NUMBER | IMPLANTATION SITES | | RESORPTION SITES | DEAD FETUSES | VIABLE FETUSES | | |
|---|---|---|---|---|---|---|---|
| | LEFT HORN | RIGHT HORN | | | NUMBER | MEAN WEIGHT (G) | MEAN LENGTH (CM) |
| 6690 | 8 | 7 | 1 | 0 | 14 | 2.6 | 2.9 |
| 6691 | 6 | 13 | 0 | 0 | 19 | 2.5 | 2.8 |
| 6692 | 6 | 8 | 2 | 0 | 12 | 2.9 | 3.1 |
| 6693 | 9 | 11 | 2 | 0 | 18 | 2.6 | 2.8 |
| 6694 | 4 | 8 | 0 | 0 | 12 | 3.1 | 3.1 |
| 6695 | 7 | 7 | 0 | 0 | 14 | 2.8 | 2.9 |
| 6696 | 5 | 11 | 0 | 0 | 16 | 2.6 | 2.8 |
| 6697 | 11 | 5 | 0 | 0 | 16 | 3.0 | 3.0 |
| 6698 | 5 | 11 | 0 | 0 | 16 | 2.5 | 2.7 |
| 6699 | 6 | 8 | 0 | 0 | 14 | 2.5 | 2.7 |
| 6700 | 6 | 9 | 0 | 0 | 15 | 1.7 | 2.2 |
| 6701 | 10 | 4 | 2 | 0 | 12 | 2.2 | 2.3 |
| 6702 | 11 | 5 | 3 | 0 | 13 | 2.0 | 2.1 |
| 6703 | 4 | 12 | 1 | 0 | 15 | 2.3 | 2.6 |
| 6704 | 0 | 0 | 0 | 0 | 0 | ---- | ---- |
| 6705 | 7 | 13 | 0 | 0 | 20 | 1.9 | 2.5 |
| 6706 | 8 | 11 | 0 | 0 | 19 | 2.1 | 2.7 |
| 6707 | 5 | 0 | 0 | 0 | 5 | 2.2 | 2.7 |
| 6708 | 5 | 7 | 1 | 0 | 11 | 1.6 | 2.1 |
| 6709 | 11 | 8 | 1 | 0 | 18 | 2.2 | 2.5 |
| TOTAL | 134 | 158 | 13 | 0 | 279 | | |
| MEAN* | | | | | 14.7 | 2.4 | 2.7 |
| SD | | | | | 3.54 | 0.42 | 0.31 |
| SE | | | | | 0.813 | 0.096 | 0.071 |
| N | 19 | 19 | 19 | 19 | 19 | 19 | 19 |

*Mean, SD and SE do not include non-pregnant female.

TABLE II-D-6

LITTON BIONETICS, INC.
PROJECT NO. 10734-05

TABLE 3

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE - 0 PPM

| FEMALE NO. | NO. OF FETUSES EXAMINED | | OBSERVATIONS |
|---|---|---|---|
| 6615 | 10 | 8 | NO VISIBLE ABNORMALITIES. |
| | | 1 | REDUCED OSSIFICATION OF THE STERNEBRAE. |
| | | * 1 | STERNEBRAE MALALIGNED, NON-FUSED OSSIFICATION CENTERS OF THE STERNEBRAE. |
| 6616 | 10 | 8 | NO VISIBLE ABNORMALITIES. |
| | | 1 | UNILATERAL RIB 14. |
| | | 1 | REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE ISCHIUM, PUBES NOT OSSIFIED. |
| 6617 | 12 | 9 | REDUCED OSSIFICATION OF THE HYOID BONE, STERNEBRAE NOT OSSIFIED, ISCHIUM NOT OSSIFIED, PUBES NOT OSSIFIED. |
| | | 1 | REDUCED OSSIFICATION OF THE HYOID BONE, REDUCED OSSIFICATION OF THE ISCHIUM, STERNEBRAE NOT OSSIFIED, PUBES NOT OSSIFIED. |
| | | 1 | REDUCED OSSIFICATION OF THE HYOID BONE, REDUCED OSSIFICATION OF THE THORACIC VERTEBRAL CENTRA, STERNEBRAE NOT OSSIFIED, ISCHIUM NOT OSSIFIED, PUBES NOT OSSIFIED. |
| | | 1 | REDUCED OSSIFICATION OF THE HYOID BONE, REDUCED OSSIFICATION OF THE STERNEBRAE, ISCHIUM NOT OSSIFIED, PUBES NOT OSSIFIED. |
| 6619 | 11 | 7 | NO VISIBLE ABNORMALITIES. |
| | | 2 | UNILATERAL RIB 14. |
| | | 2 | REDUCED OSSIFICATION OF THE PUBES. |
| 6620 | 10 | 9 | NO VISIBLE ABNORMALITIES. |
| | | 1 | UNILATERAL RIB 14, REDUCED OSSIFICATION OF THE PUBES. |
| 6621 | 12 | 11 | NO VISIBLE ABNORMALITIES. |
| | | 1 | REDUCED OSSIFICATION OF THE HYOID BONE, REDUCED OSSIFICATION OF THE STERNEBRAE, PUBES NOT OSSIFIED. |

*Some of these findings not commonly encountered.

LITTON BIONETICS, INC.
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TABLE 3 (CONTINUED)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE - 0 PPM

| FEMALE NO. | NO. OF FETUSES EXAMINED | OBSERVATIONS |
|---|---|---|
| 6622 | 10 | 2 NO VISIBLE ABNORMALITIES.<br>8 REDUCED OSSIFICATION OF THE PUBES. |
| 6623 | 12 | 10 NO VISIBLE ABNORMALITIES.<br>1 UNILATERAL RIB 14.<br>1 REDUCED OSSIFICATION OF THE PUBES. |
| 6624 | 9 | 5 NO VISIBLE ABNORMALITIES.<br>3 REDUCED OSSIFICATION OF THE PUBES.<br>1 REDUCED OSSIFICATION OF THE STERNEBRAE, PUBES NOT OSSIFIED. |
| 6625 | 10 | 10 NO VISIBLE ABNORMALITIES. |
| 6627 | 8 | 8 NO VISIBLE ABNORMALITIES. |
| 6628 | 10 | 9 NO VISIBLE ABNORMALITIES.<br>1 REDUCED OSSIFICATION OF THE PUBES. |
| 6629 | 13 | 4 NO VISIBLE ABNORMALITIES.<br>1 UNILATERAL RIB 14.<br>3 PUBES NOT OSSIFIED.<br>2 REDUCED OSSIFICATION OF THE PUBES.<br>1 REDUCED OSSIFICATION OF THE STERNEBRAE, PUBES NOT OSSIFIED.<br>1 REDUCED OSSIFICATION OF THE STERNEBRAE, NON-FUSED OSSIFICATION CENTERS OF THE STERNEBRAE.<br>1 REDUCED OSSIFICATION OF THE HYOID BONE, REDUCED OSSIFICATION OF THE STERNEBRAE, NON-FUSED OSSIFICATION CENTERS OF THE STERNEBRAE, (PORTIONS OF FORE EXTREMITIES DAMAGED DURING PREPARATION AND HANDLING, UNABLE TO EVALUATE COMPLETELY). |
| 6630 | 10 | 7 NO VISIBLE ABNORMALITIES.<br>1 REDUCED OSSIFICATION OF THE PUBES.<br>1 NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA,<br>1 REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES. |

LITTON BIONETICS, INC.
PROJECT NO. 10734-05

TABLE 3 (CONTINUED)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE - 0 PPM

| FEMALE NO. | NO. OF FETUSES EXAMINED | | OBSERVATIONS |
|---|---|---|---|
| 6631 | 8 | 5 | NO VISIBLE ABNORMALITIES. |
| | | 1 | PUBES NOT OSSIFIED. |
| | | 1 | REDUCED OSSIFICATION OF THE STERNEBRAE, PUBES NOT OSSIFIED. |
| | | 1 | REDUCED OSSIFICATION OF THE HYOID BONE, STERNEBRAE NOT OSSIFIED. |
| 6632 | 13 | 3 | REDUCED OSSIFICATION OF THE STERNEBRAE, (PORTIONS OF SKULL, PELVIC GIRDLE AND HIND EXTREMITIES DAMAGED DURING PREPARATION AND HANDLING, UNABLE TO EVALUATE COMPLETELY). |
| | | 1 | REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES, (PORTIONS OF THE SKULL AND HIND EXTREMITIES DAMAGED DURING PREPARATION AND HANDLING, UNABLE TO EVALUATE COMPLETELY). |
| | | 1 | PUBES NOT OSSIFIED, (PORTIONS OF THE SKULL AND HIND EXTREMITIES DAMAGED DURING PREPARATION AND HANDLING, UNABLE TO EVALUATE COMPLETELY). |
| | | 1 | UNILATERAL RIB 14, NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, (PORTIONS OF SKULL, PELVIC GIRDLE AND HIND EXTREMITIES DAMAGED DURING PREPARATION AND HANDLING, UNABLE TO EVALUATE COMPLETELY). |
| | | 1 | REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE ISCHIUM, REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 | PUBES NOT OSSIFIED, (PORTIONS OF SKULL AND FORE EXTREMITIES DAMAGED DURING PREPARATION AND HANDLING, UNABLE TO EVALUATE COMPLETELY). |
| | | 1 | REDUCED OSSIFICATION OF THE PUBES, (PORTIONS OF THE SKULL AND HIND EXTREMITIES DAMAGED DURING PREPARATION AND HANDLING, UNABLE TO EVALUATE COMPLETELY). |

LITTON BIONETICS, INC.
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TABLE 3 (CONTINUED)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE - 0 PPM

| FEMALE NO. | NO. OF FETUSES EXAMINED | OBSERVATIONS |
|---|---|---|
| 6632 (CONTD) | 13 | 1 REDUCED OSSIFICATION OF THE STERNEBRAE, UNILATERAL RIB 14, REDUCED OSSIFICATION OF THE PUBES, (PORTIONS OF FORE EXTREMITIES DAMAGED DURING PREPARATION AND HANDLING, UNABLE TO EVALUATE COMPLETELY). |
| | | 1 REDUCED OSSIFICATION OF THE STERNEBRAE, UNILATERAL RIB 14, REDUCED OSSIFICATION OF THE ISCHIUM, PUBES NOT OSSIFIED, (PORTIONS OF SKULL DAMAGED DURING PREPARATION AND HANDLING, UNABLE TO EVALUATE COMPLETELY). |
| | | 1 REDUCED OSSIFICATION OF THE STERNEBRAE, (PORTIONS OF THE SKULL, PELVIC GIRDLE, FORE AND HIND EXTREMITIES DAMAGED DURING PREPARATION AND HANDLING, UNABLE TO EVALUATE COMPLETELY). |
| | | 1 REDUCED OSSIFICATION OF THE STERNEBRAE, UNILATERAL RIB 14, REDUCED OSSIFICATION OF THE ISCHIUM, PUBES NOT OSSIFIED. |
| 6633 | 9 | 1 NO VISIBLE ABNORMALITIES. |
| | | 2 REDUCED OSSIFICATION OF THE PUBES. |
| | | 2 PUBES NOT OSSIFIED. |
| | | 1 REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES. |
| | | 2 REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE ISCHIUM, PUBES NOT OSSIFIED. |
| | | 1 REDUCED OSSIFICATION OF THE HYOID BONE, REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE ISCHIUM, PUBES NOT OSSIFIED. |
| 6634 | 10 | 4 PUBES NOT OSSIFIED, REDUCED OSSIFICATION OF THE STERNEBRAE. |
| | | 1 UNILATERAL RIB 14, STERNEBRAE NOT OSSIFIED. |
| | | 3 STERNEBRAE NOT OSSIFIED, PUBES NOT OSSIFIED. |
| | | * 1 NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, STERNEBRAE NOT OSSIFIED, PUBES NOT OSSIFIED, METATARSALS NOT OSSIFIED. |
| | | 1 REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES. |

*Some of these findings not commonly encountered.

LITTON BIONETICS, INC.
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TABLE 3 (CONTINUED)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE - 0 PPM

| FEMALE NO. | NO. OF FETUSES EXAMINED | OBSERVATIONS |
|---|---|---|
| 6635 | 12 | 2 NO VISIBLE ABNORMALITIES.<br>1 REDUCED OSSIFICATION OF THE PUBES.<br>3 REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES.<br>4 REDUCED OSSIFICATION OF THE STERNEBRAE, PUBES NOT OSSIFIED.<br>1 PUBES NOT OSSIFIED.<br>1 PUBES NOT OSSIFIED, STERNEBRAE NOT OSSIFIED. |

LITTON BIONETICS, INC.
PROJECT NO. 10734-05

TABLE 3 (CONTINUED)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE - 80 PPM

| FEMALE NO. | NO. OF FETUSES EXAMINED | OBSERVATIONS |
|---|---|---|
| 6640 | 3 | 1 NO VISIBLE ABNORMALITIES. |
| | | 1 UNILATERAL RIB 14. |
| | | 1 REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE. |
| 6641 | 13 | 5 NO VISIBLE ABNORMALITIES. |
| | | 1 REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE. |
| | | 1 NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA. |
| | | 1 NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 UNILATERAL RIB 14, NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA. |
| | | 1 REDUCED OSSIFICATION OF THE THORACIC VERTEBRAL CENTRA, REDUCED OSSIFICATION OF THE LUMBAR VERTEBRAL CENTRA, NON-FUSED OSSIFICATION CENTERS OF THE LUMBAR VERTEBRAL CENTRA., REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE. |
| | | 1 REDUCED OSSIFICATION OF THE INTERPARIETAL BONE, REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, REDUCED OSSIFICATION OF THE THORACIC VERTEBRAL CENTRA, NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE ISCHIUM, PUBES NOT OSSIFIED. |
| | | 1 REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 REDUCED OSSIFICATION OF THE THORACIC VERTEBRAL CENTRA, NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, NON-FUSED OSSIFICATION CENTERS OF THE LUMBAR VERTEBRAL CENTRA. |
| 6642 | 4 | 4 NO VISIBLE ABNORMALITIES. |
| 6643 | 10 | 8 NO VISIBLE ABNORMALITIES. |
| | | 1 REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 REDUCED OSSIFICATION OF THE INTERPARIETAL BONE. |

LITTON BIONETICS, INC.
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TABLE 3 (CONTINUED)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE - 80 PPM

| FEMALE NO. | NO. OF FETUSES EXAMINED | | OBSERVATIONS |
|---|---|---|---|
| 6644 | 12 | 8 | NO VISIBLE ABNORMALITIES. |
| | | 1 | UNILATERAL RIB 14. |
| | | 1 | NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA. |
| | | 1 | NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, UNILATERAL RIB 14. |
| | | 1 | REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, REDUCED OSSIFICATION OF THE PUBES. |
| 6645 | 13 | 8 | NO VISIBLE ABNORMALITIES. |
| | | 2 | UNILATERAL RIB 14. |
| | | 1 | BILATERAL RIB 14. |
| | | 1 | REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, REDUCED OSSIFICATION OF THE HYOID BONE, STERNEBRAE NOT OSSIFIED, REDUCED OSSIFICATION OF THE ISCHIUM, PUBES NOT OSSIFIED. |
| | | * 1 | REDUCED OSSIFICATION OF THE MAXILLA, REDUCED OSSIFICATION OF THE NASAL BONES, REDUCED OSSIFICATION OF THE INTERPARIETAL BONE, REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, HYOID BONE NOT OSSIFIED, REDUCED OSSIFICATION OF THE THORACIC VERTEBRAL CENTRA, STERNEBRAE NOT OSSIFIED, BILATERAL RIB 14, ISCHIUM NOT OSSIFIED, PUBES NOT OSSIFIED, METATARSALS NOT OSSIFIED. |
| 6646 | 10 | 6 | NO VISIBLE ABNORMALITIES. |
| | | 2 | REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 | REDUCED OSSIFICATION OF THE INTERPARIETAL BONE. |
| | | 1 | REDUCED OSSIFICATION OF THE STERNEBRAE. |
| 6647 | 12 | 2 | NO VISIBLE ABNORMALITIES. |
| | | 6 | REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 | REDUCED OSSIFICATION OF THE STERNEBRAE. |
| | | 1 | UNILATERAL RIB 14, REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 | REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, REDUCED OSSIFICATION OF THE STERNEBRAE, PUBES NOT OSSIFIED. |
| | | 1 | UNILATERAL RIB 14, REDUCED OSSIFICATION OF THE STERNEBRAE. |

*Some of these findings not commonly encountered.

LITTON BIONETICS, INC.
PROJECT NO. 10734-05

TABLE 3 (CONTINUED)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE - 80 PPM

| FEMALE NO. | NO. OF FETUSES EXAMINED | | OBSERVATIONS |
|---|---|---|---|
| 6648 | 7 | 5 | NO VISIBLE ABNORMALITIES. |
| | | 2 | REDUCED OSSIFICATION OF THE PUBES. |
| 6649 | 6 | 2 | REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, STERNEBRAE NOT OSSIFIED, ISCHIUM NOT OSSIFIED, PUBES NOT OSSIFIED. |
| | | * 1 | REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, REDUCED OSSIFICATION OF THE NASAL BONES, REDUCED OSSIFICATION OF THE HYOID BONE, STERNEBRAE NOT OSSIFIED, ISCHIUM NOT OSSIFIED, PUBES NOT OSSIFIED. |
| | | 1 | REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, REDUCED OSSIFICATION OF THE THORACIC VERTEBRAL CENTRUM, STERNEBRAE NOT OSSIFIED, ISCHIUM NOT OSSIFIED, PUBES NOT OSSIFIED. |
| | | 1 | STERNEBRAE NOT OSSIFIED, REDUCED OSSIFICATION OF THE ISCHIUM, PUBES NOT OSSIFIED. |
| | | 1 | REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, REDUCED OSSIFICATION OF THE THORACIC VERTEBRAL CENTRUM, STERNEBRAE NOT OSSIFIED, REDUCED OSSIFICATION OF THE ISCHIUM, PUBES NOT OSSIFIED. |
| 6650 | 11 | 8 | NO VISIBLE ABNORMALITIES. |
| | | 2 | REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 | REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES. |
| 6651 | 10 | 2 | NO VISIBLE ABNORMALITIES. |
| | | 3 | REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 | REDUCED OSSIFICATION OF THE INTERPARIETAL BONE, REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 | REDUCED OSSIFICATION OF THE INTERPARIETAL BONE. |
| | | 3 | REDUCED OSSIFICATION OF THE THORACIC VERTEBRAL CENTRUM. |
| 6652 | 11 | 10 | NO VISIBLE ABNORMALITIES. |
| | | 1 | NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA. |

*Some of these findings not commonly encountered.

LITTON BIONETICS, INC.
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TABLE 3 (CONTINUED)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE - 80 PPM

| FEMALE NO. | NO. OF FETUSES EXAMINED | OBSERVATIONS |
|---|---|---|
| 6653 | 10 | 6 NO VISIBLE ABNORMALITIES. |
| | | 1 UNILATERAL RIB 14. |
| | | 1 REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, REDUCED OSSIFICATION OF THE STERNEBRAE, PUBES NOT OSSIFIED. |
| | | 1 NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA. |
| 6654 | 9 | 1 NO VISIBLE ABNORMALITIES. |
| | | 1 REDUCED OSSIFICATION OF THE HYOID BONE, REDUCED OSSIFICATION OF THE STERNEBRAE. |
| | | 1 REDUCED OSSIFICATION OF THE STERNEBRAE, NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, PUBES NOT OSSIFIED. |
| | | 1 HYOID BONE NOT OSSIFIED, REDUCED OSSIFICATION OF THE STERNEBRAE, PUBES NOT OSSIFIED. |
| | | 1 REDUCED OSSIFICATION OF THE STERNEBRAE, PUBES NOT OSSIFIED, REDUCED OSSIFICATION OF THE ISCHIUM. |
| | | 1 STERNEBRAE NOT OSSIFIED, PUBES NOT OSSIFIED, REDUCED OSSIFICATION OF THE ISCHIUM. |
| | | * 1 SUPRAOCCIPITAL BONE NOT OSSIFIED, REDUCED OSSIFICATION OF THE INTERPARIETAL BONE, REDUCED OSSIFICATION OF THE THORACIC VERTEBRAL CENTRA, LUMBAR VERTEBRAL CENTRA NOT OSSIFIED, STERNEBRAE NOT OSSIFIED, REDUCED OSSIFICATION OF THE ISCHIUM, PUBES NOT OSSIFIED. |
| | | 1 REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, REDUCED OSSIFICATION OF THE INTERPARIETAL BONE, HYOID BONE NOT OSSIFIED, REDUCED OSSIFICATION OF THE THORACIC VERTEBRAL CENTRA, REDUCED OSSIFICATION OF THE LUMBAR VERTEBRAL CENTRA, STERNEBRAE NOT OSSIFIED, REDUCED OSSIFICATION OF THE ISCHIUM, PUBES NOT OSSIFIED. |

*Some of these findings not commonly encountered.

TABLE II-D-6 (Continued)

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TABLE 3 (CONTINUED)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE - 80 PPM

| FEMALE NO. | NO. OF FETUSES EXAMINED | | OBSERVATIONS |
|---|---|---|---|
| 6654 (CONTD) | 9 | * 1 | HYOID BONE NOT OSSIFIED, REDUCED OSSIFICATION OF THE INTERPARIETAL BONE, SUPRAOCCIPITAL BONE NOT OSSIFIED, REDUCED OSSIFICATION OF THE THORACIC AND LUMBAR VERTEBRAL CENTRA, STERNEBRAE NOT OSSIFIED, REDUCED OSSIFICATION OF THE ISCHIUM, PUBES NOT OSSIFIED. |
| 6655 | 10 | 2 | NO VISIBLE ABNORMALITIES. |
| | | 5 | REDUCED OSSIFICATION OF THE PUBES. |
| | | 2 | PUBES NOT OSSIFIED. |
| | | 1 | PUBES NOT OSSIFIED, REDUCED OSSIFICATION OF THE STERNEBRAE. |
| 6656 | 11 | 5 | PUBES NOT OSSIFIED, REDUCED OSSIFICATION OF THE STERNEBRAE. |
| | | 5 | REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 | PUBES NOT OSSIFIED. |
| 6657 | 11 | 1 | REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, STERNEBRAE NOT OSSIFIED, ISCHIUM NOT OSSIFIED, PUBES NOT OSSIFIED. |
| | | 6 | PUBES NOT OSSIFIED, REDUCED OSSIFICATION OF THE STERNEBRAE. |
| | | 2 | PUBES NOT OSSIFIED. |
| | | 1 | NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, REDUCED OSSIFICATION OF THE STERNEBRAE, PUBES NOT OSSIFIED. |
| | | 1 | REDUCED OSSIFICATION OF THE PUBES, REDUCED OSSIFICATION OF THE STERNEBRAE. |
| 6658 | 10 | 9 | NO VISIBLE ABNORMALITIES. |
| | | 1 | NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA. |

*Some of these findings not commonly encountered.

LITTON BIONETICS, INC.
PROJECT NO. 10734-05

TABLE 3 (CONTINUED)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE - 80 PPM

| FEMALE NO. | NO. OF FETUSES EXAMINED | OBSERVATIONS |
|---|---|---|
| 6659 | 9 | 1 PUBES NOT OSSIFIED.<br>4 PUBES NOT OSSIFIED, REDUCED OSSIFICATION OF THE STERNEBRAE.<br>2 REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES.<br>1 NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, PUBES NOT OSSIFIED.<br>1 REDUCED OSSIFICATION OF THE HYOID BONE, NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, REDUCED OSSIFICATION OF THE STERNEBRAE, PUBES NOT OSSIFIED. |

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TABLE 3 (CONTINUED)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE - 250 PPM

| FEMALE NO. | NO. OF FETUSES EXAMINED | | OBSERVATIONS |
|---|---|---|---|
| 6665 | 10 | 10 | NO VISIBLE ABNORMALITIES. |
| 6666 | 11 | 11 | NO VISIBLE ABNORMALITIES. |
| 6667 | 8 | 2 | NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, STERNEBRAE NOT OSSIFIED, PUBES NOT OSSIFIED. |
| | | 1 | REDUCED OSSIFICATION OF THE THORACIC VERTEBRAL CENTRA, STERNEBRAE NOT OSSIFIED, PUBES NOT OSSIFIED. |
| | | 1 | REDUCED OSSIFICATION OF THE HYOID BONE, STERNEBRAE NOT OSSIFIED, PUBES NOT OSSIFIED. |
| | | 1 | NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, REDUCED OSSIFICATION OF THE STERNEBRAE, PUBES NOT OSSIFIED. |
| | | 1 | REDUCED OSSIFICATION OF THE STERNEBRAE, PUBES NOT OSSIFIED. |
| | | 1 | STERNEBRAE NOT OSSIFIED, PUBES NOT OSSIFIED. |
| 6668 | 10 | 5 | NO VISIBLE ABNORMALITIES. |
| | | 2 | REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 | UNILATERAL RIB 14. |
| | | 1 | BILATERAL RIB 14, REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 | UNILATERAL RIB 14, REDUCED OSSIFICATION OF THE PUBES. |
| 6669 | 10 | 10 | NO VISIBLE ABNORMALITIES. |
| 6670 | 10 | 8 | NO VISIBLE ABNORMALITIES. |
| | | 2 | REDUCED OSSIFICATION OF THE PUBES. |
| 6671 | 9 | 3 | NO VISIBLE ABNORMALITIES. |
| | | 2 | REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 | REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 | PUBES NOT OSSIFIED, REDUCED OSSIFICATION OF THE STERNEBRAE. |
| | | 1 | REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, REDUCED OSSIFICATION OF THE STERNEBRAE, PUBES NOT OSSIFIED. |
| | | 1 | NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES. |

LITTON BIONETICS, INC.
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TABLE 3 (CONTINUED)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE - 250 PPM

| FEMALE NO. | NO. OF FETUSES EXAMINED | | OBSERVATIONS |
|---|---|---|---|
| 6672 | 8 | 8 | NO VISIBLE ABNORMALITIES. |
| 6673 | 11 | 9 | NO VISIBLE ABNORMALITIES. |
| | | 1 | REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 | BILATERAL RIB 14, REDUCED OSSIFICATION OF THE PUBES. |
| 6675 | 10 | 3 | REDUCED OSSIFICATION OF THE PUBES. |
| | | 3 | PUBES NOT OSSIFIED. |
| | | 1 | REDUCED OSSIFICATION OF THE INTERPARIETAL BONE, REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 | STERNEBRAE NOT OSSIFIED, REDUCED OSSIFICATION OF THE ISCHIUM, PUBES NOT OSSIFIED. |
| | | 1 | REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 | REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES. |
| 6676 | 11 | 8 | NO VISIBLE ABNORMALITIES. |
| | | 1 | BILATERAL RIB 14. |
| | | 1 | NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA. |
| | | 1 | REDUCED OSSIFICATION OF THE STERNEBRAE. |
| 6677 | 9 | 1 | NO VISIBLE ABNORMALITIES. |
| | | 5 | REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 | REDUCED OSSIFICATION OF THE PUBES, REDUCED OSSIFICATION OF THE STERNEBRAE. |
| | | 1 | REDUCED OSSIFICATION OF THE STERNEBRAE. |
| | | 1 | REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES. |

LITTON BIONETICS, INC.
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TABLE 3 (CONTINUED)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE - 250 PPM

| FEMALE NO. | NO. OF FETUSES EXAMINED | OBSERVATIONS |
|---|---|---|
| 6678 | 8 | 2 PUBES NOT OSSIFIED.<br>1 REDUCED OSSIFICATION OF THE PUBES.<br>1 REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES.<br>2 REDUCED OSSIFICATION OF THE STERNEBRAE, PUBES NOT OSSIFIED.<br>1 NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, REDUCED OSSIFICATION OF THE PUBES.<br>1 REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, HYOID BONE NOT OSSIFIED, REDUCED OSSIFICATION OF THE THORACIC VERTEBRAL CENTRA, REDUCED OSSIFICATION OF THE LUMBAR VERTEBRAL CENTRA, NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, REDUCED OSSIFICATION OF THE STERNEBRAE, ISCHIUM NOT OSSIFIED, PUBES NOT OSSIFIED. |
| 6679 | 6 | 6 NO VISIBLE ABNORMALITIES. |
| 6680 | 12 | 1 NO VISIBLE ABNORMALITIES.<br>5 PUBES NOT OSSIFIED.<br>3 REDUCED OSSIFICATION OF THE PUBES.<br>2 PUBES NOT OSSIFIED, REDUCED OSSIFICATION OF THE STERNEBRAE.<br>1 REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, STERNEBRAE NOT OSSIFIED, REDUCED OSSIFICATION OF THE ISCHIUM, PUBES NOT OSSIFIED. |
| 6681 | 11 | 3 STERNEBRAE NOT OSSIFIED, PUBES NOT OSSIFIED, REDUCED OSSIFICATION OF THE ISCHIUM.<br>2 PUBES NOT OSSIFIED, STERNEBRAE NOT OSSIFIED.<br>1 BILATERAL RIB 14, PUBES NOT OSSIFIED, STERNEBRAE NOT OSSIFIED.<br>1 REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES.<br>1 HYOID BONE NOT OSSIFIED, STERNEBRAE NOT OSSIFIED, PUBES NOT OSSIFIED. |

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TABLE 3 (CONTINUED)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE - 250 PPM

| FEMALE NO. | NO. OF FETUSES EXAMINED | OBSERVATIONS |
|---|---|---|
| 6681 (CONTD) | 11 | 1 STERNEBRAE NOT OSSIFIED, UNILATERAL RIB 14, REDUCED OSSIFICATION OF THE ISCHIUM, PUBES NOT OSSIFIED. |
| | | 1 STERNEBRAE NOT OSSIFIED, BILATERAL RIB 14, REDUCED OSSIFICATION OF THE ISCHIUM, PUBES NOT OSSIFIED. |
| | | 1 REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE ISCHIUM, PUBES NOT OSSIFIED. |
| 6682 | 10 | 4 REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES. |
| | | 3 REDUCED OSSIFICATION OF THE STERNEBRAE, PUBES NOT OSSIFIED. |
| | | 1 REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, REDUCED OSSIFICATION OF THE STERNEBRAE, PUBES NOT OSSIFIED. |
| | | 1 STERNEBRAE NOT OSSIFIED, REDUCED OSSIFICATION OF THE ISCHIUM, PUBES NOT OSSIFIED. |
| 6683 | 12 | 1 NO VISIBLE ABNORMALITIES. |
| | | 6 REDUCED OSSIFICATION OF THE PUBES. |
| | | 3 PUBES NOT OSSIFIED. |
| | | 2 REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES. |
| 6684 | 11 | 11 NO VISIBLE ABNORMALITIES. |

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TABLE 3 (CONTINUED)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE - 750 PPM

| FEMALE NO. | NO. OF FETUSES EXAMINED | | OBSERVATIONS |
|---|---|---|---|
| 6690 | 10 | 9 | NO VISIBLE ABNORMALITIES. |
| | | 1 | UNILATERAL RIB 14. |
| 6691 | 13 | 8 | NO VISIBLE ABNORMALITIES. |
| | | 1 | BILATERAL RIB 14. |
| | | 3 | REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 | NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA. |
| 6692 | 8 | 8 | NO VISIBLE ABNORMALITIES. |
| 6693 | 12 | 7 | NO VISIBLE ABNORMALITIES. |
| | | 3 | UNILATERAL RIB 14. |
| | | 2 | BILATERAL RIB 14. |
| 6694 | 8 | 4 | NO VISIBLE ABNORMALITIES. |
| | | 1 | BILATERAL RIB 14. |
| | | 1 | REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 | NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA. |
| | | 1 | UNILATERAL RIB 14, REDUCED OSSIFICATION OF THE INTERPARIETAL BONE, REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE. |
| 6695 | 10 | 10 | NO VISIBLE ABNORMALITIES. |
| 6696 | 11 | 8 | NO VISIBLE ABNORMALITIES. |
| | | 1 | UNILATERAL RIB 14. |
| | | 1 | NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA. |
| | | 1 | REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES. |

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TABLE 3 (CONTINUED)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE - 750 PPM

| FEMALE NO. | NO. OF FETUSES EXAMINED | | OBSERVATIONS |
|---|---|---|---|
| 6697 | 11 | 8 | NO VISIBLE ABNORMALITIES. |
| | | 2 | NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA. |
| | | * 1 | STERNEBRAE MALALIGNED. |
| 6698 | 11 | 8 | NO VISIBLE ABNORMALITIES. |
| | | 2 | NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA. |
| | | 1 | REDUCED OSSIFICATION OF THE PUBES. |
| 6699 | 10 | 6 | NO VISIBLE ABNORMALITIES. |
| | | 3 | REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 | NON-FUSED OSSIFICATION CENTERS OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES. |
| 6700 | 10 | 1 | REDUCED OSSIFICATION OF THE HYOID BONE, STERNEBRAE NOT OSSIFIED, ISCHIUM NOT OSSIFIED, PUBES NOT OSSIFIED. |
| | | 3 | REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, STERNEBRAE NOT OSSIFIED, REDUCED OSSIFICATION OF THE ISCHIUM, PUBES NOT OSSIFIED. |
| | | 1 | REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, REDUCED OSSIFICATION OF THE HYOID BONE, REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE ISCHIUM, PUBES NOT OSSIFIED. |
| | | 1 | REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, STERNEBRAE NOT OSSIFIED, PUBES NOT OSSIFIED. |
| | | 1 | REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, STERNEBRAE NOT OSSIFIED, BILATERAL RIB 14, ISCHIUM NOT OSSIFIED, PUBES NOT OSSIFIED. |
| | | 1 | REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, STERNEBRAE NOT OSSIFIED, BILATERAL RIB 14, PUBES NOT OSSIFIED. |
| | | 1 | REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, REDUCED OSSIFICATION OF THE HYOID BONE, STERNEBRAE NOT OSSIFIED, REDUCED OSSIFICATION OF THE ISCHIUM, PUBES NOT OSSIFIED. |

*Some of these findings not commonly encountered.

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TABLE 3 (CONTINUED)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE - 750 PPM

| FEMALE NO. | NO. OF FETUSES EXAMINED | | OBSERVATIONS |
|---|---|---|---|
| 6700 (CONTD) | 10 | 1 | REDUCED OSSIFICATION OF THE HYOID BONE, REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, STERNEBRAE NOT OSSIFIED, PUBES NOT OSSIFIED, ISCHIUM NOT OSSIFIED. |
| 6701 | 8 | 4 | NO VISIBLE ABNORMALITIES. |
| | | 2 | REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 | REDUCED OSSIFICATION OF THE HYOID BONE, REDUCED OSSIFICATION OF THE STERNEBRAE, UNILATERAL RIB 14, PUBES NOT OSSIFIED. |
| | | 1 | REDUCED OSSIFICATION OF THE HYOID BONE, REDUCED OSSIFICATION OF THE STERNEBRAE, UNILATERAL RIB 14, REDUCED OSSIFICATION OF THE PUBES. |
| 6702 | 9 | 2 | STERNEBRAE NOT OSSIFIED, PUBES NOT OSSIFIED. |
| | | 1 | REDUCED OSSIFICATION OF THE STERNEBRAE. |
| | | 1 | REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 | REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, STERNEBRAE NOT OSSIFIED, REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 | REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, STERNEBRAE NOT OSSIFIED, PUBES NOT OSSIFIED. |
| | | 1 | REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, STERNEBRAE NOT OSSIFIED, REDUCED OSSIFICATION OF THE ISCHIUM, REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 | REDUCED OSSIFICATION OF THE HYOID BONE, REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, STERNEBRAE NOT OSSIFIED, PUBES NOT OSSIFIED. |
| | | 1 | NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, STERNEBRAE NOT OSSIFIED, REDUCED OSSIFICATION OF THE PUBES. |

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TABLE 3 (CONTINUED)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE - 750 PPM

| FEMALE NO. | NO. OF FETUSES EXAMINED | OBSERVATIONS |
|---|---|---|
| 6703 | 10 | 7 NO VISIBLE ABNORMALITIES.<br>3 REDUCED OSSIFICATION OF THE PUBES. |
| 6704 | 14 | 1 NO VISIBLE ABNORMALITIES.<br>5 REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES.<br>1 REDUCED OSSIFICATION OF THE STERNEBRAE.<br>5 PUBES NOT OSSIFIED, REDUCED OSSIFICATION OF THE STERNEBRAE.<br>1 REDUCED OSSIFICATION OF THE PUBES.<br>1 STERNEBRAE NOT OSSIFIED. |
| 6706 | 13 | 2 NO VISIBLE ABNORMALITIES<br>4 REDUCED OSSIFICATION OF THE PUBES.<br>1 PUBES NOT OSSIFIED.<br>1 REDUCED OSSIFICATION OF THE STERNEBRAE.<br>2 PUBES NOT OSSIFIED, REDUCED OSSIFICATION OF THE STERNEBRAE.<br>2 REDUCED OSSIFICATION OF THE HYOID BONE, REDUCED OSSIFICATION OF THE STERNEBRAE, PUBES NOT OSSIFIED.<br>1 REDUCED OSSIFICATION OF THE HYOID BONE, NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, STERNEBRAE NOT OSSIFIED, (PORTIONS OF PELVIC GIRDLE AND HIND EXTREMITIES DAMAGED DURING PREPARATION AND HANDLING, UNABLE TO EVALUATE COMPLETELY). |
| 6707 | 4 | 1 NO VISIBLE ABNORMALITIES.<br>1 REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES.<br>1 REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, REDUCED OSSIFICATION OF THE PUBES.<br>1 NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES. |

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TABLE 3 (CONTINUED)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE - 750 PPM

| FEMALE NO. | NO. OF FETUSES EXAMINED | | OBSERVATIONS |
|---|---|---|---|
| 6708 | 8 | 1 | STERNEBRAE NOT OSSIFIED, PUBES NOT OSSIFIED. |
| | | 1 | REDUCED OSSIFICATION OF THE THORACIC VERTEBRAL CENTRA, STERNEBRAE NOT OSSIFIED, PUBES NOT OSSIFIED. |
| | | 2 | REDUCED OSSIFICATION OF THE INTERPARIETAL BONE, REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, HYOID BONE NOT OSSIFIED, REDUCED OSSIFICATION OF THE THORACIC VERTEBRAL CENTRA, REDUCED OSSIFICATION OF THE LUMBAR VERTEBRAL CENTRA, STERNEBRAE NOT OSSIFIED, ISCHIUM NOT OSSSIFIED, PUBES NOT OSSIFIED, METATARSALS NOT OSSIFIED. |
| | | 1 | STERNEBRAE NOT OSSIFIED, REDUCED OSSIFICATION OF THE ISCHIUM, PUBES NOT OSSIFIED. |
| | | 1 | REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, STERNEBRAE NOT OSSIFIED, PUBES NOT OSSIFIED. |
| | | * 1 | REDUCED OSSIFICATION OF THE INTERPARIETAL BONE, REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, REDUCED OSSIFICATION OF THE HYOID BONE, NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, STERNEBRAE NOT OSSIFIED, REDUCED OSSIFICATION OF THE ISCHIUM, PUBES NOT OSSIFIED, METATARSALS NOT OSSIFIED. |
| | | * 1 | REDUCED OSSIFICATION OF THE INTERPARIETAL BONE, REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, REDUCED OSSIFICATION OF THE MAXILLA, HYOID BONE NOT OSSIFIED, REDUCED OSSIFICATION OF THE LUMBAR VERTEBRAL CENTRA, STERNEBRAE NOT OSSIFIED, ISCHIUM NOT OSSIFIED, PUBES NOT OSSIFIED. |
| 6709 | 12 | 2 | REDUCED OSSIFICATION OF THE PUBES. |
| | | 5 | PUBES NOT OSSIFIED, REDUCED OSSIFICATION OF THE STERNEBRAE. |
| | | 1 | UNILATERAL RIB 14, REDUCED OSSIFICATION OF THE STERNEBRAE, PUBES NOT OSSIFIED. |
| | | 1 | REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES. |
| | | 1 | NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES. |

*Some of these findings not commonly encountered.

LITTON BIONETICS, INC.
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TABLE 3 (CONTINUED)

OBSERVATIONS RESULTING FROM EXAMINATION OF CLEARED SPECIMENS

DOSE - 750 PPM

| FEMALE NO. | NO. OF FETUSES EXAMINED | OBSERVATIONS |
|---|---|---|
| 6709 (CONTD) | 12 | 1 REDUCED OSSIFICATION OF THE HYOID BONE, REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, NON-FUSED OSSIFICATION OF THE THORACIC VERTEBRAL CENTRA, REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE ISCHIUM, PUBES NOT OSSIFIED. |
| | | 1 REDUCED OSSIFICATION OF THE SUPRAOCCIPITAL BONE, NON-FUSED OSSIFICATION CENTERS OF THE THORACIC VERTEBRAL CENTRA, REDUCED OSSIFICATION OF THE STERNEBRAE, REDUCED OSSIFICATION OF THE PUBES. |

PART II - SECTION E

THREE-GENERATION REPRODUCTION IN RATS

DCPD

LBI PROJECT NO. 10734-07


## SUMMARY

Two groups of 10 male and 20 female albino rats each (F0 generation) were given dicyclopentadiene (DCPD) in the diet at 80 or 750 ppm, with a similar group maintained as controls. The rats in each group were mated twice to produce the F1a and F1b litters.

The same number of F1b pups per sex per group were likewise mated to produce F2a and F2b pups, and the F2b animals were maintained to produce F3a and F3b litters. Analyses of the diet mixes indicated 87 and 92% of the desired concentrations were achieved, on the average, for the low- and high-dose levels, respectively.

For each generation in each group there were determined fertility indices, live-to-total pup ratios, mean litter sizes, pup survival indices and mean body weights at Day 4 post partum and at weaning. Gross necropsy observations were made of representative pups of all Fa litters, of the F3b litters, and of the parent rats. Body weights and food consumption were determined for parent rats at various intervals, also.

It is concluded no deleterious effects on reproductive processes or general condition of the rats were produced by DCPD in this study. Likewise, no evidence of dose-related teratologic effect was seen.


## 1. OBJECTIVE

The purpose of this study was to evaluate the effects of the test material, dicyclopentadiene (DCPD), on the reproductive processes of the albino rat through three consecutive generations, with two matings per generation. Test material was given in the diet at two concentrations.

## 2. MATERIAL

Refer to Part II - Section A.

## 3. EXPERIMENTAL DESIGN

Weanling albino rats [CRL:COB (SD) BR] were obtained from the Charles River Breeding Laboratories, Inc., Portage, Michigan, and acclimated to laboratory conditions for 11 days at the Falls Church facility of the Department of Toxicology. They were started on study on May 22, 1977, after being randomly assigned to groups as follows:

| Group Number | Number of Animals | | Dietary Concentration (ppm) |
|---|---|---|---|
| | Male | Female | |
| 1 | 10 | 20 | 0 (Control) |
| 2 | 10 | 20 | 80 |
| 3 | 10 | 20 | 750 |

These rats, the FO generation, were identified by ear tags and cage cards, and housed individually (except when mating) in shoe box cages on AB-SORB-DRI bedding. Food and water were provided ad libitum.

Fresh diets were prepared weekly by adding the appropriate quantity of DCPD, dissolved in 300 ml of corn oil, to 10 kg of Purina Laboratory Chow meal, and mixing for at least 15 minutes in a twin shell blender. Control diet was mixed with corn oil in the same fashion.

Because of the possible loss from the diet through volatility of DCPD, samples of each week's dietary batch were analyzed by the LBI Chemistry Department. The analytical method employed gas-liquid chromatography and was supplied by the sponsor and developed at LBI.

Seven weeks after starting on compound the rats were mated for the first time. For this purpose each male was caged with two females of its dose group for two weeks. At the end of this time the rats were returned to their respective cages and the females were allowed to litter.

One week after weaning the first litters (F1a pups), the FO parents were remated, each male with a different pair of females from that of the first mating. One week after weaning the second litters (F1b pups), parent FO rats were killed and a gross necropsy was performed on each.

One male and two female F1b pups from each litter (where possible) were selected to be the parents for the next generation, and were caged, fed and watered just as the FO rats were maintained. When the F1b rats were approximately 100 days of age, they were mated to produce the F2a litters, and subsequently the F2b pups. Selected F2b pups in turn were used to produce the F3a and F3b litters.

At 4 and at 8-9 weeks, parent rats were weighed and their food consumption was estimated. These measurements were made again shortly before each mating. Daily observations were made of parent rats for mortality and general condition.

3. EXPERIMENTAL DESIGN (Continued)

For each litter the following observations were made:

Gross abnormalities of pups
Numbers of live and dead pups, and their mean body weight by sex at birth
Number per sex at Day 4 of lactation
Number per sex and body weights at Day 21 of lactation (weaning)

At Day 4 each litter was reduced to eight total pups, four per sex if possible. At weaning, gross necropsies were performed on approximately one-third of the first litters from all three generations, and on one-third of the F3b litters.

4. RESULTS

A. Diet Concentrations Found

Results of the DCPD weekly feed analyses are presented in a separate report from the LBI Department of Chemistry. Overall, the results showed a 69.3 ppm (87%) average value for the 80-ppm diet level, and 693 ppm (92%) for the 750-ppm diet level. Considering the volatility of DCPD, these results are thought to indicate reasonable achievement of the intended dietary concentrations.

B. First Generation (F0 Parents, F1a and F1b Offspring)

Detailed litter data, mean parent body weights and food consumption figures, and pertinent necropsy observations have been presented in numbered Tables of the Appendix for this and succeeding generations. Summaries of reproductive data have been incorporated in the text in lettered tables.

One F0 female (No. 5196, 80 ppm) was found dead at Week 28, but all other F0 rats survived their portion of the study in generally good condition. Body weight means and daily food consumption means are presented in Appendix Tables 1 and 2, respectively. Data for compound-treated groups were entirely comparable to control figures at each interval.

Table 3 gives litter data for F1a pups, and these are summarized in Text Table A. There is nothing in these data to distinguish DCPD-treated groups from control rats. Likewise, observations of the pups (Table 4) indicate nothing of importance in the three groups. One pup in a 80-ppm litter had an opaque left eye, and one pup in a 750-ppm litter had a crooked tail. Such isolated findings are not meaningful. Table 5 gives necropsy findings of F1a pups. No compound-related findings were reported.

TABLE II-E-7

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE A

SUMMARY OF FIRST GENERATION - FIRST MATING (F1a)

| | DOSE (PPM) 0 | | 80 | | 750 | |
|---|---|---|---|---|---|---|
| | RATIO | PERCENT | RATIO | PERCENT | RATIO | PERCENT |
| INDICES | | | | | | |
| Male fertility (males producing litter/mated) | 10/10 | 100 | 10/10 | 100 | 9/10 | 90 |
| Female fertility (females producing litter/mated) | 19/20 | 95 | 18/20 | 90 | 16/20 | 80 |
| Gestation (females live litter/pregnant) | 19/19 | 100 | 18/18 | 100 | 16/16 | 100 |
| Newborn viability (live pups/total pups) | 209/211 | 99 | 210/212 | 99 | 198/200 | 99 |
| Pup viability (pups Day 4/pups Day 0) | 205/209 | 98 | 207/210 | 99 | 194/198 | 98 |
| Lactation (pups Day 21/pups Day 4)[a] | 140/140 | 100 | 140/140 | 100 | 128/128 | 100 |
| PUP WEIGHT IN GRAMS (MEAN ± SD) | | | | | | |
| Day 0 males | 7 ± 0.66 | | 7 ± 0.68 | | 7 ± 0.60 | |
| Day 0 females | 7 ± 0.75 | | 6 ± 0.59 | | 6 ± 0.72 | |
| Day 21 males | 52 ± 5.4 | | 50 ± 5.6 | | 48 ± 5.1 | |
| Day 21 females | 49 ± 4.6 | | 46 ± 5.1 | | 46 ± 4.7 | |
| Sex ratio offspring (M/F) Day 0 | 110/101 | | 111/101 | | 94/106 | |
| Live pups per litter (Mean ± SD) | 11 ± 3.7 | | 12 ± 2.8 | | 12 ± 2.3 | |

[a]After litters reduced.

TABLE II-E-8

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE B

SUMMARY OF FO GENERATION - SECOND MATING - F1b

| | DOSE (PPM) 0 | | 80 | | 750 | |
|---|---|---|---|---|---|---|
| | RATIO | PERCENT | RATIO | PERCENT | RATIO | PERCENT |
| **INDICES** | | | | | | |
| Male fertility (males producing litter/mated) | 10/10 | 100 | 10/10 | 100 | 10/10 | 100 |
| Female fertility (females producing litter/mated) | 18/20 | 90 | 18/20 | 90 | 19/20 | 95 |
| Gestation (females live litter/pregnant) | 18/18 | 100 | 18/18 | 100 | 19/19 | 100 |
| Newborn viability (live pups/total pups) | 199/201 | 99 | 196/202 | 97 | 229/231 | 99 |
| Pup viability (pups Day 4/pups Day 0) | 193/199 | 97 | 187/196 | 95 | 216/229 | 94 |
| Lactation (pups Day 21/pups Day 4)[a] | 128/132 | 97 | 128/132 | 97 | 139/145 | 96 |
| **PUP WEIGHT IN GRAMS (MEAN ± SD)** | | | | | | |
| Day 0 males | 6 ± 1.1 | | 5 ± 1.6 | | 6 ± 0.61 | |
| Day 0 females | 6 ± 1.1 | | 5 ± 1.6 | | 6 ± 0.61 | |
| Day 21 males | 46 ± 7.8 | | 47 ± 8.8 | | 42 ± 6.8 | |
| Day 21 females | 44 ± 6.9 | | 44 ± 8.2 | | 40 ± 5.7 | |
| Sex ratio offspring (M/F) Day 0 | 100/101 | | 94/108 | | 108/123 | |
| Live pups per litter (Mean ± SD) | 11 ± 3.5 | | 11 ± 3.7 | | 12 ± 3.2 | |

[a]After litters reduced.

4. RESULTS (Continued)

Tables 6 and 7 present, respectively, litter data and pup observations for the F1b offspring, with the litter data summarized in Table B. All groups were comparable to one another with respect to both litter data and pup observations. Again, the single instance of a pup in the 80-ppm group with an abnormality (a deformed hind foot) cannot be considered meaningful.

Necropsy findings of F0 parents (Table 8) indicate no dose-related changes.

C. Second Generation (F1b Parents, F2a and F2b Offspring)

Tables 9 and 10 show mean body weights and daily food consumption figures, respectively, for F1b parent rats. At all intervals, rats in the compound-treated groups weighed as much as or more than the controls, except for the 80-ppm females at 20 weeks (just prior to the second mating). In this instance, the slightly lower mean body weight was not statistically significant. Similarly, food consumption means were comparable among the groups, except that in both males and females of the 750-ppm group, the reductions at 20 weeks in food intake were statistically significant ($p<0.05$, Student's t-test).

F2a litter data, pup general observations and pup necropsy observations are presented in Tables 11, 12 and 13, respectively; litter data are summarized in Table C. Except for reduced female fertility in the 750-ppm group (discussed below) litter data in all groups were comparable. Similarly, no general or necropsy findings of significance were recorded, but one male pup in the 80-ppm group was found to have had hydrocephalus.

F2b litter data and pup observations are presented in Tables 14 and 15, respectively, with litter data summarized in Table D. General pup observations were unexceptional, but, as with the F2a litters, fertility in the 750-ppm females was reduced. However, neither the 70% figure for the F2a's nor the 85% for the F2b's was statistically significantly different (Chi-square test) from the control index (95% in each instance). In addition, it may be noted that male No. 7349 in the 750-ppm group failed to sire a litter in either mating, and could thus be responsible for the lack of litters from two of six and two of three non-productive females at the first and second matings, respectively. It is therefore concluded that the apparently lowered fertility of the high-dose females at each mating is not related to compound administration.

At necropsy, no gross lesions were found in the F1b parent rats.

TABLE II-E-9

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE C

SUMMARY OF F1b GENERATION - FIRST MATING - F2a

| | DOSE (PPM) 0 | | 80 | | 750 | |
|---|---|---|---|---|---|---|
| | RATIO | PERCENT | RATIO | PERCENT | RATIO | PERCENT |
| **INDICES** | | | | | | |
| Male fertility (males producing litter/mated) | 10/10 | 100 | 10/10 | 100 | 9/10 | 90 |
| Female fertility (females producing litter/mated) | 19/20 | 95 | 18/20 | 90 | 14/20 | 70 |
| Gestation (females live litter/ pregnant) | 19/19 | 100 | 18/18 | 100 | 14/14 | 100 |
| Newborn viability (live pups/total pups) | 241/242 | 100 | 209/216 | 97 | 162/162 | 100 |
| Pup viability (pups Day 4/pups Day 0) | 237/241 | 98 | 196/209 | 94 | 159/162 | 98 |
| Lactation (pups Day 21/pups Day 4)[a] | 147/150 | 98 | 135/139 | 97 | 107/109 | 98 |
| **PUP WEIGHT IN GRAMS (MEAN ± S D)** | | | | | | |
| Day 0 males | 6 ± 0.90 | | 6 ± 0.84 | | 6 ± 0.83 | |
| Day 0 females | 6 ± 0.79 | | 6 ± 0.92 | | 6 ± 0.95 | |
| Day 21 males | 44 ± 5.9 | | 46 ± 6.4 | | 44 ± 5.5 | |
| Day 21 females | 41 ± 5.3 | | 43 ± 6.6 | | 42 ± 5.3 | |
| Sex ratio offspring (M/F) Day 0 | 111/131[b] | | 94/122[b] | | 84/78[b] | |
| Live pups per litter (Mean ± SD) | 13 ± 2.6 | | 12 ± 2.7 | | 12 ± 2.7 | |

[a]After litters reduced.
[b]Some pups mis-sexed.

4. RESULTS (Continued)

D. Third Generation (F2b Parents, F3a and F3b Offspring)

Tables 16 and 17 show, respectively, body weights and food consumption data for the F2b parents. No meaningful differences between groups at the various intervals were seen with respect to these observations.

Litter data (Table 18), pup observations (Table 19) and pup necropsy observations (Table 20) for the F3a offspring are appended. The litter data are summarized in Table E. There was nothing in these records to suggest a compound-related effect, and although female fertility was only 80% and 83% in the DCPD-treated groups, control fertility was worse, only 65%.

Tables 21, 22 and 23 show, respectively, the litter observations, pup general observations and pup necropsy findings for the F3b offspring. Table F summarizes the litter data, and it may be seen that all groups were generally comparable with respect to the various indices. Female fertility percentages were 85, 80 and 83 for the controls, 80- and 750-ppm groups, respectively. The differences are not meaningful. A slight reduction in mean pup weight at weaning (compared to controls) was noted in each compound-treated group, that for the high-dose female pups being statistically significant ($p<0.05$; Student's t-test). The low-dose female pup weight, while numerically the same as that of the 750-ppm weanlings, was not statistically significant. Since mean weanling pup weights in the other generations (Tables A, B, C, D and E) were not appreciably different among the groups involved, it is felt that the F3b differences are fortuitous.

Pup general observations and necropsy observations showed nothing to indicate compound-related effects. Similarly, necropsy findings of the F2b parents (Table 24) were unexceptional.

Thirty days after transmittal of this report, original data from the Department of Toxicology will be transferred to the LBI Archivist, 5516 Nicholson Lane, Kensington, Maryland, for distribution to the proper repositories. A copy of this report was reviewed by the LBI Quality Assurance Unit.

TABLE II-E-10

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE D

SUMMARY OF F1b GENERATION - SECOND MATING - F2b

| | DOSE (PPM) 0 | | 80 | | 750 | |
|---|---|---|---|---|---|---|
| | RATIO | PERCENT | RATIO | PERCENT | RATIO | PERCENT |
| INDICES | | | | | | |
| Male fertility (males producing litter/mated) | 10/10 | 100 | 10/10 | 100 | 9/10 | 90 |
| Female fertility (females producing litter/mated) | 19/20 | 95 | 19/20 | 95 | 17/20 | 85 |
| Gestation (females live litter/ pregnant) | 19/19 | 100 | 19/19 | 100 | 17/17 | 100 |
| Newborn viability (live pups/total pups) | 263/266 | 99 | 286/287 | 100 | 230/235 | 98 |
| Pup viability (pups Day 4/pups Day 0) | 250/263 | 95 | 280/286 | 98 | 214/230 | 93 |
| Lactation (pups Day 21/pups Day 4)[a] | 149/151 | 99 | 149/152 | 98 | 127/128 | 99 |
| PUP WEIGHT IN GRAMS (MEAN ± SD) | | | | | | |
| Day 0 males | 6 ± 0.84 | | 6 ± 0.63 | | 6 ± 0.54 | |
| Day 0 females | 6 ± 0.75 | | 6 ± 0.52 | | 6 ± 0.66 | |
| Day 21 males | 45 ± 6.8 | | 48 ± 7.2 | | 51 ± 6.6 | |
| Day 21 females | 43 ± 7.4 | | 46 ± 6.6 | | 48 ± 6.6 | |
| Sex ratio offspring (M/F) Day 0 | 121/145 | | 146/141 | | 119/116 | |
| Live pups per litter (Mean ± SD) | 14 ± 2.5 | | 15 ± 1.6 | | 14 ± 1.4 | |

[a]After litters reduced.

TABLE II-E-11

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE E

SUMMARY OF F2b GENERATION - FIRST MATING - F3a

| | DOSE (PPM) 0 | | 80 | | 750 | |
|---|---|---|---|---|---|---|
| | RATIO | PERCENT | RATIO | PERCENT | RATIO | PERCENT |
| INDICES | | | | | | |
| Male fertility (males producing litter/mated) | 9/10 | 90 | 10/10 | 100 | 8/9 | 89 |
| Female fertility (females producing litter/mated) | 13/20 | 65 | 16/20 | 80 | 15/18 | 83 |
| Gestation (females live litter/ pregnant) | 13/13 | 100 | 16/16 | 100 | 15/15 | 100 |
| Newborn viability (live pups/total pups) | 162/163 | 99 | 195/196 | 99 | 204/206 | 99 |
| Pup viability (pups Day 4/pups Day 0) | 156/162 | 96 | 187/195 | 96 | 201/204 | 99 |
| Lactation (pups Day 21/pups Day 4)[a] | 92/100 | 92 | 118/118 | 100 | 117/120 | 98 |
| PUP WEIGHT IN GRAMS (MEAN ± SD) | | | | | | |
| Day 0 males | 6 ± 0.77 | | 6 ± 1.3 | | 7 ± 0.82 | |
| Day 0 females | 7 ± 0.80 | | 5 ± 1.2 | | 6 ± 0.80 | |
| Day 21 males | 46 ± 5.8 | | 46 ± 4.7 | | 48 ± 6.1 | |
| Day 21 females | 45 ± 7.6 | | 42 ± 4.2 | | 45 ± 5.7 | |
| Sex ratio offspring (M/F) Day 0 | 81/82 | | 103/93 | | 108/98 | |
| Live pups per litter (Mean ± SD) | 12 ± 3.3 | | 12 ± 3.9 | | 14 ± 2.0 | |

[a]After litters reduced.

TABLE II-E-12

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE F

SUMMARY OF F2b GENERATION - SECOND MATING - F3b

| | DOSE (PPM) 0 | | 80 | | 750 | |
|---|---|---|---|---|---|---|
| | RATIO | PERCENT | RATIO | PERCENT | RATIO | PERCENT |
| INDICES | | | | | | |
| Male fertility (males producing litter/mated) | 9/10 | 90 | 10/10 | 100 | 9/9 | 100 |
| Female fertility (females producing litter/mated) | 17/20 | 85 | 16/20 | 80 | 15/18 | 83 |
| Gestation (females live litter/pregnant) | 17/17 | 100 | 16/16 | 100 | 15/15 | 100 |
| Newborn viability (live pups/total pups) | 211/215 | 98 | 206/213 | 97 | 188/191 | 98 |
| Pup viability (pups Day 4/pups Day 0) | 207/211 | 98 | 206/206 | 100 | 185/188 | 98 |
| Lactation (pups Day 21/pups Day 4)[a] | 134/135 | 99 | 127/128 | 99 | 114/117 | 97 |
| PUP WEIGHT IN GRAMS (MEAN ± SD) | | | | | | |
| Day 0 males | 6 ± 0.79 | | 7 ± 0.98 | | 7 ± 0.83 | |
| Day 0 females | 6 ± 0.64 | | 6 ± 0.87 | | 6 ± 0.83 | |
| Day 21 males | 49 ± 10 | | 44 ± 11 | | 43 ± 11 | |
| Day 21 females | 48 ± 9.3 | | 41 ± 12 | | 41 ± 9.5* | |
| Sex ratio offspring (M/F) Day 0 | 93/122 | | 107/106 | | 93/98 | |
| Live pups per litter (Mean ± SD) | 12 ± 2.7 | | 13 ± 2.5 | | 13 ± 2.8 | |

[a]After litters reduced.
*$p<0.05$ compared to control: Student's t-test.

5. CONCLUSION

Dietary administration of dicyclopentadiene (DCPD) at nominal concentrations of 80 and 750 ppm to three successive generations of male and female albino rats had no deleterious effects on reproductive performance or general condition of the animals, in comparison to performance of control rats maintained concurrently. Analyses of the diet throughout the study indicated actual DCPD concentrations averaged 87 and 92% of those intended for the 80- and 750-ppm levels, respectively. No evidence of dose-related teratogenic effect was seen in pups of any generation.

Submitted by:

Carter D. Johnston, Ph.D. Date
Senior Toxicologist
Department of Toxicology

Robert P. Beliles, Ph.D. 7/30/79 Date
Director
Department of Toxicology

Reviewed by:

Robert J. Weir, Ph.D. 7/30/79 Date
Vice President

TABLE II-E-13

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 1

MEAN BODY WEIGHTS (G) OF FO RATS

| DOSE (PPM) | SEX | | WEEK 4 | 8 | 11 | 19 |
|---|---|---|---|---|---|---|
| 0 | M | MEAN | 313 | 413 | 447 | 517 |
| | | SD | 22 | 40 | 39 | 40 |
| | | SE | 7.1 | 13 | 12 | 13 |
| | | N | 10 | 10 | 10 | 10 |
| 80 | M | MEAN | 319 | 426 | 465 | 538 |
| | | SD | 15 | 24 | 28 | 38 |
| | | SE | 4.6 | 7.5 | 9.0 | 12 |
| | | N | 10 | 10 | 10 | 10 |
| 750 | M | MEAN | 312 | 416 | 456 | 529 |
| | | SD | 16 | 32 | 34 | 52 |
| | | SE | 5.2 | 10 | 11 | 17 |
| | | N | 10 | 10 | 10 | 10 |
| 0 | F | MEAN | 199 | 237 | [illegible] | 290 |
| | | SD | 10 | 17 | [illegible] | 23 |
| | | SE | 2.2 | 3.9 | 4.9 | 5.1 |
| | | N | 20 | 20 | 20 | 20 |
| 80 | F | MEAN | 206 | 249 | 275 | 295 |
| | | SD | 18 | 27 | 46 | 32 |
| | | SE | 4.1 | 6.0 | 10 | 7.1 |
| | | N | 20 | 20 | 20 | 20 |
| 750 | F | MEAN | 206 | 242 | 264 | 293 |
| | | SD | 20 | 36 | 27 | 31 |
| | | SE | 4.4 | 8.0 | 6.1 | 7.0 |
| | | N | 20 | 20 | 20 | 20 |

TABLE II-E-14

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 2

MEAN FOOD CONSUMPTION (G) IN FO RATS

| DOSE (PPM) | SEX | | WEEK 4 | 8 | 11 | 19 |
|---|---|---|---|---|---|---|
| 0 | M | MEAN | 22 | 22 | 21 | 19 |
| | | SD | 8.4 | 3.0 | 3.0 | 2.3 |
| | | SE | 3.0 | 1.0 | 0.99 | 0.77 |
| | | N | 8 | 10 | 9 | 9 |
| 80 | M | MEAN | 24 | 23 | 22 | 21 |
| | | SD | 3.0 | 2.2 | 2.4 | 4.0 |
| | | SE | 0.96 | 0.74 | 0.75 | 1.3 |
| | | N | 10 | 9 | 10 | 10 |
| 750 | M | MEAN | 20 | 23 | 22 | 20 |
| | | SD | 4.2 | 2.4 | 2.7 | 3.0 |
| | | SE | 1.3 | 0.81 | 0.86 | 0.99 |
| | | N | 10 | 9 | 10 | 9 |
| 0 | F | MEAN | 18 | 19 | 16 | 18 |
| | | SD | 3.8 | 5.4 | 4.1 | 2.6 |
| | | SE | 0.84 | 1.2 | 0.91 | 0.64 |
| | | N | 20 | 19 | 20 | 17 |
| 80 | F | MEAN | 18 | 18 | 16 | 19 |
| | | SD | 3.3 | 2.4 | 3.3 | 3.7 |
| | | SE | 0.74 | 0.55 | 0.74 | 0.85 |
| | | N | 20 | 19 | 20 | 19 |
| 750 | F | MEAN | 16 | 19 | 16 | 19 |
| | | SD | 3.8 | 4.7 | 4.9 | 4.2 |
| | | SE | 0.87 | 1.1 | 1.1 | 0.95 |
| | | N | 19 | 19 | 20 | 20 |

# TABLE II-E-15

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 3

RESULTS OF FIRST GENERATION - FIRST MATING (F1a)

DOSE - 0 PPM (CONTROL)

| | | DAY 0 | | | | | | DAY 4 | | | | | | DAY 21 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | MEAN PUP WEIGHT (G) | | | | | | LITTER REDUCED | | | | | | MEAN PUP WEIGHT (G) | |
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX MALE | FEMALE | MALE | FEMALE | DEATHS DAY 1-4 | LIVE PUPS | SEX MALE | FEMALE | MALE | FEMALE | DEATHS DAY 5-21 | LIVE PUPS | SEX MALE | FEMALE | MALE | FEMALE |
| 5150 | 5140 | 13 | 0 | 4 | 9 | 7 | 7 | 0 | 13 | 4 | 9 | 4 | 4 | 0 | 8 | 4 | 4 | 48 | 47 |
| 5151 | | 14 | 0 | 8 | 6 | 7 | 7 | 0 | 14 | 8 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 58 | 53 |
| 5152 | 5141 | 11 | 1 | 9 | 3 | 8 | 7 | 0 | 11 | 9 | 2 | 6 | 2 | 0 | 8 | 6 | 2 | 51 | 47 |
| 5153 | | 9 | 0 | 5 | 4 | 8 | 8 | 0 | 9 | 5 | 4 | 4 | 4 | 0 | 8 | 4 | 4 | 57 | 54 |
| 5154 | 5142 | 14 | 0 | 6 | 8 | 6 | 6 | 0 | 14 | 6 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 47 | 43 |
| 5155 | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 5156 | 5143 | 11 | 0 | 6 | 5 | 7 | 7 | 0 | 11 | 6 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 49 | 46 |
| 5157 | | 15 | 0 | 8 | 7 | 8 | 7 | 0 | 15 | 8 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 54 | 47 |
| 5158 | 5144 | 4 | 0 | 3 | 1 | 7 | 7 | 0 | 4 | 3 | 1 | 3 | 1 | 0 | 4 | 3 | 1 | 64 | 55 |
| 5159 | | 13 | 0 | 5 | 8 | 6 | 6 | 0 | 13 | 5 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 55 | 54 |
| 5160 | 5145 | 14 | 0 | 8 | 6 | 6 | 6 | 0 | 14 | 8 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 48 | 50 |
| 5161 | | 14 | 0 | 7 | 7 | 7 | 7 | 0 | 14 | 7 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 46 | 45 |
| 5162 | 5146 | 9 | 0 | 3 | 6 | 7 | 6 | 0 | 9 | 3 | 6 | 3 | 5 | 0 | 8 | 3 | 5 | 47 | 45 |
| 5163 | | 1 | 1 | 2 | 0 | 7 | - | 0 | 1 | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 55 | - |
| 5164 | 5147 | 9 | 0 | 6 | 3 | 8 | 8 | 1 | 8 | 5 | 3 | 5 | 3 | 0 | 8 | 5 | 3 | 54 | 52 |
| 5165 | | 8 | 0 | 4 | 4 | 8 | 8 | 1 | 7 | 4 | 3 | 4 | 3 | 0 | 7 | 4 | 3 | 58 | 47 |
| 5166 | 5148 | 13 | 0 | 7 | 6 | 7 | 6 | 2 | 11 | 6 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 52 | 50 |
| 5167 | | 13 | 0 | 6 | 7 | 7 | 6 | 0 | 13 | 6 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 55 | 52 |
| 5168 | 5149 | 11 | 0 | 6 | 5 | 7 | 6 | 0 | 11 | 6 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 42 | 41 |
| 5169 | | 13 | 0 | 7 | 6 | 7 | 6 | 0 | 13 | 7 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 57 | 58 |
| TOTAL | | 209 | 2 | 110 | 101 | | | 4 | 205 | 107 | 98 | 74 | 66 | 0 | 140 | 74 | 66 | | |
| MEAN | | 11 | | | | 7 | 7 | | 11 | | | | | | 7 | | | 52 | 49 |
| SD | | 3.7 | | | | 0.66 | 0.75 | | 3.7 | | | | | | | | | 5.4 | 4.6 |
| SE | | 0.84 | | | | 0.40 | 0.18 | | 0.85 | | | | | | | | | 1.2 | 1.1 |
| N | | 19 | | | | 19 | 18 | | 19 | | | | | | | | | 19 | 18 |

TABLE II-E-15 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 3 (CONTINUED)

RESULTS OF FIRST GENERATION - FIRST MATING (F1a)

DOSE - 80 PPM

| | | DAY 0 | | | | | | DAY 4 | | | | | | DAY 21 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE | DEATHS DAY 1-4 | LIVE PUPS | SEX MALE | SEX FEMALE | LITTER REDUCED MALE | LITTER REDUCED FEMALE | DEATHS DAY 5-21 | LIVE PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE |
| 5160 | 5170 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 5181 | | 12 | 1 | 7 | 6 | 7 | 6 | 0 | 12 | 6 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 37 | 34 |
| 5182 | 5171 | 7 | 0 | 2 | 5 | 7 | 6 | 1 | 6 | 2 | 4 | 2 | 4 | 0 | 6 | 2 | 4 | 51 | 46 |
| 5183 | | 11 | 0 | 4 | 7 | 7 | 7 | 0 | 11 | 4 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 45 | 49 |
| 5184 | 5172 | 16 | 0 | 11 | 5 | 6 | 5 | 0 | 16 | 11 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 45 | 40 |
| 5185 | | 15 | 0 | 8 | 7 | 7 | 7 | 0 | 15 | 8 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 54 | 48 |
| 5186 | 5173 | 9 | 0 | 5 | 4 | 7 | 6 | 0 | 9 | 5 | 4 | 4 | 4 | 0 | 8 | 4 | 4 | 52 | 45 |
| 5187 | | 13 | 0 | 7 | 6 | 7 | 6 | 0 | 13 | 7 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 56 | 52 |
| 5188 | 5174 | 16 | 0 | 7 | 9 | 7 | 6 | 0 | 16 | 7 | 9 | 4 | 4 | 0 | 8 | 4 | 4 | 54 | 52 |
| 5189 | | 12 | 0 | 6 | 6 | 8 | 7 | 0 | 12 | 6 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 50 | 46 |
| 5190 | 5175 | 7 | 0 | 5 | 2 | 8 | 7 | 0 | 7 | 5 | 2 | 5 | 2 | 0 | 7 | 5 | 2 | 52 | 47 |
| 5191 | | 14 | 0 | 7 | 7 | 6 | 6 | 0 | 14 | 7 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 56 | 51 |
| 5192 | 5176 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 5193 | | 12 | 0 | 8 | 4 | 7 | 6 | 0 | 12 | 8 | 4 | 4 | 4 | 0 | 8 | 4 | 4 | 42 | 42 |
| 5194 | 5177 | 10 | 0 | 2 | 8 | 7 | 6 | 0 | 10 | 2 | 8 | 2 | 6 | 0 | 8 | 2 | 6 | 47 | 42 |
| 5195 | | 14 | 0 | 10 | 4 | 6 | 6 | 0 | 14 | 10 | 4 | 4 | 4 | 0 | 8 | 4 | 4 | 42 | 42 |
| 5196 | 5178 | 11 | 1 | 10 | 2 | 7 | 7 | 1 | 10 | 8 | 2 | 6 | 2 | 0 | 8 | 6 | 2 | 54 | 53 |
| 5197 | | 8 | 0 | 3 | 5 | 6 | 6 | 1 | 7 | 3 | 4 | 3 | 4 | 0 | 7 | 3 | 4 | 52 | 49 |
| 5198 | 5179 | 11 | 0 | 4 | 7 | 8 | 7 | 0 | 11 | 4 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 57 | 52 |
| 5199 | | 12 | 0 | 5 | 7 | 8 | 7 | 0 | 12 | 5 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 48 | 42 |
| TOTAL | | 210 | 2 | 111 | 101 | | | 3 | 207 | 108 | 99 | 70 | 70 | 0 | 140 | 70 | 70 | | |
| MEAN | | 12 | | | | 7 | 6 | | 12 | | | | | | 8 | | | 50 | 46 |
| SD | | 2.8 | | | | 0.68 | 0.59 | | 3.0 | | | | | | | | | 5.6 | 5.1 |
| SE | | 0.65 | | | | 0.16 | 0.14 | | 0.70 | | | | | | | | | 1.3 | 1.2 |
| N | | 18 | | | | 18 | 18 | | 18 | | | | | | | | | 18 | 18 |

TABLE II-E-15 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 3 (CONTINUED)

RESULTS OF FIRST GENERATION - FIRST MATING (F1a)

*DOSE - 750 PPM*

| | | DAY 0 | | | | | | DAY 4 | | | | | | DAY 21 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE | DEATHS DAY 1-4 | LIVE PUPS | SEX MALE | SEX FEMALE | LITTER REDUCED MALE | LITTER REDUCED FEMALE | DEATHS DAY 5-21 | LIVE PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE |
| 5210 | 5200 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 5211 | | 11 | 0 | 5 | 6 | 6 | 6 | 0 | 11 | 5 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 44 | 49 |
| 5212 | 5201 | 10 | 0 | 5 | 5 | 7 | 6 | 0 | 10 | 5 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 45 | 44 |
| 5213 | | 9 | 1 | 5 | 5 | 7 | 6 | 0 | 9 | 5 | 4 | 4 | 4 | 0 | 8 | 4 | 4 | 44 | 40 |
| 5214 | 5202 | 9 | 0 | 3 | 6 | 7 | 7 | 0 | 9 | 3 | 6 | 3 | 5 | 0 | 8 | 3 | 5 | 50 | 44 |
| 5215 | | 16 | 0 | 8 | 8 | 7 | 6 | 0 | 16 | 8 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 49 | 45 |
| 5216 | 5203 | 10 | 0 | 5 | 5 | 6 | 6 | 2 | 8 | 4 | 4 | 4 | 4 | 0 | 8 | 4 | 4 | 50 | 48 |
| 5217 | | 12 | 0 | 7 | 5 | 7 | 7 | 0 | 12 | 7 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 45 | 43 |
| 5218 | 5204 | 13 | 0 | 5 | 8 | 7 | 7 | 0 | 13 | 5 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 49 | 44 |
| 5219 | | 14 | 0 | 7 | 7 | 5 | 5 | 1 | 13 | 6 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 37 | 37 |
| 5220 | 5205 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 5221 | | 11 | 0 | 3 | 8 | 7 | 7 | 0 | 11 | 3 | 8 | 3 | 5 | 0 | 8 | 3 | 5 | 54 | 50 |
| 5222 | 5206 | 14 | 0 | 8 | 6 | 7 | 7 | 0 | 14 | 8 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 57 | 52 |
| 5223 | | 11 | 1 | 7 | 5 | 7 | 6 | 0 | 11 | 6 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 45 | 41 |
| 5224 | 5207 | 15 | 0 | 5 | 10 | 6 | 5 | 0 | 15 | 5 | 10 | 4 | 4 | 0 | 8 | 4 | 4 | 56 | 54 |
| 5225 | | 14 | 0 | 7 | 7 | 7 | 7 | 0 | 14 | 7 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 51 | 50 |
| 5226 | 5208 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 5227 | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 5228 | 5209 | 15 | 0 | 5 | 10 | 7 | 7 | 1 | 14 | 5 | 9 | 4 | 4 | 0 | 8 | 4 | 4 | 49 | 47 |
| 5229 | | 14 | 0 | 9 | 5 | 7 | 7 | 0 | 14 | 9 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 45 | 42 |
| TOTAL | | 198 | 2 | 94 | 106 | | | 4 | 194 | 91 | 103 | 62 | 66 | 0 | 128 | 62 | 66 | | |
| MEAN | | 12 | | | | 7 | 6 | | 12 | | | | | | 8 | | | 48 | 46 |
| SD | | 2.3 | | | | 0.60 | 0.72 | | 2.4 | | | | | | | | | 5.1 | 4.7 |
| SE | | 0.57 | | | | 0.15 | 0.18 | | 0.59 | | | | | | | | | 1.1 | 0.018 |
| N | | 16 | | | | 16 | 16 | | 16 | | | | | | | | | 16 | 16 |

TABLE II-E-16

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 4

PUP OBSERVATIONS (F1a)

| DOSE (PPM) | FEMALE NUMBER | DAY OF LACTATION | OBSERVATIONS |
|---|---|---|---|
| 0 | 5150 | 0 | ONE FEMALE - HEMATOMA MID-DORSAL THORACIC REGION. |
| | | 0 | ONE MALE - SMALL SCAB ON SURFACE OF RIGHT EYELID. |
| | 5151 | 0 | ONE MALE - HEMATOMA TOP OF HEAD. |
| | 5154 | 0 | FIVE FEMALES - HEMATOMAS MID-DORSAL THORACIC REGION. |
| | 5156 | 0 | ONE MALE - LESION BETWEEN RIGHT EYE AND RIGHT EAR. |
| | 5159 | 0 | ONE FEMALE - HEMATOMA MID-DORSAL THORACIC REGION. |
| | 5160 | 0 | THREE MALES - HEMATOMAS MID-DORSAL THORACIC REGION. |
| | | 0 | ONE FEMALE - SMALL LESION MID-DORSAL LUMBAR REGION. |
| | 5162 | 0 | ONE MALE - FOUND DEAD; NO VISIBLE ABNORMALITIES. |
| | 5165 | 4 | ONE MALE - FOUND DEAD; SMALL; YELLOW COLOR SKIN. |
| | | 4 | ONE FEMALE - APPEARS SMALL. |
| | 5167 | 0 | ONE FEMALE - HEMATOMA HEAD. |
| | | 0 | ONE FEMALE - HEMATOMA LEFT HIND FOOT. |
| | 5168 | 0 | ONE FEMALE - HEMATOMA MID-DORSAL THORACIC REGION. |
| 80 | 5181 | 0 | ONE MALE - FOUND DEAD. |
| | | 0 | ONE FEMALE - LACERATION BETWEEN EYES. |
| | | 0 | ONE FEMALE - LACERATION ABOVE NOSE. |
| | 5184 | 0 | ONE MALE - HEMATOMAS LEFT SIDE MOUTH; LEFT SIDE NOSE. |
| | 5185 | 0 | ONE FEMALE - HEMATOMA RIGHT SIDE NOSE. |
| | 5186 | 0 | ONE MALE - HEMATOMA NOSE. |
| | 5187 | 0 | ONE FEMALE - HEMATOMA NOSE. |
| | 5188 | 0 | ONE FEMALE - ABDOMINAL SKIN YELLOW. |
| | 5191 | 0 | ONE MALE - HEMATOMA LEFT HIND FOOT. |
| | | 0 | ONE MALE - HEMATOMA MID-DORSAL THORACIC REGION. |
| | 5196 | 0 | ONE MALE - HEMATOMA MID-DORSAL THORACIC REGION. |
| | 5199 | 21 | ONE FEMALE - LEFT EYE OPAQUE; SMALLER THAN RIGHT EYE. |
| 750 | 5211 | 0 | ONE FEMALE - SMALL LESION MID-DORSAL THORACIC REGION. |
| | 5215 | 0 | ONE MALE - SCAB OVER NOSE. |
| | | 0 | ONE FEMALE - HEMATOMA MID-DORSAL THORACIC REGION. |
| | 5216 | 0 | ONE MALE - HEMATOMA EXTENSIVE OVER HIND LIMBS; SACRUM. |
| | | 0 | ONE MALE - HEMATOMA HEAD. |
| | 5218 | 0 | ONE FEMALE - HEMATOMA MID-DORSAL THORACIC REGION. |
| | 5219 | 0 | ONE MALE - HEMATOMA UNDER JAW. |
| | | 4 | ONE MALE - CROOKED TAIL. |
| | 5225 | 0 | ONE MALE - HEMATOMA MID-DORSAL THORACIC REGION. |
| | | 0 | ONE FEMALE - HEMATOMA MID-DORSAL THORACIC REGION. |
| | 5228 | 0 | TWO MALES - HEMATOMAS FACE. |

TABLE II-E-17

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 5

PUP NECROPSY OBSERVATIONS (F1a)

| DOSE (PPM) | FEMALE NUMBER | NUMBER OF PUPS | OBSERVATIONS |
|---|---|---|---|
| 0 | 5150 | 8 | NO VISIBLE ABNORMALITIES. |
| | 5152 | 8 | ONE MALE - PORTIONS OF LUNGS DARK RED. |
| | 5153 | 8 | NO VISIBLE ABNORMALITIES. |
| | 5156 | 8 | NO VISIBLE ABNORMALITIES. |
| | 5160 | 8 | NO VISIBLE ABNORMALITIES. |
| | 5168 | 8 | NO VISIBLE ABNORMALITIES. |
| 80 | 5181 | 8 | ONE MALE, ONE FEMALE - PORTIONS OF LUNGS DARK RED. |
| | 5182 | 6 | NO VISIBLE ABNORMALITIES. |
| | 5184 | 8 | NO VISIBLE ABNORMALITIES. |
| | 5187 | 8 | NO VISIBLE ABNORMALITIES. |
| | 5190 | 7 | NO VISIBLE ABNORMALITIES. |
| | 5198 | 8 | NO VISIBLE ABNORMALITIES. |
| 750 | 5211 | 8 | NO VISIBLE ABNORMALITIES. |
| | 5212 | 8 | TWO MALES, TWO FEMALES - VERY DARK LUNGS. |
| | 5214 | 8 | NO VISIBLE ABNORMALITIES. |
| | 5218 | 8 | NO VISIBLE ABNORMALITIES. |
| | 5221 | 8 | NO VISIBLE ABNORMALITIES. |
| | 5229 | 8 | NO VISIBLE ABNORMALITIES. |

# TABLE II-E-18

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 6

RESULTS OF FO GENERATION - SECOND MATING (F1b)

DOSE - 0 PPM (CONTROL)

| | | DAY 0 | | | | | | DAY 4 | | | | | | DAY 21 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE | DEATHS DAY 1-4 | LIVE PUPS | SEX MALE | SEX FEMALE | LITTER REDUCED MALE | LITTER REDUCED FEMALE | DEATHS DAY 5-21 | LIVE PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE |
| 5150 | 5149 | 10 | 0 | 6 | 4 | 7 | 7 | 0 | 10 | 6 | 4 | 4 | 4 | 1 | 7 | 3 | 4 | 40 | 37 |
| 5151 | | 14 | 0 | 7 | 7 | 7 | 7 | 0 | 14 | 7 | 7 | 4 | 4 | 1 | 7 | 3 | 4 | 49 | 45 |
| 5152 | 5148 | 16 | 0 | 10 | 6 | 6 | 6 | 2 | 14 | 8 | 6 | 4 | 4 | 1 | 7 | 4 | 3 | 42 | 40 |
| 5153 | | 11 | 0 | 6 | 5 | 7 | 6 | 0 | 11 | 6 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 37 | 36 |
| 5154 | 5147 | 10 | 0 | 4 | 6 | 4 | 4 | 1 | 9 | 4 | 5 | 4 | 4 | 1 | 7 | 4 | 3 | 37 | 35 |
| 5155 | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 5156 | 5146 | 14 | 0 | 5 | 9 | 6 | 6 | 0 | 14 | 5 | 9 | 4 | 4 | 0 | 8 | 4 | 4 | 36 | 37 |
| 5157 | | 13 | 0 | 7 | 6 | 6 | 5 | 0 | 13 | 7 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 62 | 57 |
| 5158 | 5145 | 6 | 0 | 4 | 2 | 7 | 7 | 0 | 6 | 4 | 2 | 4 | 2 | 0 | 6 | 4 | 2 | 52 | 52 |
| 5159 | | 14 | 0 | 5 | 9 | 5 | 4 | 1 | 13 | 4 | 9 | 4 | 4 | 0 | 8 | 4 | 4 | 38 | 35 |
| 5160 | 5144 | 11 | 0 | 7 | 4 | 6 | 6 | 0 | 11 | 7 | 4 | 4 | 4 | 0 | 8 | 4 | 4 | 43 | 40 |
| 5161 | | 12 | 2 | 6 | 8 | 6 | 6 | 1 | 11 | 5 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 45 | 47 |
| 5162 | 5143 | 5 | 0 | 2 | 3 | 7 | 7 | 0 | 5 | 2 | 3 | 2 | 3 | 0 | 5 | 2 | 3 | 48 | 47 |
| 5163 | | 9 | 0 | 7 | 2 | 6 | 6 | 0 | 9 | 7 | 2 | 4 | 2 | 0 | 6 | 4 | 2 | 51 | 47 |
| 5164 | 5142 | 11 | 0 | 6 | 5 | 8 | 8 | 0 | 11 | 6 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 56 | 55 |
| 5165 | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 5166 | 5141 | 14 | 0 | 4 | 10 | 4 | 4 | 1 | 13 | 4 | 9 | 4 | 4 | 0 | 8 | 4 | 4 | 49 | 47 |
| 5167 | | 12 | 0 | 5 | 7 | 8 | 7 | 0 | 12 | 5 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 54 | 50 |
| 5168 | 5140 | 14 | 0 | 8 | 6 | 7 | 6 | 0 | 14 | 8 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 40 | 42 |
| 5169 | | 3 | 0 | 1 | 2 | 7 | 6 | 0 | 3 | 1 | 2 | 1 | 2 | 0 | 3 | 1 | 2 | 56 | 50 |
| TOTAL | | 199 | 2 | 100 | 101 | | | 6 | 193 | 96 | 97 | 67 | 65 | 4 | 128 | 65 | 63 | | |
| MEAN | | 11 | | | | 6 | 6 | | 11 | | | | | | 7 | | | 46 | 44 |
| SD | | 3.5 | | | | 1.1 | 1.1 | | 3.3 | | | | | | | | | 7.8 | 6.9 |
| SE | | 0.8 | | | | 0.26 | 0.26 | | 0.78 | | | | | | | | | 1.8 | 1.6 |
| N | | 18 | | | | 18 | 18 | | 18 | | | | | | | | 18 | 18 | 18 |

# TABLE II-E-18 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 6 (CONTINUED)

RESULTS OF F0 GENERATION - SECOND MATING (F1b)

DOSE - 80 PPM

| | | DAY 0 | | | | | | DAY 4 | | | | | | DAY 21 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE | DEATHS DAY 1-4 | LIVE PUPS | SEX MALE | SEX FEMALE | LITTER REDUCED MALE | LITTER REDUCED FEMALE | DEATHS DAY 5-21 | LIVE PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE |
| 5180 | 5179 | 15 | 0 | 8 | 7 | 8 | 7 | 1 | 14 | 7 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 59 | 56 |
| 5181 | | 12 | 0 | 6 | 6 | 7 | 6 | 0 | 12 | 6 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 39 | 36 |
| 5182 | 5178 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 5183 | | 7 | 0 | 2 | 5 | 8 | 8 | 0 | 7 | 2 | 5 | 2 | 4 | 0 | 6 | 2 | 4 | 56 | 52 |
| 5184 | 5177 | 11 | 0 | 6 | 5 | 4 | 3 | 0 | 11 | 6 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 43 | 40 |
| 5185 | | 15 | 0 | 4 | 11 | 6 | 6 | 0 | 15 | 4 | 11 | 4 | 4 | 0 | 8 | 4 | 4 | 32 | 31 |
| 5186 | 5176 | 11 | 1 | 5 | 7 | 4 | 3 | 0 | 11 | 4 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 46 | 47 |
| 5187 | | 12 | 0 | 6 | 6 | 5 | 5 | 0 | 12 | 6 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 48 | 43 |
| 5188 | 5175 | 12 | 0 | 5 | 7 | 6 | 6 | 1 | 11 | 5 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 51 | 50 |
| 5189 | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 5190 | 5174 | 10 | 0 | 6 | 4 | 8 | 7 | 0 | 10 | 6 | 4 | 4 | 4 | 0 | 8 | 3 | 5[a] | 53 | 45 |
| 5191 | | 11 | 1 | 9 | 3 | 4 | 4 | 0 | 11 | 9 | 2 | 6 | 2 | 0 | 8 | 6 | 2 | 48 | 44 |
| 5192 | 5173 | 11 | 0 | 6 | 5 | 6 | 6 | 2 | 9 | 5 | 4 | 4 | 4 | 2 | 6 | 3 | 3 | 56 | 53 |
| 5193 | | 3 | 0 | 3 | 0 | 4 | - | 0 | 3 | 3 | 0 | 3 | 0 | 0 | 3 | 3 | 0 | 55 | - |
| 5194 | 5172 | 14 | 0 | 6 | 8 | 6 | 5 | 0 | 14 | 6 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 55 | 52 |
| 5195 | | 14 | 1 | 6 | 9 | 3 | 3 | 2 | 12 | 6 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 32 | 33 |
| 5196 | 5171 | 16 | 1 | 5 | 12 | 4 | 3 | 2 | 14 | 5 | 9 | 4 | 4 | 0 | 8 | 4 | 4 | 41 | 37 |
| 5197 | | 3 | 0 | 1 | 2 | 5 | 5 | 0 | 3 | 1 | 2 | 1 | 2 | 0 | 3 | 1 | 2 | 56 | 56 |
| 5198 | 5170 | 11 | 0 | 4 | 7 | 4 | 4 | 0 | 11 | 4 | 7 | 4 | 4 | 2 | 6 | 3 | 3 | 37 | 38 |
| 5199 | | 8 | 2 | 6 | 4 | 4 | 4 | 1 | 7 | 5 | 2 | 4 | 4 | 0 | 8 | 4 | 4 | 38 | 35 |
| TOTAL | | 196 | 6 | 94 | 108 | | | 9 | 187 | 90 | 97 | 68 | 64 | 4 | 128 | 65 | 63 | | |
| MEAN | | 11 | | | | 5 | 5 | | 10 | | | | | | 7 | | | 47 | 44 |
| SD | | 3.7 | | | | 1.6 | 1.6 | | 3.5 | | | | | | | | | 8.8 | 8.2 |
| SE | | 0.87 | | | | 0.4 | 0.4 | | 0.82 | | | | | | | | | 2.1 | 2.0 |
| N | | 18 | | | | 18 | 17 | | 18 | | | | | | | | | 18 | 17 |

[a]Pup mis-sexed.

TABLE II-E-18 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 6 (CONTINUED)

RESULTS OF FO GENERATION - SECOND MATING (F1b)

DOSE - 750 PPM

| | | DAY 0 | | | | | | DAY 4 | | | | | | DAY 21 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE | DEATHS DAY 1-4 | LIVE PUPS | SEX MALE | SEX FEMALE | LITTER REDUCED MALE | LITTER REDUCED FEMALE | DEATHS DAY 5-21 | LIVE PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE |
| 5210 | 5209 | 13 | 0 | 4 | 9 | 7 | 6 | 0 | 13 | 4 | 9 | 4 | 4 | 0 | 8 | 4 | 4 | 39 | 40 |
| 5211 | | 18 | 0 | 7 | 11 | 6 | 6 | 1 | 17 | 6 | 11 | 4 | 4 | 0 | 8 | 4 | 4 | 50 | 44 |
| 5212 | 5208 | 13 | 0 | 6 | 7 | 6 | 6 | 0 | 13 | 6 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 44 | 44 |
| 5213 | | 6 | 0 | 2 | 4 | 6 | 6 | 0 | 6 | 2 | 4 | 2 | 4 | 0 | 6 | 2 | 4 | 50 | 46 |
| 5214 | 5207 | 8 | 0 | 2 | 6 | 7 | 7 | 0 | 8 | 2 | 6 | 2 | 6 | 0 | 8 | 2 | 6 | 40 | 39 |
| 5215 | | 16 | 0 | 6 | 10 | 7 | 6 | 0 | 16 | 6 | 10 | 4 | 4 | 0 | 8 | 4 | 4 | 27 | 24 |
| 5216 | 5206 | 11 | 1 | 7 | 5 | 6 | 6 | 0 | 11 | 6 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 46 | 44 |
| 5217 | | 11 | 1 | 8 | 4 | 6 | 5 | 0 | 11 | 7 | 4 | 4 | 4 | 2 | 6 | 2 | 4 | 39 | 37 |
| 5218 | 5205 | 13 | 0 | 7 | 6 | 5 | 5 | 0 | 13 | 7 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 33 | 32 |
| 5219 | | 11 | 0 | 6 | 5 | 7 | 7 | 1 | 10 | 5 | 5 | 4 | 4 | 2 | 6 | 3 | 3 | 38 | 40 |
| 5220 | 5204 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 5221 | | 14 | 0 | 7 | 7 | 7 | 6 | 0 | 14 | 7 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 49 | 47 |
| 5222 | 5203 | 17 | 0 | 8 | 9 | 6 | 6 | 1 | 16 | 8 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 49 | 44 |
| 5223 | | 11 | 0 | 7 | 4 | 6 | 6 | 0 | 11 | 7 | 4 | 4 | 4 | 0 | 8 | 4 | 4 | 38 | 39 |
| 5224 | 5202 | 15 | 0 | 6 | 9 | 7 | 7 | 0 | 15 | 6 | 9 | 4 | 4 | 0 | 8 | 4 | 4 | 51 | 44 |
| 5225 | | 12 | 0 | 3 | 9 | 7 | 7 | 8 | 4 | 3 | 1 | 3 | 1 | 0 | 4 | 3 | 1 | 35 | 37 |
| 5226 | 5201 | 10 | 0 | 5 | 5 | 6 | 6 | 1 | 9 | 4 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 38 | 36 |
| 5227 | | 13 | 0 | 7 | 6 | 6 | 6 | 0 | 13 | 7 | 6 | 4 | 4 | 1 | 7 | 4 | 3 | 34 | 33 |
| 5228 | 5200 | 10 | 0 | 6 | 4 | 7 | 6 | 1 | 9 | 5 | 4 | 4 | 4 | 1 | 7 | 4 | 3 | 45 | 41 |
| 5229 | | 7 | 0 | 4 | 3 | 7 | 7 | 0 | 7 | 4 | 3 | 4 | 3 | 0 | 7 | 4 | 3 | 46 | 44 |
| TOTAL | | 229 | 2 | 108 | 123 | | | 13 | 216 | 102 | 114 | 71 | 74 | 6 | 139 | 68 | 71 | | |
| MEAN | | 12 | | | | 6 | 6 | | 11 | | | | | | 7 | | | 42 | 40 |
| SD | | 3.2 | | | | 0.61 | 0.61 | | 3.6 | | | | | | | | | 6.8 | 5.7 |
| SE | | 0.73 | | | | 0.14 | 0.14 | | 0.82 | | | | | | | | | 1.6 | 1.3 |
| N | | 19 | | | | 19 | 19 | | 19 | | | | | | | | | 19 | 19 |

TABLE II-E-19

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 7

PUP OBSERVATIONS (F1b)

| DOSE (PPM) | FEMALE NUMBER | DAY OF LACTATION | OBSERVATIONS |
|---|---|---|---|
| 0 | 5152 | 6 | ONE FEMALE - FOUND DEAD; NO VISIBLE ABNORMALITIES. |
| | 5154 | 4 | ONE FEMALE - FOUND DEAD; NO VISIBLE ABNORMALITIES. |
| | 5159 | 0 | TWO MALES - HEMATOMA MID-DORSAL THORACIC REGION. |
| | 5160 | 0 | ONE MALE - HEMATOMA RIGHT SIDE OF FACE; ONE MALE - HEMATOMA MID-DORSAL THORACIC REGION. |
| | 5166 | 0 | ONE FEMALE - HEMATOMA LEFT DORSAL THORACIC REGION. |
| 80 | 5180 | 0 | ONE FEMALE - HEMATOMA MID-DORSAL THORACIC REGION. |
| | | 4 | ONE MALE - FOUND DEAD; NO VISIBLE ABNORMALITIES. |
| | 5185 | 0 | ONE FEMALE - HEMATOMA RIGHT HIND LEG. |
| | 5186 | 0 | ONE MALE - FOUND DEAD. |
| | 5188 | 0 | ONE FEMALE - HEMATOMA ON FACE. |
| | 5191 | 0 | ONE FEMALE - FOUND DEAD; NO VISIBLE ABNORMALITIES. |
| | 5195 | 0 | ONE FEMALE - FOUND DEAD; MISSING TAIL; RIGHT HIND FOOT DEFORMED. |
| | 5196 | 0 | ONE FEMALE - FOUND DEAD; HEMATOMA RIGHT SIDE OF FACE. |
| | 5199 | 0 | ONE MALE - FOUND DEAD; ONE FEMALE - FOUND DEAD; ONE MALE - HEMATOMA ENTIRE ABDOMEN AND INGUINAL REGION. |
| 750 | 5217 | 0 | ONE PUP FOUND DEAD; PARTIALLY CANNIBALIZED. |
| | | 11 | ONE MALE - FOUND DEAD; NO VISIBLE ABNORMALITIES. |
| | 5222 | 4 | ONE MALE - FOUND DEAD; NO VISIBLE ABNORMALITIES. |
| | 5225 | 4 | ALL PUPS VERY SMALL. |
| | 5227 | 0 | ONE FEMALE - HEMATOMA LEFT HIND FOOT. |
| | 5228 | 0 | ONE MALE - LABORED RESPIRATION. |

TABLE II-E-20

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 8

ADULT NECROPSY OBSERVATIONS (F0)

| DOSE (PPM) | SEX | ANIMAL NUMBER | OBSERVATIONS |
|---|---|---|---|
| 0 | M | | NO VISIBLE ABNORMALITIES. |
| | F | 5161 | FIRM MASS (1 $CM^2$) LEFT VENTRAL THORACIC REGION. |
| 80 | M | | NO VISIBLE ABNORMALITIES. |
| | F | 5181 | CLEAR FLUID-FILLED SAC (0.5 $CM^2$) ON LEFT OVARY. |
| | F | 5199 | STONE (1 X 0.5 CM) IN URETER; STONE (1 X 0.5 CM) IN BLADDER. |
| 750 | M | 5207 | HAIR LOSS; DISCHARGE LEFT EYE. |
| | F | | NO VISIBLE ABNORMALITIES. |

TABLE II-E-21

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 9

MEAN BODY WEIGHTS (G) OF F1b RATS

| DOSE (PPM) | SEX | | WEEK 4 | 9 | 11 | 20 |
|---|---|---|---|---|---|---|
| 0 | M | MEAN | 281 | 416 | 432 | 513 |
| | | SD | 29 | 31 | 39 | 45 |
| | | SE | 9.0 | 9.8 | 12 | 14 |
| | | N | 10 | 10 | 10 | 10 |
| 80 | M | MEAN | 290 | 447 | 472 | 574 |
| | | SD | 36 | 34 | 35 | 51 |
| | | SE | 12 | 11 | 11 | 16 |
| | | N | 10 | 10 | 10 | 10 |
| 750 | M | MEAN | 281 | 429 | 449 | 569 |
| | | SD | 27 | 36 | 29 | 48 |
| | | SE | 8.4 | 12 | 9.2 | 15 |
| | | N | 10 | 10 | 10 | 10 |
| 0 | F | MEAN | 183 | 239 | 246 | 291 |
| | | SD | 16 | 14 | 16 | 18 |
| | | SE | 3.6 | 3.1 | 3.6 | 4.0 |
| | | N | 20 | 20 | 20 | 20 |
| 80 | F | MEAN | 183 | 246 | 251 | 283 |
| | | SD | 22 | 22 | 23 | 24 |
| | | SE | 5.0 | 4.9 | 5.2 | 5.4 |
| | | N | 20 | 20 | 20 | 20 |
| 750 | F | MEAN | 185 | 250 | 256 | 309 |
| | | SD | 20 | 24 | 24 | 26 |
| | | SE | 4.4 | 5.3 | 5.3 | 5.7 |
| | | N | 20 | 20 | 20 | 20 |

TABLE II-E-22

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 10

MEAN FOOD CONSUMPTION (G) IN F1b RATS

| DOSE (PPM) | SEX | | WEEK 4 | 9 | 11 | 20 |
|---|---|---|---|---|---|---|
| 0 | M | MEAN | 25 | 26 | 26 | 32 |
| | | SD | 3.8 | 3.0 | 3.7 | 5.7 |
| | | SE | 1.2 | 1.1 | 1.4 | 1.8 |
| | | N | 10 | 8 | 7 | 10 |
| 80 | M | MEAN | 26 | 28 | 27 | 30 |
| | | SD | 3.2 | 1.3 | 1.7 | 3.2 |
| | | SE | 1.3 | 0.46 | 0.55 | 1.0 |
| | | N | 6 | 8 | 10 | 10 |
| 750 | M | MEAN | 25 | 25 | 25 | 25* |
| | | SD | 1.9 | 1.9 | 0.58 | 3.2 |
| | | SE | 0.67 | 0.63 | 0.20 | 1.0 |
| | | N | 8 | 9 | 8 | 10 |
| 0 | F | MEAN | 22 | 22 | 23 | 29 |
| | | SD | 4.6 | 4.2 | 6.0 | 4.0 |
| | | SE | 1.1 | 0.89 | 1.4 | 1.0 |
| | | N | 17 | 18 | 18 | 16 |
| 80 | F | MEAN | 25 | 25 | 26 | 33 |
| | | SD | 2.6 | 3.6 | 4.4 | 6.1 |
| | | SE | 0.91 | 0.96 | 1.2 | 1.4 |
| | | N | 8 | 14 | 13 | 18 |
| 750 | F | MEAN | 21 | 22 | 21 | 24* |
| | | SD | 4.9 | 4.3 | 5.0 | 5.9 |
| | | SE | 1.3 | 1.0 | 1.2 | 1.6 |
| | | N | 15 | 17 | 19 | 14 |

*$p<0.05$ as compared to controls: Student's t-test.

# TABLE II-E-23

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 11

RESULTS OF F1b GENERATION - FIRST MATING (F2a)

DOSE - 0 PPM (CONTROL)

| | | DAY 0 | | | | | | DAY 4 | | | | | | DAY 21 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE | DEATHS DAY 1-4 | LIVE PUPS | SEX MALE | SEX FEMALE | LITTER REDUCED MALE | LITTER REDUCED FEMALE | DEATHS DAY 5-21 | LIVE PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE |
| 7296 | 7295 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 7297 | | 10 | 0 | 4 | 6 | 7 | 7 | 0 | 10 | 4 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 47 | 42 |
| 7298 | 7287 | 13 | 0 | 10 | 3 | 6 | 6 | 0 | 13 | 10 | 3 | 5 | 3 | 0 | 8 | 5 | 3 | 46 | 43 |
| 7299 | | 13 | 0 | 9 | 4[a] | 5 | 6 | 0 | 13 | 7 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 35 | 34 |
| 7300 | 7288 | 6 | 0 | 2 | 4 | 9 | 8 | 0 | 6 | 2 | 4 | 2 | 4 | 0 | 6 | 2 | 4 | 59 | 56 |
| 7301 | | 15 | 0 | 8 | 7 | 7 | 6 | 1 | 14 | 7 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 41 | 41 |
| 7302 | 7289 | 14 | 0 | 5 | 9[a] | 7 | 7 | 0 | 14 | 4 | 10 | 4 | 4 | 0 | 8 | 4 | 4 | 55 | 49 |
| 7303 | | 11 | 0 | 2 | 9 | 7 | 6 | 0 | 11 | 2 | 9 | 2 | 6 | 0 | 8 | 3 | 5[a] | 39 | 35 |
| 7304 | 7290 | 15 | 0 | 10 | 5[a] | 6 | 6 | 0 | 15 | 8 | 7 | 4 | 4 | 0 | 8 | 5 | 3[a] | 44 | 42 |
| 7305 | | 12 | 0 | 3 | 9 | 7 | 6 | 1 | 11 | 3 | 8 | 3 | 5 | 0 | 8 | 3 | 5 | 43 | 42 |
| 7306 | 7291 | 14 | 0 | 6 | 8[a] | 6 | 6 | 0 | 14 | 5 | 9 | 4 | 4 | 0 | 8 | 4 | 4 | 39 | 37 |
| 7307 | | 11 | 1 | 5 | 7 | 6 | 6 | 0 | 11 | 4 | 7 | 4 | 4 | 2 | 6 | 2 | 4 | 43 | 43 |
| 7308 | 7292 | 14 | 0 | 7 | 7[a] | 6 | 5 | 0 | 14 | 5 | 9 | 4 | 4 | 0 | 8 | 4 | 4 | 34 | 35 |
| 7309 | | 12 | 0 | 5 | 7[a] | 6 | 6 | 1 | 11 | 6 | 5 | 4 | 4 | 0 | 8 | 2 | 6[a] | 43 | 39 |
| 7310 | 7293 | 12 | 0 | 5 | 7[a] | 6 | 6 | 0 | 12 | 6 | 6 | 4 | 4 | 1 | 7 | 4 | 3 | 42 | 40 |
| 7311 | | 9 | 0 | 2 | 7 | 6 | 6 | 0 | 9 | 2 | 7 | 2 | 6 | 0 | 8 | 2 | 6 | 42 | 39 |
| 7312 | 7294 | 12 | 0 | 6 | 6[a] | 7 | 8 | 0 | 12 | 6 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 42 | 43 |
| 7313 | | 16 | 0 | 7 | 9[a] | 5 | 5 | 0 | 16 | 8 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 41 | 37 |
| 7314 | 7286 | 17 | 0 | 8 | 9[a] | 6 | 6 | 1 | 16 | 8 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 45 | 44 |
| 7315 | | 15 | 0 | 7 | 8[a] | 6 | 6 | 0 | 15 | 10 | 5 | 4 | 4 | 0 | 8 | 5 | 3[a] | 48 | 46 |
| TOTAL | | 241 | 1 | 111 | 131 | | | 4 | 237 | 107 | 130 | 70 | 80 | 3 | 147 | 69 | 78 | | |
| MEAN | | 13 | | | | 6 | 6 | | 12 | | | | | | 8 | | | 44 | 41 |
| SD | | 2.6 | | | | 0.90 | 0.79 | | 2.5 | | | | | | | | | 5.9 | 5.3 |
| SE | | 0.60 | | | | 0.21 | 0.18 | | 0.58 | | | | | | | | | 1.4 | 1.2 |
| N | | 19 | | | | 19 | 19 | | 19 | | | | | | | | | 19 | 19 |

[a]Pups mis-sexed.

TABLE II-E-23 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 11 (CONTINUED)

RESULTS OF F1b GENERATION - FIRST MATING (F2a)

DOSE - 80 PPM

| | | DAY 0 | | | | | | DAY 4 | | | | | | DAY 21 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE | DEATHS DAY 1-4 | LIVE PUPS | SEX MALE | SEX FEMALE | LITTER REDUCED MALE | LITTER REDUCED FEMALE | DEATHS DAY 5-21 | LIVE PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE |
| 7326 | 7325 | 15 | 0 | 7 | 8[a] | 6 | 6 | 0 | 15 | 8 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 39 | 41 |
| 7327 | | 10 | 0 | 5 | 5[a] | 7 | 7 | 0 | 10 | 6 | 4 | 4 | 4 | 0 | 8 | 4 | 4 | 58 | 54 |
| 7328 | 7317 | 13 | 1 | 7 | 7 | 6 | 6 | 0 | 13 | 6 | 7 | 4 | 4 | 1 | 7 | 3 | 4 | 47 | 40 |
| 7329 | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 7330 | 7318 | 10 | 0 | 4 | 6[a] | 6 | 6 | 0 | 10 | 5 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 38 | 36 |
| 7331 | | 11 | 0 | 5 | 6[a] | 7 | 7 | 0 | 11 | 8 | 3 | 5 | 3 | 0 | 8 | 5 | 3 | 51 | 44 |
| 7332 | 7319 | 11 | 1 | 6 | 6 | 6 | 6 | 0 | 11 | 5 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 39 | 35 |
| 7333 | | 13 | 1 | 5 | 9 | 6 | 5 | 6 | 7 | 2 | 5 | 2 | 5 | 0 | 7 | 2 | 5 | 50 | 48 |
| 7334 | 7320 | 14 | 0 | 7 | 7 | 6 | 5 | 1 | 13 | 7 | 6 | 4 | 4 | 1 | 7 | 4 | 3 | 41 | 36 |
| 7335 | | 11 | 0 | 5 | 6[a] | 6 | 5 | 1 | 10 | 5 | 5 | 4 | 4 | 1 | 7 | 4 | 3 | 43 | 41 |
| 7336 | 7321 | 13 | 0 | 4 | 9[a] | 5 | 5 | 0 | 13 | 5 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 43 | 37 |
| 7337 | | 14 | 0 | 6 | 8 | 6 | 5 | 0 | 14 | 6 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 45 | 45 |
| 7338 | 7322 | 7 | 0 | 4 | 3 | 7 | 7 | 0 | 7 | 4 | 3 | 4 | 3 | 0 | 7 | 4 | 3 | 59 | 57 |
| 7339 | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 7340 | 7323 | 5 | 0 | 2 | 3 | 8 | 7 | 0 | 5 | 2 | 3 | 2 | 3 | 0 | 5 | 2 | 3 | 53 | 51 |
| 7341 | | 16 | 0 | 8 | 8 | 6 | 5 | 4 | 12 | 7 | 5 | 4 | 4 | 1 | 7 | 4 | 3 | 42 | 39 |
| 7342 | 7324 | 10 | 1 | 4 | 7 | 7 | 7 | 0 | 10 | 3 | 7 | 3 | 5 | 0 | 8 | 4 | 4[a] | 50 | 50 |
| 7343 | | 12 | 2 | 6 | 8[a] | 8 | 7 | 0 | 12 | 6 | 6 | 4 | 4 | 0 | 8 | 3 | 5[a] | 48 | 44 |
| 7344 | 7316 | 13 | 0 | 6 | 7[a] | 6 | 6 | 0 | 13 | 7 | 6 | 4 | 4 | 0 | 8 | 4 | 4[a] | 43 | 42 |
| 7345 | | 11 | 1 | 3 | 9 | 5 | 4 | 1 | 10 | 2 | 8 | 2 | 6 | 0 | 8 | 4 | 4[a] | 39 | 36 |
| TOTAL | | 209 | 7 | 94 | 122 | | | 13 | 196 | 94 | 102 | 66 | 73 | 4 | 135 | 67 | 68 | | |
| MEAN | | 12 | | | | 6 | 6 | | 11 | | | | | | 8 | | | 46 | 43 |
| SD | | 2.7 | | | | 0.84 | 0.92 | | 2.61 | | | | | | | | | 6.4 | 6.6 |
| SE | | 0.64 | | | | 0.20 | 0.22 | | 0.62 | | | | | | | | | 1.5 | 1.6 |
| N | | 18 | | | | 18 | 18 | | 18 | | | | | | | | | 18 | 18 |

[a]Pups mis-sexed.

TABLE II-E-23 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 11 (CONTINUED)

*RESULTS OF F1b GENERATION - FIRST MATING (F2a)*

DOSE - 750 PPM

| | | DAY 0 | | | | | | DAY 4 | | | | | | DAY 21 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE | DEATHS DAY 1-4 | LIVE PUPS | SEX MALE | SEX FEMALE | LITTER REDUCED MALE | LITTER REDUCED FEMALE | DEATHS DAY 5-21 | LIVE PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE |
| 7356 | 7355 | 13 | 0 | 6 | 7 | 7 | 7 | 0 | 13 | 6 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 40 | 40 |
| 7357 | | 14 | 0 | 6 | 8 | 6 | 6 | 0 | 14 | 6 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 49 | 47 |
| 7358 | 7347 | 15 | 0 | 10 | 5 | 7 | 7 | 0 | 15 | 10 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 48 | 44 |
| 7359 | | 13 | 0 | 5 | 8 | 6 | 6 | 0 | 13 | 5 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 39 | 36 |
| 7360 | 7348 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 7361 | | 13 | 0 | 6 | 7 | 6 | 6 | 0 | 13 | 6 | 7 | 4 | 4 | 1 | 7 | 4 | 3 | 47 | 43 |
| 7362 | 7349 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 7363 | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 7364 | 7350 | 6 | 0 | 4 | 2 | 8 | 8 | 0 | 6 | 4 | 2 | 4 | 2 | 0 | 6 | 4 | 2 | 51 | 42 |
| 7365 | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 7366 | 7351 | 14 | 0 | 8 | 6 | 5 | 5 | 0 | 14 | 8 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 41 | 42 |
| 7367 | | 10 | 0 | 4 | 6[a] | 6 | 5 | 0 | 10 | 3 | 7 | 3 | 5 | 1 | 7 | 3 | 4 | 41 | 37 |
| 7368 | 7352 | 9 | 0 | 3 | 6 | 7 | 7 | 0 | 9 | 3 | 6 | 3 | 5 | 0 | 8 | 3 | 5 | 52 | 51 |
| 7369 | | 7 | 0 | 5 | 2 | 6 | 6 | 0 | 7 | 5 | 2 | 5 | 2 | 0 | 7 | 5 | 2 | 54 | 47 |
| 7370 | 7353 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 7371 | | 11 | 0 | 8 | 3[a] | 7 | 7 | 0 | 11 | 7 | 4 | 4 | 4 | 0 | 8 | 4 | 4 | 40 | 37 |
| 7372 | 7354 | 13 | 0 | 8 | 5[a] | 5 | 5 | 0 | 13 | 7 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 39 | 37 |
| 7373 | | 12 | 0 | 6 | 6[a] | 6 | 5 | 3 | 9 | 7 | 2 | 6 | 2 | 0 | 8 | 6 | 2 | 42 | 40 |
| 7374 | 7346 | 12 | 0 | 5 | 7[a] | 6 | 6 | 0 | 12 | 6 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 39 | 40 |
| 7375 | | | | | | | | | | | | | | | | | | | |
| TOTAL | | 162 | 0 | 84 | 78 | | | 3 | 159 | 83 | 76 | 57 | 52 | 2 | 107 | 57 | 50 | | |
| MEAN | | 12 | | | | 6 | 6 | | 11 | | | | | | 8 | | | 44 | 42 |
| SD | | 2.7 | | | | 0.83 | 0.95 | | 2.8 | | | | | | | | | 5.5 | 4.4 |
| SE | | 0.72 | | | | 0.22 | 0.25 | | 0.74 | | | | | | | | | 1.5 | 1.2 |
| N | | 14 | | | | 14 | 14 | | 11 | | | | | | | | | 14 | 14 |

[a]Pup mis-sexed.

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 12

PUP OBSERVATIONS (F2a)

| DOSE (PPM) | FEMALE NUMBER | DAY OF LACTATION | OBSERVATIONS |
|---|---|---|---|
| 0 | 7301 | 0 | ONE MALE - HEMATOMAS BOTH HIND LIMBS. |
| | | 4 | ONE MALE - FOUND DEAD. |
| .80 | 7334 | 20 | ONE MALE - FOUND DEAD; NO VISIBLE ABNORMALITIES. |
| | 7335 | 4 | ONE FEMALE - FOUND DEAD; ONE FEMALE - EMACIATED. |
| | 7341 | 4 | ONE FEMALE - MORIBUND; KILLED. |
| | 7342 | 21 | ONE MALE - SWOLLEN CEPHALIC REGION; NECROPSY SHOWED BRAIN WAS SMALL AND VERY SOFT, SURROUNDED BY LARGE QUANTITY OF FLUID. |
| 750 | 7373 | 4 | ONE FEMALE - FOUND DEAD. |

TABLE II-E-25

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 13

PUP NECROPSY OBSERVATIONS (F2a)

| DOSE (PPM) | FEMALE NUMBER | NUMBER OF PUPS | OBSERVATIONS |
|---|---|---|---|
| 0 | 7298 | 8 | ALL PUPS APPEAR NORMAL. |
| | 7299 | 8 | ALL PUPS APPEAR NORMAL. |
| | 7300 | 8 | ALL PUPS APPEAR NORMAL. |
| | 7305 | 8 | ALL PUPS APPEAR NORMAL. |
| | 7312 | 8 | ALL PUPS APPEAR NORMAL. |
| | 7314 | 8 | ALL PUPS APPEAR NORMAL. |
| | 7315 | 8 | ALL PUPS APPEAR NORMAL. |
| 80 | 7326 | 8 | ALL PUPS APPEAR NORMAL. |
| | 7332 | 8 | ALL PUPS APPEAR NORMAL. |
| | 7337 | 8 | ALL PUPS APPEAR NORMAL. |
| | 7340 | 5 | ALL PUPS APPEAR NORMAL. |
| | 7343 | 8 | ALL PUPS APPEAR NORMAL. |
| | 7345 | 8 | ALL PUPS APPEAR NORMAL. |
| 750 | 7357 | 8 | ALL PUPS APPEAR NORMAL |
| | 7359 | 8 | ALL PUPS APPEAR NORMAL. |
| | 7361 | 7 | ALL PUPS APPEAR NORMAL. |
| | 7367 | 7 | ALL PUPS APPEAR NORMAL. |
| | 7374 | 8 | ALL PUPS APPEAR NORMAL. |

# TABLE II-E-26

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 14

RESULTS OF F1b GENERATION - SECOND MATING (F2b)

DOSE - 0 PPM

| | | DAY 0 | | | | | | DAY 4 | | | | | | DAY 21 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE | DEATHS DAY 1-4 | LIVE PUPS | SEX MALE | SEX FEMALE | LITTER REDUCED MALE | LITTER REDUCED FEMALE | DEATHS DAY 5-21 | LIVE PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE |
| 7296 | 7288 | 8 | 0 | 3 | 5 | 8 | 7 | 1 | 7 | 2 | 5 | 2 | 5 | 0 | 7 | 2 | 5 | 56 | 55 |
| 7297 | 7289 | 16 | 0 | 5 | 11 | 6 | 6 | 1 | 15 | 5 | 10 | 4 | 4 | 0 | 8 | 4 | 4 | 45 | 45 |
| 7298 | 7291 | 15 | 0 | 4 | 11 | 7 | 6 | 0 | 15 | 4 | 11 | 4 | 4 | 0 | 8 | 4 | 4 | 49 | 47 |
| 7299 | 7291 | 10 | 1 | 6 | 5 | 6 | 6 | 2 | 8 | 4 | 4 | 4 | 4 | 0 | 8 | 4 | 4 | 38 | 37 |
| 7300 | 7293 | 13 | 0 | 8 | 5 | 6 | 5 | 0 | 13 | 8 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 47 | 45 |
| 7301 | 7295 | 17 | 0 | 9 | 8 | 8 | 7 | 0 | 17 | 9 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 40 | 38 |
| 7302 | 7286 | 14 | 0 | 4 | 10 | 6 | 6 | 0 | 14 | 4 | 10 | 4 | 4 | 0 | 8 | 4 | 4 | 49 | 51 |
| 7303 | 7286 | 13 | 0 | 5 | 8 | 6 | 6 | 0 | 13 | 5 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 37 | 29 |
| 7304 | 7289 | 14 | 2 | 6 | 10 | 5 | 5 | 1 | 13 | 4 | 9 | 4 | 4 | 0 | 8 | 4 | 4 | 45 | 45 |
| 7305 | 7287 | 12 | 0 | 4 | 8 | 6 | 6 | 0 | 12 | 4 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 40 | 34 |
| 7306 | 7293 | 13 | 0 | 8 | 5 | 6 | 6 | 0 | 13 | 8 | 5 | 4 | 4 | 0 | 8 | 5 | 3[a] | 45 | 41 |
| 7307 | 7292 | 17 | 0 | 8 | 9 | 6 | 5 | 6 | 11 | 2 | 9 | 2 | 6 | 0 | 8 | 2 | 6 | 45 | 41 |
| 7308 | 7294 | 12 | 0 | 5 | 7 | 6 | 6 | 0 | 12 | 5 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 32 | 32 |
| 7309 | 7290 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 7310 | 7287 | 13 | 0 | 7 | 6 | 6 | 5 | 1 | 12 | 6 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 45 | 41 |
| 7311 | 7294 | 14 | 0 | 9 | 5 | 7 | 7 | 1 | 13 | 8 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 36 | 43 |
| 7312 | 7292 | 12 | 0 | 6 | 6 | 8 | 7 | 0 | 12 | 6 | 6 | 4 | 4 | 1 | 7 | 4 | 3 | 55 | 55 |
| 7313 | 7295 | 17 | 0 | 8 | 9 | 7 | 7 | 0 | 17 | 8 | 9 | 4 | 4 | 0 | 8 | 4 | 4 | 56 | 53 |
| 7314 | 7288 | 16 | 0 | 9 | 7 | 6 | 5 | 0 | 16 | 9 | 7 | 4 | 4 | 1 | 7 | 3 | 4 | 50 | 48 |
| 7315 | 7290 | 17 | 0 | 7 | 10 | 6 | 6 | 0 | 17 | 7 | 10 | 4 | 4 | 0 | 8 | 4 | 4 | 50 | 46 |
| TOTAL | | 263 | 3 | 121 | 145 | | | 13 | 250 | 108 | 142 | 72 | 79 | 2 | 149 | 72 | 77 | | |
| MEAN | | 14 | | | | 6 | 6 | | 13 | | | | | | 8 | | | 45 | 43 |
| SD | | 2.5 | | | | 0.84 | 0.75 | | 2.7 | | | | | | | | | 6.8 | 7.4 |
| SE | | 0.57 | | | | 0.19 | 0.17 | | 0.63 | | | | | | | | | 1.6 | 1.7 |
| N | | 19 | | | | 19 | 19 | | 19 | | | | | | | | | 19 | 19 |

[a]Mis-sexed.

TABLE II-E-26 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 14 (CONTINUED)

RESULTS OF F1b GENERATION SECOND MATING (F2b)

DOSE - 80 PPM

| | | DAY 0 | | | | | | DAY 4 | | | | | | DAY 21 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE | DEATHS DAY 1-4 | LIVE PUPS | SEX MALE | SEX FEMALE | LITTER REDUCED MALE | LITTER REDUCED FEMALE | DEATHS DAY 5-21 | LIVE PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE |
| 7326 | 7317 | 17 | 1 | 6 | 11[a] | 5 | 6 | 1 | 16 | 6 | 10 | 4 | 4 | 0 | 8 | 5 | 3[a] | 50 | 47 |
| 7327 | 7318 | 17 | 0 | 9 | 8[a] | 6 | 6 | 1 | 16 | 7 | 9 | 4 | 4 | 0 | 8 | 4 | 4 | 55 | 51 |
| 7328 | 7317 | 16 | 0 | 7 | 9[a] | 7 | 7 | 0 | 16 | 7 | 9 | 4 | 4 | 0 | 8 | 4 | 4 | 59 | 56 |
| 7329 | 7318 | 13 | 1 | 9 | 5[a] | 7 | 6 | 0 | 13 | 9 | 4 | 4 | 4 | 0 | 8 | 4 | 4 | 50 | 48 |
| 7330 | 7321 | 11 | 0 | 6 | 5[a] | 6 | 5 | 0 | 11 | 5 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 35 | 31 |
| 7331 | 7324 | 12 | 0 | 7 | 5 | 6 | 6 | 0 | 12 | 7 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 57 | 54 |
| 7332 | 7321 | 17 | 0 | 6 | 11 | 6 | 6 | 0 | 17 | 6 | 11 | 4 | 4 | 0 | 8 | 4 | 4 | 52 | 51 |
| 7333 | 7320 | 14 | 0 | 6 | 8 | 6 | 6 | 0 | 14 | 6 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 54 | 50 |
| 7334 | 7320 | 16 | 0 | 8 | 8[a] | 7 | 7 | 0 | 16 | 8 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 47 | 48 |
| 7335 | 7324 | 14 | 0 | 7 | 7[a] | 6 | 6 | 1 | 13 | 4 | 9 | 4 | 4 | 0 | 8 | 4 | 4 | 42 | 44 |
| 7336 | 7322 | 18 | 0 | 7 | 11[a] | 6 | 6 | 1 | 17 | 10 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 51 | 48 |
| 7337 | 7322 | 13 | 0 | 7 | 6[a] | 6 | 6 | 0 | 13 | 6 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 38 | 38 |
| 7338 | 7316 | 13 | 0 | 7 | 6[a] | 7 | 6 | 0 | 13 | 7 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 43 | 37 |
| 7339 | 7316 | 14 | 0 | 5 | 9[a] | 7 | 6 | 0 | 14 | 6 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 53 | 49 |
| 7340 | 7319 | 17 | 0 | 10 | 7 | 7 | 5 | 1 | 16 | 10 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 34 | 34 |
| 7341 | 7319 | 17 | 0 | 10 | 7 | 6 | 6 | 0 | 17 | 10 | 7 | 4 | 4 | 1 | 7 | 3 | 4 | 46 | 46 |
| 7342 | 7325 | 15 | 0 | 10 | 5 | 5 | 5 | 1 | 14 | 9 | 5 | 4 | 4 | 1 | 7 | 4 | 3 | 43 | 43 |
| 7343 | 7323 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 7344 | 7325 | 17 | 0 | 11 | 6[a] | 6 | 6 | 0 | 17 | 10 | 7 | 4 | 4 | 0 | 8 | 5 | 3[a] | 53 | 47 |
| 7345 | 7323 | 15 | 0 | 8 | 7 | 6 | 6 | 0 | 15 | 8 | 7 | 4 | 4 | 1 | 7 | 3 | 4 | 45 | 46 |
| TOTAL | | 286 | 1 | 146 | 141 | | | 6 | 280 | 141 | 139 | 76 | 76 | 3 | 149 | 76 | 73 | | |
| MEAN | | 15 | | | | 6 | 6 | | 15 | | | | | | 8 | | | 48 | 46 |
| SD | | 1.6 | | | | 0.63 | 0.52 | | 1.9 | | | | | | | | | 7.2 | 6.6 |
| SE | | 0.36 | | | | 0.14 | 0.12 | | 0.43 | | | | | | | | | 1.7 | 1.7 |
| N | | 19 | | | | 19 | 19 | | 19 | | | | | | | | | | |

[a]Pups mis-sexed.

TABLE II-E-26 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 14 (CONTINUED)

RESULTS OF F1b GENERATION - SECOND MATING (F2b)

DOSE - 750 PPM

| | | DAY 0 | | | | | | DAY 4 | | | | | | DAY 21 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE | DEATHS DAY 1-4 | LIVE PUPS | SEX MALE | SEX FEMALE | LITTER REDUCED MALE | LITTER REDUCED FEMALE | DEATHS DAY 5-21 | LIVE PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE |
| 7356 | 7351 | 13 | 1 | 6 | 8[a] | 7 | 7 | 0 | 13 | 7 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 58 | 56 |
| 7357 | 3753 | 13 | 0 | 5 | 8[a] | 7 | 7 | 0 | 13 | 6 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 54 | 50 |
| 7358 | 7354 | 16 | 0 | 7 | 9 | 6 | 6 | 0 | 16 | 7 | 9 | 4 | 4 | 0 | 8 | 4 | 4 | 55 | 54 |
| 7359 | 7346 | 14 | 0 | 4 | 10 | 6 | 5 | 0 | 14 | 4 | 10 | 4 | 4 | 0 | 8 | 4 | 4 | 50 | 47 |
| 7360 | 7353 | 12 | 0 | 5 | 7 | 6 | 6 | 0 | 12 | 5 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 38 | 34 |
| 7361 | 7348 | 14 | 0 | 6 | 8 | 6 | 6 | 0 | 14 | 6 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 42 | 45 |
| 7362 | 7354 | 12 | 1 | 8 | 5[a] | 5 | 5 | 0 | 12 | 9 | 3 | 5 | 3 | 1 | 7 | 4 | 3 | 42 | 38 |
| 7363 | 7349 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 7364 | 7351 | 15 | 0 | 11 | 4 | 6 | 6 | 2 | 13 | 9 | 4 | 4 | 4 | 0 | 8 | 4 | 4 | 44 | 38 |
| 7365 | 7352 | 14 | 0 | 8 | 6 | 6 | 7 | 0 | 14 | 8 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 54 | 56 |
| 7366 | 7355 | 15 | 0 | 8 | 7[a] | 6 | 5 | 0 | 15 | 7 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 49 | 46 |
| 7367 | 7346 | 12 | 0 | 5 | 7 | 6 | 6 | 0 | 12 | 5 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 56 | 52 |
| 7368 | 7355 | 12 | 1 | 10 | 3 | 7 | 6 | 0 | 12 | 9 | 3 | 5 | 3 | 0 | 8 | 5 | 3 | 63 | 52 |
| 7369 | 7349 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 7370 | 7350 | 15 | 0 | 8 | 7 | 6 | 6 | 0 | 15 | 8 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 53 | 54 |
| 7371 | 7352 | 11 | 2 | 7 | 6 | 7 | 6 | 0 | 11 | 6 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 51 | 47 |
| 7372 | 7347 | 15 | 0 | 6 | 9 | 6 | 6 | 0 | 15 | 6 | 9 | 4 | 4 | 0 | 8 | 4 | 4 | 53 | 49 |
| 7373 | 7347 | 13 | 0 | 5 | 8 | 6 | 6 | 0 | 13 | 5 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 49 | 46 |
| 7374 | 7348 | 14 | 0 | 10 | 4 | 6 | 5 | 14 | - | - | - | - | - | - | - | - | - | - | - |
| 7375 | 7350 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| TOTAL | | 230 | 5 | 119 | 116 | | | 16 | 214 | 107 | 107 | 66 | 62 | 1 | 127 | 66 | 62 | | |
| MEAN | | 14 | | | | 6 | 6 | | 13 | | | | | | 8 | | | 51 | 48 |
| SD | | 1.4 | | | | 0.64 | 0.66 | | 1.4 | | | | | | | | | 6.6 | 6.6 |
| SE | | 0.34 | | | | 0.13 | 0.16 | | 0.36 | | | | | | | | | 1.6 | 1.6 |
| N | | 17 | | | | 17 | 17 | | 16 | | | | | | | | | 16 | 16 |

[a]Pups mis-sexed.

TABLE II-E-27

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 15

PUP OBSERVATIONS (F2b)

| DOSE (PPM) | FEMALE NUMBER | DAY OF LACTATION | OBSERVATIONS |
|---|---|---|---|
| 0 | 7303 | 4 | ONE FEMALE - HEMATOMA ON NOSE. |
| | 7311 | 4 | ONE MALE - FOUND DEAD. |
| 80 | 7327 | 4 | ONE MALE - FOUND DEAD. |
| | 7336 | 2 | ONE MALE - FOUND DEAD. |
| 750 | 7361 | 0 | ONE MALE - HEMATOMA ON NOSE. |
| | 7374 | 4 | ONE MALE - FOUND DEAD; NO OTHERS FOUND. |

TABLE II-E-28

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 16

MEAN BODY WEIGHTS (G) OF F2b RATS

| DOSE (PPM) | SEX | | WEEK 4 | 9 | 11 | 20 |
|---|---|---|---|---|---|---|
| 0 | M | MEAN | 347 | 455 | 495 | 560 |
| | | SD | 31 | 33 | 43 | 53 |
| | | SE | 9.7 | 10 | 14 | 17 |
| | | N | 10 | 10 | 10 | 10 |
| 80 | M | MEAN | 345 | 465 | 498 | 559 |
| | | SD | 23 | 26 | 30 | 33 |
| | | SE | 7.2 | 8.3 | 9.6 | 10 |
| | | N | 10 | 10 | 10 | 10 |
| 750 | M | MEAN | 340 | 476 | 517 | 590 |
| | | SD | 35 | 40 | 36 | 54 |
| | | SE | 12 | 13 | 12 | 18 |
| | | N | 9 | 9 | 9 | 9 |
| 0 | F | MEAN | 217 | 254 | 267 | 296 |
| | | SD | 15 | 22 | 23 | 22 |
| | | SE | 3.3 | 5.0 | 5.0 | 4.8 |
| | | N | 20 | 20 | 20 | 20 |
| 80 | F | MEAN | 212 | 251 | 270 | 299 |
| | | SD | 20 | 31 | 27 | 32 |
| | | SE | 4.4 | 6.9 | 5.9 | 7.1 |
| | | N | 20 | 20 | 20 | 20 |
| 750 | F | MEAN | 220 | 262 | 270 | 305 |
| | | SD | 16 | 25 | 24 | 23 |
| | | SE | 3.4 | 5.4 | 5.2 | 4.9 |
| | | N | 21 | 21 | 21 | 21 |

TABLE II-E-29

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 17

MEAN FOOD CONSUMPTION (G) IN MALE F2b RATS

| DOSE (PPM) | SEX | | WEEK 4 | 9 | 11 | 20 |
|---|---|---|---|---|---|---|
| 0 | M | MEAN | 38 | 30 | 28 | 25 |
| | | SD | 4.2 | 6.4 | 5.4 | 4.9 |
| | | SE | 1.3 | 2.1 | 1.7 | 1.6 |
| | | N | 10 | 9 | 10 | 9 |
| 80 | M | MEAN | 35 | 31 | 28 | 30 |
| | | SD | 2.8 | 5.1 | 4.0 | 6.6 |
| | | SE | 0.87 | 1.6 | 1.3 | 2.1 |
| | | N | 10 | 10 | 10 | 10 |
| 750 | M | MEAN | 36 | 31 | 31 | 25 |
| | | SD | 1.6 | 8.9 | 3.6 | 3.2 |
| | | SE | 0.57 | 3.0 | 1.2 | 1.1 |
| | | N | 8 | 9 | 9 | 9 |
| 0 | F | MEAN | 36 | 27 | 24 | 30 |
| | | SD | 5.0 | 6.9 | 5.2 | 8.6 |
| | | SE | 1.5 | 1.6 | 1.3 | 2.1 |
| | | N | 11 | 18 | 17 | 17 |
| 80 | F | MEAN | 37 | 27 | 24 | 33 |
| | | SD | 5.1 | 6.0 | 6.2 | 4.7 |
| | | SE | 1.3 | 1.4 | 1.6 | 1.1 |
| | | N | 15 | 19 | 15 | 17 |
| 750 | F | MEAN | 33 | 25 | 25 | 29 |
| | | SD | 5.2 | 5.9 | 4.1 | 5.2 |
| | | SE | 1.6 | 1.4 | 1.1 | 1.1 |
| | | N | 11 | 18 | 15 | 21 |

# TABLE II-E-30

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 18

RESULTS OF THIRD GENERATION - FIRST MATING (F3a)

DOSE - 0 PPM (CONTROL)

| | | DAY 0 | | | | | | DAY 4 | | | | | | DAY 21 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | MEAN PUP WEIGHT (G) | | | | | | LITTER REDUCED | | | | | | MEAN PUP WEIGHT (G) | |
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX MALE | SEX FEMALE | MALE | FEMALE | DEATHS DAY 1-4 | LIVE PUPS | SEX MALE | SEX FEMALE | MALE | FEMALE | DEATHS DAY5-21 | LIVE PUPS | SEX MALE | SEX FEMALE | MALE | FEMALE |
| 1547A | 1539A | 12 | 0 | 7 | 5 | 7 | 7 | 0 | 12 | 7 | 5 | 4 | 4 | 8 | 0 | - | - | - | - |
| 1548A | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 1549A | 1540A | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 1550A | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 1551A | 1541A | 14 | 0 | 5 | 9 | 6 | 6 | 0 | 14 | 5 | 9 | 4 | 4 | 0 | 8 | 4 | 4 | 43 | 43 |
| 1552A | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 1553A | 1542A | 4 | 0 | 1 | 3 | 8 | 8 | 0 | 4 | 1 | 3 | 1 | 3 | 0 | 4 | 1 | 3 | 53 | 56 |
| 1554A | | 16 | 0 | 4 | 12 | 5 | 5 | 4 | 12 | 4 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 34 | 29 |
| 1555A | 1543A | 12 | 0 | 8 | 4 | 7 | 7 | 0 | 12 | 8 | 4 | 4 | 4 | 0 | 8 | 4 | 4 | 53 | 51 |
| 1556A | | 13 | 0 | 8 | 5 | 7 | 6 | 0 | 13 | 8 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 53 | 53 |
| 1557A | 1544A | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 1558A | | 11 | 1 | 8 | 4 | 7 | 6 | 0 | 11 | 7 | 4 | 4 | 4 | 0 | 8 | 4 | 4 | 50 | 49 |
| 1559A | 1545A | 11 | 0 | 5 | 6 | 6 | 6 | 0 | 11 | 5 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 42 | 36 |
| 1560A | | 17 | 0 | 8 | 9 | 6 | 6 | 0 | 17 | 8 | 9 | 4 | 4 | 0 | 8 | 4 | 4 | 41 | 40 |
| 1561A | 1546A | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 1562A | | 11 | 0 | 6 | 5 | 6 | 6 | 0 | 11 | 6 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 45 | 43 |
| 1563A | 1537A | 15 | 0 | 5 | 10 | 6 | 5 | 0 | 15 | 5 | 10 | 4 | 4 | 0 | 8 | 4 | 4 | 47 | 48 |
| 1564A | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 1565A | 1538A | 15 | 0 | 9 | 6 | 6 | 6 | 2 | 13 | 8 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 42 | 41 |
| 1566A | | 11 | 0 | 7 | 4 | 6 | 6 | 0 | 11 | 7 | 4 | 4 | 4 | 0 | 8 | 4 | 4 | 45 | 47 |
| TOTAL | | 162 | 1 | 81 | 82 | | | 6 | 156 | 79 | 77 | 49 | 51 | 8 | 92 | 45 | 47 | | |
| MEAN | | 12 | | | | 6 | 7 | | 12 | | | | | | 8 | | | 45 | 45 |
| SD | | 3.3 | | | | 0.77 | 0.80 | | 3.0 | | | | | | | | | 5.8 | 7.6 |
| SE | | 0.91 | | | | 0.21 | 0.22 | | 0.83 | | | | | | | | | 1.7 | 2.2 |
| N | | 13 | | | | 13 | 13 | | 13 | | | | | | | | | 12 | 12 |

TABLE II-E-30 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 18 (CONTINUED)

RESULTS OF THIRD GENERATION - FIRST MATING (F3a)

DOSE - 80 PPM

| | | DAY 0 | | | | | | DAY 4 | | | | | | DAY 21 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE | DEATHS DAY 1-4 | LIVE PUPS | SEX MALE | SEX FEMALE | LITTER REDUCED MALE | LITTER REDUCED FEMALE | DEATHS DAY 5-21 | LIVE PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE |
| 1577A | 1568A | 12 | 0 | 4 | 8 | 4 | 4 | 0 | 12 | 4 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 41 | 41 |
| 1578A | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 1579A | 1569A | 4 | 0 | 1 | 3 | 7 | 7 | 0 | 4 | 1 | 3 | 1 | 3 | 0 | 4 | 1 | 3 | 61 | 57 |
| 1580A | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 1581A | 1570A | 12 | 0 | 7 | 5 | 6 | 6 | 0 | 12 | 7 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 42 | 41 |
| 1582A | | 13 | 0 | 8 | 5 | 4 | 4 | 2 | 11 | 6 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 46 | 46 |
| 1583A | 1571A | 14 | 0 | 8 | 6 | 7 | 7 | 0 | 14 | 8 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 47 | 43 |
| 1584A | | 14 | 0 | 9 | 5 | 4 | 4 | 0 | 14 | 9 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 46 | 43 |
| 1585A | 1572A | 12 | 0 | 6 | 6 | 4 | 3 | 0 | 12 | 6 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 48 | 48 |
| 1586A | | 16 | 0 | 10 | 6 | 5 | 5 | 0 | 16 | 10 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 46 | 44 |
| 1587A | 1573A | 14 | 0 | 6 | 8 | 6 | 6 | 0 | 14 | 6 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 42 | 40 |
| 1588A | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 1589A | 1574A | 13 | 0 | 5 | 8 | 7 | 6 | 0 | 13 | 5 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 41 | 45 |
| 1590A | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 1591A | 1575A | 15 | 0 | 8 | 7 | 6 | 6 | 0 | 15 | 8 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 45 | 41 |
| 1592A | | 13 | 0 | 7 | 6 | 6 | 5 | 0 | 13 | 7 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 48 | 45 |
| 1593A | 1576A | 14 | 1 | 7 | 8 | 6 | 5 | 6 | 8 | 6 | 2 | 6 | 2 | 0 | 8 | 6 | 2 | 46 | 48 |
| 1594A | | 2 | 0 | 2 | 0 | 8 | - | 0 | 2 | 2 | 0 | 2 | 0 | 0 | 2 | 2 | 0 | 47 | - |
| 1595A | 1567A | 11 | 0 | 6 | 5 | 7 | 6 | 0 | 11 | 6 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 47 | 46 |
| 1596A | | 16 | 0 | 9 | 7 | 7 | 6 | 0 | 16 | 8 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 49 | 47 |
| TOTAL | | 195 | 1 | 103 | 93 | | | 8 | 187 | 99 | 88 | 61 | 57 | 0 | 118 | 61 | 57 | | |
| MEAN | | 12 | | | | 6 | 5 | | 12 | | | | | | 7 | | | 46 | 42 |
| SD | | 3.9 | | | | 1.3 | 1.2 | | 4.0 | | | | | | | | | 4.7 | 4.2 |
| SE | | 0.97 | | | | 0.32 | 0.30 | | 0.99 | | | | | | | | | 1.2 | 1.1 |
| N | | 16 | | | | 16 | 15 | | | | | | | | | | | | |

TABLE II-E-30 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 18 (CONTINUED)

RESULTS OF THIRD GENERATION - FIRST MATING (F3a)

DOSE - 750 PPM

| | | DAY 0 | | | | | | DAY 4 | | | | | | DAY 21 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE | DEATHS DAY 1-4 | LIVE PUPS | SEX MALE | SEX FEMALE | LITTER REDUCED MALE | LITTER REDUCED FEMALE | DEATHS DAY 5-12 | LIVE PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE |
| 1607A | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 1608A | 1597A | 15 | 1 | 10 | 6 | 6 | 5 | 0 | 15 | 9 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 44 | 43 |
| 1609A | | 18 | 0 | 7 | 11 | 7 | 6 | 1 | 17 | 7 | 10 | 4 | 4 | 0 | 8 | 4 | 4 | 45 | 45 |
| 1610A | 1598A | 12 | 0 | 6 | 6 | 8 | 8 | 0 | 12 | 6 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 55 | 47 |
| 1611A | | 13 | 0 | 4 | 9 | 6 | 6 | 0 | 13 | 4 | 9 | 4 | 4 | 0 | 8 | 4 | 4 | 54 | 50 |
| 1612A | 1599A | 12 | 0 | 7 | 5 | 8 | 7 | 1 | 11 | 7 | 4 | 4 | 4 | 0 | 8 | 4 | 4 | 52 | 49 |
| 1613A | | 16 | 0 | 9 | 7 | 6 | 6 | 0 | 16 | 9 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 46 | 42 |
| 1614A | 1600A | 13 | 0 | 5 | 8 | 6 | 6 | 0 | 13 | 5 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 37 | 34 |
| 1615A | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 1616A | 1601A | 15 | 1 | 7 | 9 | 6 | 6 | 0 | 15 | 7 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 56 | 55 |
| 1617A | | 14 | 0 | 9 | 5 | 7 | 7 | 0 | 14 | 9 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 53 | 50 |
| 1618A | 1602A | 12 | 0 | 6 | 6 | 7 | 6 | 0 | 12 | 6 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 50 | 46 |
| 1619A | | 12 | 0 | 9 | 3 | 6 | 6 | 0 | 12 | 9 | 3 | 5 | 3 | 0 | 8 | 5 | 3 | 48 | 48 |
| 1620A | 1603A | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 1621A | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 1622A | 1604A | 10 | 0 | 7 | 3 | 6 | 6 | 0 | 10 | 7 | 3 | 5 | 3 | 3 | 5 | 4 | 1 | 38 | 37 |
| 1623A | | 14 | 0 | 7 | 7 | 7 | 7 | 0 | 14 | 7 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 43 | 39 |
| 1624A | 1605A | 14 | 0 | 7 | 7 | 6 | 5 | 0 | 14 | 7 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 43 | 40 |
| 1625A | | 14 | 0 | 8 | 6 | 8 | 7 | 1 | 13 | 7 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 53 | 49 |
| 1626A | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| TOTAL | | 204 | 2 | 108 | 98 | | | 3 | 201 | 106 | 95 | 62 | 58 | 3 | 117 | 61 | 56 | | |
| MEAN | | 14 | | | | 7 | 6 | | 13 | | | | | | 8 | | | 48 | 45 |
| SD | | 2.0 | | | | 0.82 | 0.80 | | 1.88 | | | | | | | | | 6.1 | 5.7 |
| SE | | 0.51 | | | | 0.21 | 0.21 | | 0.49 | | | | | | | | | 1.6 | 1.5 |
| N | | 15 | | | | 15 | 15 | | | | | | | | | | | | |

[a]Not bred; male No. 1606[A] mis-sexed.

TABLE II-E-31

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 19

PUP OBSERVATIONS (F3a)

| DOSE (PPM) | FEMALE NUMBER | DAY OF LACTATION | OBSERVATIONS |
|---|---|---|---|
| 0 | 1547 | 11 | THREE MALES - FOUND DEAD; TWO FEMALES - FOUND DEAD; ONE PUP CANNIBALIZED (SEX NOT DETERMINED). |
| | | 12 | ONE MALE - FOUND DEAD. |
| 80 | 1595 | 0 | ONE FEMALE - PART OF TAIL APPARENTLY BITTEN OFF. |
| | | 4 | ONE FEMALE - SHORTENED TAIL. |
| 750 | 1609 | 3 | ONE FEMALE - FOUND DEAD. |
| | 1625 | 4 | ONE MALE - FOUND DEAD. |

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 20

PUP NECROPSY OBSERVATIONS (F3a)

| DOSE (PPM) | FEMALE NUMBER | NUMBER OF PUPS | OBSERVATIONS |
|---|---|---|---|
| 0 | 1555A | 8 | ALL TISSUES APPEAR NORMAL. |
| | 1560A | 8 | ALL TISSUES APPEAR NORMAL. |
| | 1563A | 8 | ALL TISSUES APPEAR NORMAL. |
| | 1566A | 8 | ALL TISSUES APPEAR NORMAL. |
| 80 | 1577A | 8 | ALL TISSUES APPEAR NORMAL. |
| | 1582A | 8 | ALL TISSUES APPEAR NORMAL. |
| | 1583A | 8 | ALL TISSUES APPEAR NORMAL. |
| | 1589A | 8 | ALL TISSUES APPEAR NORMAL. |
| | 1594A | 2 | ALL TISSUES APPEAR NORMAL. |
| 750 | 1609A | 8 | ALL TISSUES APPEAR NORMAL. |
| | 1613A | 8 | ALL TISSUES APPEAR NORMAL. |
| | 1619A | 8 | THREE PUPS - MOTTLED THYMUS. |
| | 1624A | 8 | ALL TISSUES APPEAR NORMAL. |
| | 1625A | 8 | ALL TISSUES APPEAR NORMAL. |

# TABLE II-E-33

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 21

RESULTS OF F2b GENERATION - SECOND MATING (F3b)

DOSE - 0 PPM (CONTROL)

| | | DAY 0 | | | | | | DAY 4 | | | | | | DAY 21 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE | DEATHS DAY 1-4 | LIVE PUPS | SEX MALE | SEX FEMALE | LITTER REDUCED MALE | LITTER REDUCED FEMALE | DEATHS DAY 5-21 | LIVE PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE |
| 1547A | 1538A | 15 | 0 | 5 | 10 | 6 | 6 | 0 | 15 | 8 | 7[a] | 4 | 4 | 0 | 8 | 4 | 4 | 55 | 55 |
| 1548A | | 9 | 0 | 5 | 4 | 8 | 7 | 0 | 9 | 5 | 4 | 4 | 4 | 0 | 8 | 5 | 3[a] | 51 | 39 |
| 1549A | 1537A | 7 | 0 | 6 | 1 | 7 | 7 | 0 | 7 | 5 | 2[a] | 5 | 2 | 0 | 7 | 5 | 2 | 59 | 56 |
| 1550A | | 9 | 1 | 4 | 6 | 5 | 5 | 0 | 9 | 6 | 3[a] | 5 | 3 | 0 | 8 | 4 | 4[a] | 34 | 37 |
| 1551A | 1546A | 12 | 0 | 6 | 6 | 6 | 6 | 0 | 12 | 6 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 40 | 40 |
| 1552A | | 10 | 1 | 5 | 6 | 7 | 7 | 0 | 10 | 5 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 55 | 53 |
| 1553A | 1545A | 13 | 1 | 5 | 9 | 6 | 6 | 0 | 13 | 5 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 48 | 51 |
| 1554A | | 17 | 0 | 7 | 10 | 6 | 6 | 1 | 16 | 7 | 9 | 4 | 4 | 0 | 8 | 4 | 4 | 53 | 51 |
| 1555A | 1544A | 14 | 0 | 5 | 9 | 6 | 5 | 0 | 14 | 5 | 9 | 4 | 4 | 0 | 8 | 4 | 4 | 50 | 46 |
| 1556A | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 1557A | 1543A | 13 | 0 | 5 | 8 | 6 | 6 | 0 | 13 | 5 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 56 | 54 |
| 1558A | | 11 | 1 | 4 | 8 | 7 | 7 | 0 | 11 | 3 | 8 | 3 | 5 | 0 | 8 | 3 | 5 | 61 | 59 |
| 1559A | 1542A | 13 | 0 | 6 | 7 | 7 | 7 | 0 | 13 | 6 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 30 | 34 |
| 1560A | | 16 | 0 | 4 | 12 | 7 | 6 | 2 | 14 | 4 | 10 | 4 | 4 | 1 | 7 | 4 | 3 | 34 | 36 |
| 1561A | 1541A | 13 | 0 | 9 | 4 | 6 | 6 | 0 | 13 | 9 | 4 | 4 | 4 | 0 | 8 | 4 | 4 | 58 | 55 |
| 1562A | | 15 | 0 | 4 | 11 | 5 | 6 | 1 | 14 | 4 | 10 | 4 | 4 | 0 | 8 | 4 | 4 | 52 | 53 |
| 1563A | 1540A | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 1564A | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 1565A | 1539A | 14 | 0 | 6 | 8 | 7 | 6 | 0 | 14 | 6 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 62 | 59 |
| 1566A | | 10 | 0 | 7 | 3 | 7 | 6 | 0 | 10 | 7 | 3 | 5 | 3 | 0 | 8 | 5 | 3 | 39 | 32 |
| TOTAL | | 211 | 4 | 93 | 122 | | | 4 | 207 | 96 | 111 | 70 | 65 | 1 | 134 | 70 | 64 | | |
| MEAN | | 12 | | | | 6 | 6 | | 12 | | | | | | 8 | | | 49 | 48 |
| SD | | 2.7 | | | | 0.79 | 0.64 | | 2.46 | | | | | | | | | 10 | 9.3 |
| SE | | 0.66 | | | | 0.19 | 0.15 | | 0.60 | | | | | | | | | 2.5 | 2.2 |
| N | | 17 | | | | | | | 17 | | | | | | | | | 17 | 17 |

[a]Pups mis-sexed.

TABLE II-E-33 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 21 (CONTINUED)

RESULTS OF F2b GENERATION - SECOND MATING (F3b)

DOSE - 80 PPM

| | | DAY 0 | | | | | | DAY 4 | | | | | | DAY 21 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | MEAN PUP WEIGHT (G) | | | | | | LITTER REDUCED | | | | | | MEAN PUP WEIGHT (G) | |
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX MALE | SEX FEMALE | MALE | FEMALE | DEATHS DAY 1-4 | LIVE PUPS | SEX MALE | SEX FEMALE | MALE | FEMALE | DEATHS DAY 5-21 | LIVE PUPS | SEX MALE | SEX FEMALE | MALE | FEMALE |
| 1577A | 1576A | 11 | 0 | 5 | 6 | 6 | 6 | 0 | 11 | 5 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 33 | 31 |
| 1578A | | 13 | 0 | 7 | 6 | 7 | 6 | 0 | 13 | 7 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 57 | 50 |
| 1579A | 1567A | 11 | 0 | 8 | 3 | 9 | 8 | 0 | 11 | 8 | 3 | 5 | 3 | 0 | 8 | 5 | 3 | 37 | 31 |
| 1580A | | 9 | 1 | 4 | 6 | 7 | 6 | 0 | 9 | 3 | 6 | 3 | 5 | 0 | 8 | 3 | 5 | 32 | 31 |
| 1581A | 1575A | 15 | 0 | 7 | 8 | 6 | 6 | 0 | 15 | 7 | 8 | 4 | 4 | 0 | 8 | 3 | 5[a] | 32 | 27 |
| 1582A | | 15 | 0 | 12 | 3 | 9 | 8 | 0 | 15 | 12 | 3 | 5 | 3 | 0 | 8 | 4 | 4[a] | 55 | 55 |
| 1583A | 1574A | 15 | 0 | 6 | 9 | 6 | 6 | 0 | 15 | 6 | 9 | 4 | 4 | 0 | 8 | 4 | 4 | 55 | 53 |
| 1584A | | 15 | 1 | 6 | 10 | 6 | 6 | 0 | 15 | 5 | 10 | 4 | 4 | 0 | 8 | 4 | 4 | 46 | 44 |
| 1585A | 1573A | - | - | - | - | - | - | 0 | - | - | - | - | - | - | - | - | - | - | - |
| 1586A | | 13 | 4 | 10 | 7 | 6 | 5 | 0 | 13 | 8 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 28 | 17 |
| 1587A | 1572A | 13 | 0 | 7 | 6 | 7 | 7 | 0 | 13 | 7 | 6 | 4 | 4 | 1 | 7 | 3 | 4 | 37 | 32 |
| 1588A | | - | - | - | - | - | - | 0 | - | - | - | - | - | - | - | - | - | - | - |
| 1589A | 1571A | 9 | 0 | 5 | 4 | 7 | 7 | 0 | 9 | 5 | 4 | 4 | 4 | 0. | 8 | 4 | 4 | 32 | 34 |
| 1590A | 1570A | - | - | - | - | - | - | 0 | - | - | - | - | - | - | - | - | - | - | - |
| 1591A | | 15 | 0 | 9 | 6 | 7 | 7 | 0 | 15 | 9 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 41 | 40 |
| 1592A | 1569A | 15 | 0 | 10 | 5 | 6 | 6 | 0 | 15 | 10 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 46 | 50 |
| 1593A | | - | - | - | - | - | - | 0 | - | - | - | - | - | - | - | - | - | - | - |
| 1594A | 1568A | 8 | 1 | 1 | 8 | 6 | 5 | 0 | 8 | 2 | 6[a] | 2 | 6 | 0 | 8 | 2 | 6 | 53 | 51 |
| 1595A | | 14 | 0 | 4 | 10 | 7 | 6 | 0 | 14 | 5 | 9[a] | 4 | 4 | 0 | 8 | 4 | 4 | 56 | 51 |
| 1596A | 1571A | 15 | 0 | 6 | 9 | 7 | 6 | 0 | 15 | 6 | 9 | 4 | 4 | 0 | 8 | 4 | 4 | 57 | 53 |
| TOTAL | | 206 | 7 | 107 | 106 | | | 0 | 206 | 105 | 101 | 63 | 65 | 1 | 127 | 60 | 67 | | |
| MEAN | | 13 | | | | 7 | 6 | | 13 | | | | | | 8 | | | 44 | 41 |
| SD | | 2.5 | | | | 0.98 | 0.87 | | 2.6 | | | | | | | | | 11 | 12 |
| SE | | 0.63 | | | | 0.25 | 0.22 | | 0.63 | | | | | | | | | 2.7 | 2.9 |
| N | | 16 | | | | 16 | 16 | | 16 | | | | | | | | | 16 | 16 |

[a]Pups mis-sexed.

TABLE II-E-33 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 21 (CONTINUED)

RESULTS OF F2b GENERATION - SECOND MATING (F3b)

DOSE - 750 PPM

| | | DAY 0 | | | | | | DAY 4 | | | | | | DAY 21 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FEMALE NUMBER | MALE NUMBER | LIVE PUPS | DEAD PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE | DEATHS DAY 1-4 | LIVE PUPS | SEX MALE | SEX FEMALE | LITTER REDUCED MALE | LITTER REDUCED FEMALE | DEATHS DAY 5-21 | LIVE PUPS | SEX MALE | SEX FEMALE | MEAN PUP WEIGHT (G) MALE | MEAN PUP WEIGHT (G) FEMALE |
| 1607A | Not bred | | | | | | | | | | | | | | | | | | |
| 1608A | 1605A | 5 | 0 | 3 | 2 | 8 | 7 | 0 | 5 | 3 | 2 | 3 | 2 | 1 | 4 | 3 | 1 | 47 | 40 |
| 1609A | | 16 | 0 | 11 | 5 | 7 | 6 | 1 | 15 | 11 | 4 | 4 | 4 | 0 | 8 | 4 | 4 | 31 | 32 |
| 1610A | 1604A | 10 | 0 | 4 | 6 | 8 | 8 | 0 | 10 | 4 | 6 | 4 | 4 | 0 | 8 | 4 | 4 | 43 | 40 |
| 1611A | | 14 | 0 | 7 | 7 | 7 | 7 | 0 | 14 | 7 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 63 | 58 |
| 1612A | 1603A | 12 | 0 | 8 | 4 | 5 | 5 | 0 | 12 | 6 | 6[a] | 4 | 4 | 1 | 7 | 4 | 3 | 28 | 30 |
| 1613A | 1602A | 13 | 0 | 8 | 5 | 6 | 6 | 0 | 13 | 8 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 28 | 30 |
| 1614A | | 13 | 0 | 5 | 8 | 7 | 6 | 1 | 12 | 5 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 32 | 26 |
| 1615A | 1601A | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 1616A | 1603A | 14 | 0 | 6 | 8 | 7 | 7 | 0 | 14 | 6 | 8 | 4 | 4 | 0 | 8 | 3 | 5[a] | 41 | 46 |
| 1617A | 1600A | 11 | 0 | 5 | 6 | 7 | 7 | 0 | 11 | 6 | 5[a] | 4 | 4 | 0 | 8 | 4 | 4 | 47 | 48 |
| 1618A | | 13 | 2 | 7 | 8 | 7 | 7 | 0 | 13 | 6 | 7 | 4 | 4 | 1 | 7 | 3 | 4 | 47 | 40 |
| 1619A | 1599A | 12 | 1 | 6 | 7 | 7 | 6 | 0 | 12 | 5 | 7 | 4 | 4 | 0 | 8 | 4 | 4 | 62 | 57 |
| 1620A | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 1621A | 1598A | 14 | 0 | 4 | 10 | 8 | 7 | 0 | 14 | 4 | 10 | 4 | 4 | 0 | 8 | 4 | 4 | 35 | 33 |
| 1622A | | 15 | 0 | 7 | 8 | 6 | 5 | 0 | 15 | 7 | 8 | 4 | 4 | 0 | 8 | 4 | 4 | 37 | 41 |
| 1623A | 1597A | 16 | 0 | 6 | 10 | 6 | 6 | 1 | 15 | 6 | 9 | 4 | 4 | 0 | 8 | 4 | 4 | 53 | 45 |
| 1624A | | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 1625A | Not bred | | | | | | | | | | | | | | | | | | |
| 1626A | 1601A | 10 | 0 | 6 | 4 | 7 | 7 | 0 | 10 | 5 | 5 | 4 | 4 | 0 | 8 | 4 | 4 | 43 | 44 |
| TOTAL | | 188 | 3 | 93 | 98 | | | 3 | 185 | 89 | 96 | 59 | 58 | 3 | 114 | 57 | 57 | | |
| MEAN | | 13 | | | | 7 | 6 | | 12 | | | | | | 8 | | | 43 | 41 |
| SD | | 2.8 | | | | 0.83 | 0.83 | | 2.6 | | | | | | | | | 11 | 9.5 |
| SE | | 0.72 | | | | 0.21 | 0.21 | | 0.68 | | | | | | | | | 2.9 | 2.4 |
| N | | 15 | | | | 15 | 15 | | 15 | | | | | | | | | 15 | 15 |

[a]Pups mis-sexed.

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 22

PUP OBSERVATIONS (F3b)

| DOSE (PPM) | FEMALE NUMBER | DAY OF LACTATION | OBSERVATIONS |
|---|---|---|---|
| 0 | 1550A | 4 | ONE FEMALE - SCAB ON NOSE. |
| | 1554A | 4 | ONE FEMALE - FOUND DEAD. |
| | 1559A | 4 | ONE MALE - BENT TAIL. |
| | 1560A | 4 | TWO FEMALES - CANNIBALIZED. |
| | 1562A | 4 | ONE FEMALE - CANNIBALIZED. |
| 80 | 1586A | 4 | ONE FEMALE - CANNIBALIZED |
| | 1587A | 4 | ONE MALE - SCAB ON NOSE. |
| 750 | 1609A | 4 | ONE FEMALE - CANNIBALIZED. |
| | 1614A | 4 | ONE FEMALE - CANNIBALIZED. |
| | 1628A | 4 | ONE FEMALE - CANNIBALIZED. |

TABLE II-E-35

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 23

PUP NECROPSY OBSERVATIONS (F3b)

| DOSE (PPM) | FEMALE NUMBER | NUMBER OF PUPS | OBSERVATIONS |
|---|---|---|---|
| 0 | 1550A | 8 | ALL TISSUES APPEAR NORMAL. |
| | 1552A | 8 | ALL TISSUES APPEAR NORMAL. |
| | 1555A | 8 | ALL TISSUES APPEAR NORMAL. |
| | 1557A | 8 | ALL TISSUES APPEAR NORMAL. |
| | 1558A | 8 | ONE FEMALE - MOTTLED KIDNEYS. |
| | 1560A | 7 | ALL TISSUES APPEAR NORMAL. |
| | 1566A | 8 | ALL TISSUES APPEAR NORMAL. |
| 80 | 1578A | 8 | ALL TISSUES APPEAR NORMAL. |
| | 1579A | 8 | ALL TISSUES APPEAR NORMAL. |
| | 1580A | 8 | ALL TISSUES APPEAR NORMAL. |
| | 1582A | 8 | ALL TISSUES APPEAR NORMAL. |
| | 1586A | 8 | ALL TISSUES APPEAR NORMAL. |
| | 1587A | 5 | ALL TISSUES APPEAR NORMAL. |
| | 1595A | 8 | ALL TISSUES APPEAR NORMAL. |
| 750 | 1608A | 4 | ALL TISSUES APPEAR NORMAL. |
| | 1613A | 8 | ALL TISSUES APPEAR NORMAL. |
| | 1616A | 8 | ALL TISSUES APPEAR NORMAL. |
| | 1617A | 8 | ALL TISSUES APPEAR NORMAL. |
| | 1619A | 8 | ALL TISSUES APPEAR NORMAL. |
| | 1622A | 8 | ALL TISSUES APPEAR NORMAL. |
| | 1623A | 8 | ALL TISSUES APPEAR NORMAL. |

TABLE II-E-36

LITTON BIONETICS, INC.
PROJECT NO. 10734-07

TABLE 24

ADULT NECROPSY OBSERVATIONS (F2b)

| DOSE (PPM) | SEX | ANIMAL NUMBER | OBSERVATIONS |
|---|---|---|---|
| 0 | M | | NO VISIBLE ABNORMALITIES. |
| | F | 1561A | HARD MASS (1.5 X 1.5 CM) MAMMARY REGION, RIGHT LATERAL THORAX. |
| 80 | M | | NO VISIBLE ABNORMALITIES. |
| | F | 1581A | MOTTLED KIDNEYS. |
| 750 | M | | NO VISIBLE ABNORMALITIES. |
| | F | 1616A | MOTTLED KIDNEYS. |
| | F | 1626A | MOTTLED KIDNEYS. |

SPONSOR: Environmental Protection Department
US Army Medical Bioengineering Research and Development Laboratory

MATERIAL: Dicyclopentadiene (DCPD)

SUBJECT: FINAL REPORT
Analysis of Diet Formulations
LBI Project No. 10734-7

## 1. OBJECTIVE

The objective of this study was to analyze DCPD in animal chow with regards to stability and formulation content in diet.

## 2. MATERIAL AND EXPERIMENTAL DESIGN

The analysis of the dosed feed was performed by the following chromatographic method.

### Scope

This method describes the analytical procedure for the determination of DCPD in dosed feed used by Litton Bionetics, Inc. (LBI) during the course of the study.

### Principle

A five gram feed subsample is extracted with 20 ml of diethyl ether by shaking for 15 min in an automated shaker. The extract is clarified by centrifugation for 10 min at 1350 rpm. The extracts are analyzed with a Varian 2100 gas chromatograph equipped with flame ionization detectors.

The DCPD content is calculated from a calibration curve obtained by GLC analysis of reference solutions of DCPD in ether.
Control and spiked control feed samples are analyzed concurrently to correct for possible feed background and compound recovery.

### Equipment and Supplies

Graduated conical Falcon tubes, 50 ml, with positive seal caps (available from Becton, Dickinson and Company, Oxnard, CA, 93030; stock number H8292-209811).

Volumetric glassware - 1, 4, 5, and 10 ml pipettes; 50 and 100 ml flasks.

Graduated cylinder - 25 ml capacity.

Graduated glass centrifuge tubes, 15 ml, with ground glass stoppers.

Mechanical shaker.

Centrifuge.

Analytical laboratory balance (accurate to 0.01 mg).

Top-loading laboratory balance (accurate to 0.01g).

Gas-liquid chromatograph - Varian 2100, equipped with a 1.8 m x 2 mm I.D. glass column packed with 10% FFAP on 80/100 mesh Supelcoport, flame ionization detectors.

Diethyl ether (Burdick and Jackson).

Dicyclopentadiene.

Preparation of Standard

Prepare a stock standard solution of DCPD by dissolving 50 mg of DCPD in 50 ml of Acetone.

Take a 5 ml aliquot and dilute to 100 ml with diethyl ether in a volumetric flask. This solution has a concentration of 0.05 mg/ml.

Prepare a standard curve by injecting 1, 2 and 3 µl of the standard solution into a Varian 2100 gas chromatograph with the following parameters:

| | |
|---|---|
| Column temperature: | 60°C |
| Injector temperature: | 225°C |
| FID temperature: | 250°C |
| Chart: | 6 min/inch |
| Carrier gas flow: | 40 cc/min nitrogen |
| Attn.: | $8 \times 10^{-11}$ |

Procedure:

Weigh a 5 g sample of the dosed feed to the nearest 0.01 g in a Falcon tube.

Extract the sample with 20 ml of diethyl ether by mixing for 15 min in a mechanical shaker, followed by centrifugation at 1300 rpm for 10 min.

Dilute the high-dose level (750 ppm) in a 15 ml graduated centrifuge tube by adding a 1 ml aliquot to 4 ml of diethyl ether.

Repeat above procedure using undosed animal feed of the same lot used for the preparation of the dosed feed. This extract will be used as a negative control to assure that there are no interfering peaks contributed by the feed itself.

Repeat above procedure using undosed animal feed of the same lot which has been spiked in the laboratory with DCPD at corresponding dose levels.

Quantitate the amount of DCPD in solution by comparing to the calibration curve prepared above.

Calculations

Calculate the ppm of DCPD in the dosed feed or spiked (recovery) sample as follows:

To determine mg of sample injected:

$$\frac{5g \text{ feed}}{20 \text{ ml ether}} = \frac{250 \text{ mg feed}}{1.0 \text{ ml ether}}$$

$$\frac{250 \text{ mg feed}}{1.0 \text{ ml ether}} \times \text{Dilution Factor} = \frac{(x) \text{ mg feed}}{1.0 \text{ ml ether}}$$

Dilution Factor = 1 for 80 ppm level
= 0.2 for 750 ppm level

$$\frac{(x) \text{ mg feed}}{1.0 \text{ ml ether}} \times \frac{\mu l \text{ sample}}{1000} = \text{mg of feed injected}$$

Calculate the intercept and slope from standard curve as determined by linear regression correlation.

$$\frac{\text{Peak Response (peak height) - intercept}}{\text{slope}} = \text{ng of DCPD injected}$$

To determine ppm:

$$\frac{\text{ng of DCPD found}}{\text{mg of feed injected}} = \text{ppm}$$

Determine method recovery from spiked samples as follows:

$$\text{percent recovery} = \frac{\text{ppm found} \times 100}{\text{ppm added}}$$

Correct the result of the dosed feed sample for method recovery of its corresponding spiked sample.

$$\text{corrected ppm} = \frac{\text{sample ppm} \times 100}{\text{percent recovery}}$$

## 3. RESULTS

### Stability Analysis

Samples were analyzed the day the mix was received by the analytical laboratory. This corresponded to Day 1 of the stability study when Day 0 is considered the mix date. Two aliquots of feed were removed from each diet level of samples 0433, 0434 and 0435 and stored at ambient conditions. One aliquot was stored in a closed container, while the other was stored in an open container.

The two aliquots were analyzed 9 days later (day 10) by the standard method. Results of the analysis are indicated in Table 1.

In the closed containers, the concentration dropped 27.6% for the 80 ppm level and 30.8% for the 750 ppm level.

In the open containers, after 10 days no DCPD could be detected in either high- or low-dose samples.

DCPD is a liquid which at ambient temperature tends to volatilize from the feed mixture. This may account for the results noted in the open container stability study. In the closed container the DCPD may volatilize as much as the head space in the storage container will permit. At the saturation point, an equilibrium between the vapors and liquid is achieved and the concentration of DCPD in feed remains constant. This appears to be at 70% of the theoretical concentration.

### Weekly Diet Analysis

DCPD samples were analyzed on a weekly basis by the method previously described. Samples were received by the analytical laboratory and stored at ambient conditions for the first five feed mixtures. Thereafter, samples were stored in the freezer. This action was required due to the volatile nature of the compound. Results of the analysis are indicated in Table 2.

For the 80 ppm level, the average value of the course of the study was $69.3 \pm 8.2$ ppm. This corresponds to $86.6 \pm 10.3\%$ of the theoretical concentration.

For the 750 ppm level, the average value obtained was $693 \pm 68.0$ ppm, which corresponds to $92.4 \pm 9.1\%$ of the theoretical value.

The values for the rat reproduction study was, on the average, approximately 10% below the theoretical value. This fact may be attributed to the volatile nature of DCPD, and the time between mixing and analysis. During the latter part of the study, the interval between the analysis and the mixing was decreased as much as possible. An improvement in the analytical values resulted.

LITTON BIONETICS, INC.
Kensington, MD 20795

SUBMITTED BY:

J.D. Mitchell
Analytical Chemist

14 May 79
Date

REVIEWED BY:

H.J. Paulin, M.S.
Analytical Chemist

E.D. Helton, Ph.D.
Director, Dept. of
Chemistry

14 May 1979
Date

PART II - SECTION F

THREE-MONTH SUBCHRONIC TOXICITY IN DOGS

DCPD

LBI PROJECT NO. 10734-09

## SUMMARY

The test material, Dicyclopentadiene, was administered by incorporation into the diet at concentrations of 100, 300, and 1000 ppm to Beagle dogs for 13 weeks. The animals were observed daily for general condition and behavior. Clinical pathological evaluations, including analysis of the clinical chemical constituents of serum, urine and hemograms, were performed at approximately monthly intervals. Tissues from the control and high dose dogs were compared histopathologically for differences. Based on the results obtained using these criteria it was concluded that treatment produced no significant toxicity with the possible exception of minor indications of intestinal distress expressed as vomiting and soft stools among dogs of the treated groups, especially the highest dose (1000 ppm).

## OBJECTIVE

The objective of this study was to evaluate and characterize the toxicity of the test material by incorporation in the diet to dogs for 13 weeks.

## MATERIAL

Refer to Part II - Section A.

## EXPERIMENTAL DESIGN

Thirty-four purebred beagle dogs (approximately five months of age) were received from Laboratory Research Enterprises, Inc. (LRE), Kalamazoo, Michigan, and maintained for 4 months in the Falls Church facility of the Department of Toxicology. The planned initiation of the study was delayed under the direction of the LBI Department of Safety and Health because of a possible hazard to personnel. The dogs were transferred to the Rockville facility of the Department of Toxicology and acclimated for 4 weeks. The animals were individually housed in stainless steel cages in temperature-controlled quarters under artificial illumination controlled to provide a 12-hour light cycle. Purina Dog Chow and water were provided ad libitum.

Prior to initiation of the study, all dogs were given a preliminary health screening which included clinical biochemical, hematological, ophthalmological and parasitological testing. Examination showed that 17 out of 34 dogs had parasites. In 16 dogs, Giardia canis cysts were found. Isopora species oocysts were found in two dogs and Trichomonas species in one dog. Since the pathogenicity of the mentioned parasites was questionable, treatment was not initiated. All dogs had been immunized by LRE against distemper, hepatitis, leptospirosis and rabies prior to receipt.

Thirty-two dogs were selected for use in the study. The dogs had been identified by tattoo at LRE and were given LBI dog numbers. Dogs were randomly selected and placed into groups as noted below.

| Group Number | Number of Animals | | Dose (ppm) |
|---|---|---|---|
| | Males | Females | |
| 1 | 4 | 4 | 0 |
| 2 | 4 | 4 | 100 |
| 3 | 4 | 4 | 300 |
| 4 | 4 | 4 | 1000 |

Initial clinical pathological determinations did not reveal any abnormalities. Following these determinations, two dogs (Nos. 00410 and 00428) were eliminated from the study. The remaining dogs were chosen for the study and assigned to groups as detailed in Text Table A. Date of first dose was May 10, 1978.

Dietary concentrations were selected by a representative of the sponsor. The feed and test material were mixed weekly. A premix was prepared in corn oil, manually mixed with the appropriate amount of test material and blended with the dog meal for 20 minutes in a blender. A sample of each weekly formulation was sent to the LBI Analytical Laboratory for analysis with respect to correctness of formulation.

TABLE II-F-37

LITTON BIONETICS, INC.
PROJECT NO. 10734-9

TABLE A

GROUP ASSIGNMENT

| GROUP NUMBER | DOSE LEVEL (PPM) | SEX | L.R.E. TATTOO NUMBER | LBI NUMBER |
|---|---|---|---|---|
| 1 | 0 | M | PK 77 | 408 |
| | | M | DI 77 | 411 |
| | | M | QS 77 | 417 |
| | | M | MK 77 | 418 |
| | | F | GZ 77 | 425 |
| | | F | EI 77 | 426 |
| | | F | LB 77 | 434 |
| | | F | EZ 77 | 435 |
| 2 | 100 | M | LS 77 | 405 |
| | | M | NW 77 | 406 |
| | | M | GB 77 | 407 |
| | | M | LI 77 | 415 |
| | | F | FJ 77 | 422 |
| | | F | LL 77 | 429 |
| | | F | OH 77 | 430 |
| | | F | IR 77 | 431 |
| 3 | 300 | M | MM 77 | 404 |
| | | M | LT 77 | 409 |
| | | M | OL 77 | 412 |
| | | M | NY 77 | 414 |
| | | F | OV 77 | 421 |
| | | F | FO 77 | 424 |
| | | F | AR 77 | 427 |
| | | F | LO 77 | 433 |
| 4 | 1000 | M | MB 77 | 413 |
| | | M | PI 77 | 416 |
| | | M | OJ 77 | 419 |
| | | M | KK 77 | 420 |
| | | F | JL 77 | 423 |
| | | F | HO 77 | 432 |
| | | F | IT 77 | 436 |
| | | F | FF 77 | 437 |

EXPERIMENTAL DESIGN (Continued)

The dogs were observed daily for general appearance, behavior, food consumption and fecal consistency. Body weights were recorded weekly on each animal. Initially and at 4, 8 and 13 weeks, blood was collected for the following pathological determinations. The dogs were fasted overnight prior to blood collection.

Hematology

hemoglobin
erythrocytes
leukocytes
differential count
packed cell volume

Blood Chemistry

glucose
calcium
urea nitrogen
serum glutamic-pyruvic transaminase
serum glutamic-oxaloacetic transaminase
uric acid
potassium[a]
alkaline phosphatase
total protein
albumin
cholesterol
lactic dehydrogenase
phosphorus
bilirubin
sodium[a]
chloride[a]

[a]Performed initially, only.

Urinalysis was performed on all animals initially and at 8 and 13 weeks. The dogs were fasted overnight prior to urine collection for determination of the following.

specific gravity
pH
color
sugar
albumin
ketones
occult blood
bilirubin
microscopic examination of sediment

Ophthalmologic examinations were performed initially and before termination of the study. These evaluations were conducted by James M. Clinton, V.M.D., Consulting Veterinary Ophthalmologist.

After 94 to 97 days of treatment, the dogs were killed. Each animal was weighed and subjected to a complete necropsy. Appropriate samples of each of the following organs and tissues were preserved in 10% neutral buffered formalin.

brain[a]
pituitary
spinal cord
eye
stomach
small intestines
large intestines
testes with epididymis[a]

EXPERIMENTAL DESIGN (Continued)

thyroid[a]
pancreas
lung
heart[a]
rib junction
gallbladder
liver[a]
spleen[a]
kidneys[a]
adrenal glands[a]
prostate
ovary[a]
uterus
bone marrow
skeletal muscle and nerve
urinary bladder
mammary gland
mesenteric lymph node
any unusual lesions

[a]Organ weights taken.

The tissues from dogs of the control and high level groups were evaluated pathologically by G.A. Parker, D.V.M.

Statistical analysis was performed using Dunnett's t-test to determine differences between treated and control means of the same sex. A probability value of $<0.05$ was used as a basis of statistical inference.

## RESULTS

All dogs survived the entire duration of the study. The clinical signs (observations) noted during the course of the study have been compiled and presented in Appendix Table 1. Review of these data suggested no remarkable difference between treated and control dogs with the possible exception of a slightly higher frequency of vomiting and soft stools among the treated dogs, especially those of the high level (1000 ppm). These signs were occasionally observed among the control dogs as well.

The body weights obtained during the course of the study have been tabulated in Appendix Table 2, and summarized in Text Table B. The mean body weights of treated and control groups were similar statistically and review of the individual body weights did not suggest any progressive effect of treatment.

The food consumption presented as daily food intake (g/day) has been tabulated in Appendix Table 3, and summarized in Text Table C. Weeks at which the food intake among the treated and control groups were statistically different were limited and were not judged to suggest a compound-related effect.

The results of the hemograms obtained initially and at 4, 8 and 13 weeks (termination) have been summarized in Text Table D. The individual data at these intervals have been detailed in Appendix Table 4. No dose-related effect was evident.

Results of the clinical chemistry determinations obtained initially and at Weeks 4, 8 and 13 (termination) of the study have been summarized in Text Table E. The individual data for these intervals have been detailed in Appendix Table 5. Statistically significant differences between control and treated groups were minimal and were not suggestive of a meaningful compound-related effect. The apparent increase in serum glucose at the 1000 ppm level for males at termination was not judged to be of real importance inasmuch as both male dogs on which data were available were well within normal limits.

The individual results of the urinalysis have been detailed in Appendix Table 6. Review of these data did not suggest any dose-related effects.

The individual organ weights and organ-to-body weight ratios have been detailed in Appendix Tables 7 and 8, respectively and summarized in Text Tables F and G, respectively. Review suggested a decreased thyroid size; however, statistical analysis did not indicate the difference was significant.

Analysis results of the diet formulations have been included in the Appendix. The diet proportions analyzed at means of 98, 101 and 99% of the theoretical concentrations for the 100, 300 and 1000 ppm dietary concentrations. Since the test material tended to vaporize, the actual intake may have been somewhat less than the intended dietary levels would have suggested.

TABLE II-F-38

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE B

MEAN BODY WEIGHTS (KG)

MALES

| DOSE LEVEL (PPM) | WEEK 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | TERMINATION |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CONTROL (0) | 10.8 | 10.7 | 10.6 | 10.8 | 11.0 | 10.6 | 10.8 | 10.8 | 10.7 | 11.1 | 11.2 | 11.1 | 11.6 | 11.0 | 10.9 |
| 100 | 12.1 | 11.8 | 11.8 | 12.0 | 12.2 | 11.8 | 12.0 | 12.2 | 12.2 | 12.3 | 12.3 | 12.5 | 12.4 | 11.9 | 11.6 |
| 300 | 10.0 | 9.8 | 9.7 | 9.9 | 10.1 | 9.8 | 10.0 | 10.2 | 10.1 | 10.3 | 10.4 | 10.3 | 10.4 | 9.9 | 9.8 |
| 1000 | 10.8 | 10.5 | 10.8 | 10.6 | 10.9 | 10.6 | 10.7 | 10.7 | 10.5 | 10.6 | 10.6 | 10.7 | 10.9 | 10.4 | 10.4 |

FEMALES

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CONTROL (0) | 8.1 | 7.7 | 7.6 | 7.8 | 7.9 | 7.5 | 7.6 | 7.6 | 7.6 | 7.8 | 8.0 | 7.9 | 8.0 | 7.6 | 7.5 |
| 100 | 9.0 | 8.8 | 8.8 | 8.8 | 9.0 | 8.6 | 8.9 | 9.0 | 9.0 | 9.3 | 9.2 | 9.1 | 9.3 | 9.1 | 8.8 |
| 300 | 8.8 | 8.8 | 8.7 | 8.9 | 9.3 | 9.1 | 9.0 | 9.1 | 9.0 | 9.4 | 9.4 | 9.5 | 9.3 | 8.9 | 8.8 |
| 1000 | 8.3 | 8.1 | 8.0 | 8.1 | 8.9 | 8.1 | 8.2 | 8.4 | 8.3 | 8.3 | 8.3 | 8.3 | 8.4 | 7.9 | 7.9 |

# TABLE II-F-39

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE C

MEAN DAILY FOOD INTAKE (G)

MALES

| DOSE LEVEL (PPM) | WEEK 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CONTROL (0) | 346.4 | 324.3 | 366.5 | 278.0 | 344.1 | 297.2 | 297.4 | 367.3 | 353.0 | 345.1 | 296.1 | 363.1 | 315.2 | 347.0 |
| 100 | 338.0 | 353.8 | 319.9 | 361.3 | 363.8 | 349.2 | 329.6 | 293.4 | 343.1 | 316.4 | 310.1 | 309.7 | 319.8 | 33[illegible] |
| 300 | 265.6 | 274.9 | 291.6 | 312.8 | 284.9 | 272.7 | 303.9 | 241.4 | 263.3 | 299.7 | 304.5 | 262.5* | 301.8 | 272.[illegible] |
| 1000 | 328.9 | 332.6 | 292.8 | 362.9 | 271.1 | 282.2 | 291.8 | 255.4 | 290.7 | 288.5 | 289.0 | 374.2 | 243.1 | 318.1 |

FEMALES

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CONTROL (0) | 262.8 | 242.2 | 267.7 | 246.7 | 345.3 | -[a] | 304.9 | 268.5 | 281.5 | 287.6 | 350.2 | 251.8 | 268.6 | 293.[illegible] |
| 100 | 244.6 | 230.5 | 266.8 | 249.9 | 245.6 | 259.3 | 264.1 | 241.9 | 243.2 | 231.5 | 243.0 | 220.6 | 200.7 | 219.[illegible] |
| 300 | 269.1 | 257.3 | 295.7 | 238.1 | 238.6 | 229.9 | 298.1 | 227.2 | 316.8 | 275.2 | 251.6 | 252.9 | 260.3 | 263.[illegible] |
| 1000 | 223.8 | 219.5 | 246.1 | 288.2 | 222.8 | 232.6 | 252.1 | 241.4 | 229.0 | 199.7 | 222.7* | 263.1 | 245.5 | 191.[illegible] |

[a]All spilled food.

*p-0.05 as compared to controls: Dunnett's t-test.

TABLE II-F-40

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE D

CLINICAL HEMATOLOGY - MEAN VALUES

INITIAL

MALES

| DOSE LEVEL (PPM) | LEUKOCYTE COUNT ($10^3/mm^3$) | ERYTHROCYTE COUNT ($10^6/mm^3$) | HEMOGLOBIN (gm%) | HEMATOCRIT (vol%) |
|---|---|---|---|---|
| 0 | 9.52 | 6.120 | 14.37 | 41.88 |
| 100 | 11.20 | 6.817 | 15.70 | 46.00 |
| 300 | 9.12 | 6.790 | 15.77 | 46.38 |
| 1000 | 10.85 | 6.462 | 15.20 | 44.63 |

FEMALES

| | | | | |
|---|---|---|---|---|
| 0 | 10.32 | 7.200 | 16.77 | 49.38 |
| 100 | 10.42 | 6.645 | 16.10 | 46.88 |
| 300 | 9.75 | 6.945 | 16.42 | 48.25 |
| 1000 | 8.70 | 6.910 | 16.42 | 48.63 |

TABLE II-F-40 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE D (CONTINUED)

CLINICAL HEMATOLOGY - MEAN VALUES

WEEK 4

MALES

| DOSE LEVEL (PPM) | LEUKOCYTE COUNT ($10^3/mm^3$) | ERYTHROCYTE COUNT ($10^6/mm^3$) | HEMOGLOBIN (gm%) | HEMATOCRIT (vol%) |
|---|---|---|---|---|
| 0 | 10.45 | 6.930 | 15.42 | 43.75 |
| 100 | 10.40 | 7.390 | 15.75 | 45.25 |
| 300 | 10.62 | 7.240 | 16.00 | 44.13 |
| 1000 | 10.90 | 6.545 | 15.42 | 43.75 |

FEMALES

| | | | | |
|---|---|---|---|---|
| 0 | 9.22 | 7.447 | 16.47 | 48.25 |
| 100 | 10.80 | 7.247 | 16.57 | 46.25 |
| 300 | 13.07 | 6.847 | 16.15 | 46.75 |
| 1000 | 12.60 | 6.972 | 16.47 | 46.63 |

TABLE II-F-40 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE D (CONTINUED)

CLINICAL HEMATOLOGY - MEAN VALUES

WEEK 8

MALES

| DOSE LEVEL (PPM) | LEUKOCYTE COUNT ($10^3/mm^3$) | ERYTHROCYTE COUNT ($10^6/mm^3$) | HEMOGLOBIN (gm%) | HEMATOCRIT (vol%) |
|---|---|---|---|---|
| 0 | 10.92 | 6.077 | 13.92 | 42.88 |
| 100 | 10.25 | 6.845 | 15.27 | 46.00 |
| 300 | 10.82 | 6.460 | 14.77 | 44.75 |
| 1000 | 10.22 | 6.687 | 14.42 | 44.25 |

FEMALES

| | | | | |
|---|---|---|---|---|
| 0 | 9.27 | 6.585 | 15.22 | 45.75 |
| 100 | 10.40 | 6.530 | 14.65 | 44.00 |
| 300 | 11.27 | 6.877 | 16.57 | 48.13 |
| 1000 | 10.82 | 6.440 | 14.92 | 44.63 |

TABLE II-F-40 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE D (CONTINUED)

CLINICAL HEMATOLOGY - MEAN VALUES

TERMINAL KILL

MALES

| DOSE LEVEL (PPM) | LEUKOCYTE COUNT ($10^3/mm^3$) | ERYTHROCYTE COUNT ($10^6/mm^3$) | HEMOGLOBIN (gm%) | HEMATOCRIT (vol%) |
|---|---|---|---|---|
| 0 | 9.62 | 6.765 | 15.25 | 42.75 |
| 100 | 11.45 | 7.157 | 16.30 | 46.25 |
| 300 | 9.37 | 6.967 | 16.00 | 45.63 |
| 1000 | 9.47 | 6.857 | 15.05 | 43.63 |

FEMALES

| | | | | |
|---|---|---|---|---|
| 0 | 10.10 | 7.175 | 15.92 | 45.25 |
| 100 | 9.37 | 6.870 | 15.97 | 44.75 |
| 300 | 12.52 | 7.365 | 16.05 | 45.13 |
| 1000 | 10.45 | 6.922 | 16.20 | 46.75 |

# TABLE II-F-41
# CLINICAL CHEMISTRY

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE E

INITIAL

MALES

| DOSE LEVEL (PPM) | BILI-RUBIN, TOTAL (mg/dl) | BLOOD UREA NITROGEN (mg/dl) | ALBUMIN (g/dl) | CALCIUM (mg/dl) | CHOLES-TEROL (mg/dl) | GLUCOSE (mg/dl) | LACTIC DEHY-DROGENASE (mU/ml) | ALKALINE PHOS-PHATASE (mU/ml) | PHOS-PHORUS (mg/dl) | PROTEIN, TOTAL (g/dl) | SERUM GLUTAMIC-OXALOACETIC TRANS-AMINASE (mU/ml) | SERUM GLUTAMIC-PYRUVIC TRANS-AMINASE (mU/ml) | URIC ACID (mg/dl) | SODIUM (g/dl) | POTASSIUM (meq/l) | CHLORIDE (meq/l) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0.07 | 13.5 | 3.80 | 11.12 | 148.5 | 96.5 | 282.0 | 75.8 | 4.90 | 6.25 | 34.8 | 37.5 | 0.40 | 147.3 | 5.10 | [illegible] |
| 100 | 0.05 | 15.8 | 3.77 | 11.12 | 162.3 | 84.3 | 144.8 | 88.0 | 5.07 | 6.32 | 31.5 | 37.5 | 0.40 | 146.3 | 4.70 | 108.0 |
| 300 | 0.07 | 11.5 | 4.20 | 11.07 | 174.0 | 90.5 | 166.8 | 69.0 | 4.47 | 6.55 | 30.5 | 39.0 | 0.45 | 145.0 | 4.82 | 107.5 |
| 1000 | 0.07 | 12.3 | 3.82 | 10.97 | 140.8 | 91.0 | 164.0 | 85.3 | 4.40 | 5.95 | 33.8 | 55.8 | 0.45 | 146.3 | [illegible] | 109.3 |

FEMALES

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0.10 | 13.3 | 4.05 | 11.07 | 145.0 | 89.8 | 157.8 | 48.8 | 3.85 | 6.20 | 29.3 | 31.0 | 0.32 | 148.0 | 4.62 | 109.5 |
| 100 | 0.10 | 13.5 | 3.42 | 11.12 | 134.3 | 80.5 | 99.0 | 61.3 | 4.60 | 6.02 | 31.3 | 40.5 | 0.25 | 147.0 | 4.92 | [illegible] |
| 300 | 0.10 | 14.3 | 3.77 | 10.92 | 157.5 | 90.8 | 177.0 | 62.5 | 3.97 | 6.20 | 30.5 | 34.0 | 0.27 | 147.0 | [illegible] | 108.5 |
| 1000 | 0.07 | 13.5 | 4.02 | 10.95 | 146.8 | 83.5 | 145.5 | 69.3 | 5.20 | 5.92 | 31.8 | 43.3 | 0.35 | 147.3 | [illegible] | [illegible] |

# TABLE II-F-41 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE E (CONTINUED)

WEEK 4

MALES

| DOSE LEVEL (PPM) | BILI-RUBIN, TOTAL (mg/dl) | BLOOD UREA NITROGEN (mg/dl) | ALBUMIN (g/dl) | CALCIUM (mg/dl) | CHOLES-TEROL (mg/dl) | GLUCOSE (mg/dl) | LACTIC DEHY-DROGENASE (mU/ml) | ALKALINE PHOS-PHATASE (mU/ml) | PHOS-PHORUS (mg/dl) | PROTEIN, TOTAL (g/dl) | SERUM GLUTAMIC-OXALOACETIC TRANS-AMINASE (mU/ml) | SERUM GLUTAMIC-PYRUVIC TRANS-AMINASE (mU/ml) | URIC ACID (mg/dl) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0.10 | 15.5 | 3.10 | 10.82 | 135.3 | 86.0 | 290.3 | 58.0 | 4.40 | 6.20 | 54.3 | 38.5 | 0.32 |
| 100 | 0.07 | 16.5 | 3.02 | 10.92 | 164.5 | 83.5 | 257.3 | 64.8 | 4.20 | 6.22 | 63.8 | 33.8 | 0.17 |
| 300 | 0.10 | 15.3 | 2.90 | 10.77 | 149.0 | 84.5 | 206.5 | 61.5 | 4.30 | 6.20 | 51.3 | 35.3 | 0.20 |
| 1000 | 0.10 | 15.3 | 2.87 | 10.62 | 143.5 | 89.0 | 231.5 | 87.5 | 4.12 | 5.12 | 53.5 | 42.3 | 0.55 |
| FEMALES | | | | | | | | | | | | | |
| 0 | 0.12 | 12.5 | 3.27 | 10.95 | 129.3 | 83.5 | 436.5 | 42.5 | 3.67 | 6.12 | 57.3 | 33.0 | 0.22 |
| 100 | 0.10 | 14.5 | 3.20 | 11.10 | 134.3 | 84.3 | 289.8 | 65.3 | 4.02 | 5.97 | 55.5 | 31.3 | 0.22 |
| 300 | 0.10 | 16.0 | 2.67 | 10.82 | 172.3 | 83.0 | 234.8 | 65.5 | 4.10 | 6.17 | 56.0 | 42.5 | 0.40 |
| 1000 | 0.10 | 16.8 | 3.02 | 11.00 | 163.3 | 77.5 | 346.8 | 69.0 | 4.12 | 6.05 | 58.8 | 30.3 | 0.37 |

TABLE II-F-41 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE E (CONTINUED)

WEEK 8

MALES

| DOSE LEVEL (PPM) | BILI-RUBIN, TOTAL (mg/dl) | BLOOD UREA NITROGEN (mg/dl) | ALBUMIN (g/dl) | CALCIUM (mg/dl) | CHOLES-TEROL (mg/dl) | GLUCOSE (mg/dl) | LACTIC DEHY-DROGENASE (mU/ml) | ALKALINE PHOS-PHATASE (mU/ml) | PHOS-PHORUS (mg/dl) | PROTEIN, TOTAL (g/dl) | SERUM GLUTAMIC-OXALOACETIC TRANS-AMINASE (mU/ml) | SERUM GLUTAMIC-PYRUVIC TRANS-AMINASE (mU/ml) | URIC ACID (mg/dl) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0.07 | 15.3 | 3.12 | 10.87 | 136.5 | 88.8 | 166.8 | 58.3 | 4.27 | 6.27 | 37.5 | 46.5 | 0.15 |
| 100 | 0.05 | 16.3 | 3.12 | 10.85 | 150.3 | 92.0 | 169.5 | 51.0 | 4.32 | 6.10 | 34.3 | 32.3 | [illegible] |
| 300 | 0.07 | 12.5 | 3.25 | 10.80 | 150.3 | 97.0 | 111.5 | 50.8 | 4.15 | 6.27 | 30.5 | 32.3 | 0.15 |
| 1000 | 0.10 | 12.0 | 3.07 | 10.45 | 114.8 | 87.3 | 147.5 | 57.5 | 4.12 | 5.87 | 36.5 | 41.5 | 0.02 |
| FEMALES | | | | | | | | | | | | | |
| 0 | 0.10 | 14.5 | 3.20 | 10.72 | 125.0 | 90.0 | 169.8 | 43.0 | 3.85 | 6.10 | 35.0 | 21.5 | [illegible] |
| 100 | 0.10 | 15.3 | 3.07 | 10.72 | 129.3 | 79.3 | 160.3 | 54.5 | 4.17 | 5.77 | 31.3 | 30.3 | [illegible] |
| 300 | 0.05 | 16.8 | 3.55 | 10.85 | 188.5 | 93.3 | 186.8 | 66.3 | 4.10 | 6.45 | 35.8 | 32.8 | [illegible] |
| 1000 | 0.12 | 16.8 | 3.15 | 10.60 | 166.8 | 82.3 | 187.3 | 61.8 | 4.20 | 5.90 | 35.3 | 29.3 | 0.25 |

# TABLE II-F-41 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE E (CONTINUED)

TERMINAL KILL

MALES

| DOSE LEVEL (PPM) | BILI-RUBIN, TOTAL (mg/dl) | BLOOD UREA NITROGEN (mg/dl) | ALBUMIN (g/dl) | CALCIUM (mg/dl) | CHOLES-TEROL (mg/dl) | GLUCOSE (mg/dl) | LACTIC DEHY-DROGENASE (mU/ml) | ALKALINE PHOS-PHATASE (mU/ml) | PHOS-PHORUS (mg/dl) | PROTEIN, TOTAL (g/dl) | SERUM GLUTAMIC-OXALOACETIC TRANS-AMINASE (mU/ml) | SERUM GLUTAMIC-PYRUVIC TRANS-AMINASE (mU/ml) | URIC ACID (mg/dl) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0.10 | 16.3 | 3.85 | 10.97 | 98.5 | 74.0 | 238.5 | 55.0 | 3.75 | 6.27 | 31.5 | 42.0 | 0.52 |
| 100 | 0.10 | 16.8 | 3.80 | 10.65 | 114.0 | 74.0 | 263.5 | 46.3 | 3.72 | 6.10 | 31.3 | 34.3 | 0.47 |
| 300 | 0.10 | 16.5 | 3.92 | 10.82 | 105.8 | 82.5 | 191.8 | 45.3 | 3.50 | 6.37 | 27.0 | 33.0 | 0.80 |
| 1000 | 0.10 | 15.5 | 3.75 | 10.67 | 92.8 | 87.5* | 229.0 | 56.5 | 3.38 | 5.92 | 34.8 | 49.3 | 0.82 |
| FEMALES | | | | | | | | | | | | | |
| 0 | 0.12 | 15.8 | 3.82 | 10.87 | 98.8 | 78.0 | 249.3 | 40.8 | 3.30 | 6.02 | 32.3 | 35.0 | 0.52 |
| 100 | 0.10 | 16.8 | 3.72 | 10.75 | 115.3 | 74.5 | 272.5 | 47.0 | 3.42 | 6.42 | 31.0 | 34.0 | 0.42 |
| 300 | 0.10 | 18.0 | 3.72 | 10.82 | 140.5 | 76.5 | 278.8 | 55.3 | 3.62 | 5.92 | 27.8 | 32.8 | 0.32 |
| 1000 | 0.12 | 17.5 | 3.80 | 10.85 | 120.0 | 74.5 | 256.5 | 54.0 | 3.60 | 5.82 | 29.8 | 33.5 | 0.70 |

*$p \leq 0.05$ as compared to controls: Dunnett's t-test.

TABLE II-F-42

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE F

MEAN ORGAN WEIGHTS

MALES

| DOSE LEVEL (PPM) | BODY WEIGHT | BRAIN | THYROID | HEART | LIVER | SPLEEN | KIDNEYS | ADRENALS | TESTES |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 10875.0 | 78.5747 | 0.8747 | 86.8325 | 322.0172 | 77.7282 | 61.7987 | 1.1417 | 20.2657 |
| 100 | 11625.0 | 89.0372* | 0.7730 | 88.0802 | 302.9150 | 95.4977 | 60.2855 | 1.0752 | 20.9540 |
| 300 | 9825.0 | 84.9087 | 0.6197 | 82.3457 | 272.0825 | 89.5575 | 53.7365 | 1.1215 | 19.1445 |
| 1000 | 10400.0 | 79.2218 | 0.6477 | 81.0655 | 285.9540 | 97.5097 | 55.9045 | 1.0907 | 18.6860 |



FEMALES

| DOSE LEVEL (PPM) | BODY WEIGHT | BRAIN | THYROID | HEART | LIVER | SPLEEN | KIDNEYS | ADRENALS | OVARIES |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 7550.0 | 75.4695 | 0.4940 | 67.6255 | 217.1627 | 80.7205 | 39.0597 | 0.8745 | 0.4472 |
| 100 | 8800.0 | 79.3445 | 0.6957 | 68.8920 | 255.7722 | 76.5630 | 40.9972 | 0.7627 | 1.4387 |
| 300 | 8850.0 | 78.2765 | 0.6425 | 64.5087 | 252.3592 | 91.7350 | 42.5392 | 0.8057 | 1.4852 |
| 1000 | 7925.0 | 72.4573 | 0.6137 | 65.9787 | 218.2760 | 91.6745 | 41.4102 | 0.7745 | 0.7730 |

*$p<0.05$ as compared to controls: Dunnett's t-test.

TABLE II-F-43

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE G

MEAN ORGAN WEIGHT - BODY WEIGHT PERCENTAGES

MALES

| DOSE LEVEL (PPM) | BRAIN | THYROID | HEART | LIVER | SPLEEN | KIDNEYS | ADRENALS | TESTES |
|---|---|---|---|---|---|---|---|---|
| 0 | 0.7653 | 0.0095 | 0.8167 | 2.9828 | 0.7667 | 0.5799 | 0.0113 | 0.1949 |
| 100 | 0.7668 | 0.0067 | 0.7593 | 2.6139 | 0.8220 | 0.5196 | 0.0093 | 0.1813 |
| 300 | 0.8699 | 0.0062 | 0.8358 | 2.7619 | 0.9207 | 0.5484 | 0.0117 | 0.1945 |
| 1000 | 0.7642 | 0.0062 | 0.7803 | 2.7655 | 0.9378 | 0.5395 | 0.0107 | 0.1815 |

FEMALES

| DOSE LEVEL (PPM) | BRAIN | THYROID | HEART | LIVER | SPLEEN | KIDNEYS | ADRENALS | OVARIES |
|---|---|---|---|---|---|---|---|---|
| 0 | 1.0051 | 0.0065 | 0.9050 | 2.8928 | 1.0571 | 0.5148 | 0.0117 | 0.0061 |
| 100 | 0.9063 | 0.0079 | 0.7837 | 2.9104 | 0.8690 | 0.4668 | 0.0088 | 0.0164 |
| 300 | 0.9038 | 0.0074 | 0.7400 | 2.8789 | 1.0678 | 0.4887 | 0.0092 | 0.0155 |
| 1000 | 0.9190 | 0.0078 | 0.8359 | 2.7519 | 1.1658 | 0.5257 | 0.0098 | 0.0099 |

RESULTS (Continued)

The reports of the consulting veterinary ophthalmologist have been included in the Appendix. The judgment of the ophthalmologist was that the compound produced no ocular changes in the dogs.

The pathological evaluation of tissues from dogs of the high dose and control groups has been included in the Appendix. This evaluation did not suggest any compound-related effect.

## CONCLUSION

The test material, Dicyclopentadiene, was administered by incorporation into the diet at concentrations of 100, 300 and 1000 ppm to beagle dogs for 13 weeks. The animals were observed daily for general condition and behavior. Clinical pathological evaluations, including analysis of the clinical chemical constituents of serum, urine and hemograms, were performed at approximately monthly intervals. Tissues from the control and high dose dogs were histopathologically evaluated. Based on the results obtained using these criteria, it was concluded that treatment produced no significant toxicity with the possible exception of minor indications of intestinal distress expressed as vomiting and soft stools among dogs of the treated groups, especially the highest dose (1000 ppm).

Submitted by:

E. Ross Hart 3/10/80

E. Ross Hart, Ph.D. Date
Study Director
Department of Toxicology

Reviewed by:

Robert J. Weir 3/11/80

Robert J. Weir, Ph.D. Date
Director
Department of Toxicology

## TABLE II-F-44

TRACK BY [illegible] STATION REPORT

### TABLE 1

[illegible] SIGNS
[illegible] - 1073409
[illegible] : 04/12/77

| [illegible] | [illegible] | NORMAL OBSERVATIONS : [illegible] | |
|---|---|---|---|
| * [illegible] SEX * | [illegible] | ***** COMMENTS | ********** |
| [illegible] | MALE | 00417 | SOFT STOOL |
| | | | STOOL LIQUID |
| [illegible] | | 00414 | SOFT STOOL |
| | | | SOFT STOOL |
| | FEMALE | 00421 | SOFT STOOL |
| | | 00427 | VOMITED-SEMISOLID |
| [illegible] | MALE | 00416 | NO FEED |
| | | | SOFT STOOL |
| | | ***** | NO FEED |
| | | | SOFT STOOL |
| | | ***** | NO FEED |
| | | | WEIGHT LOSS-MARKED |
| | | ***** | FED |
| | | | SOFT STOOL |
| | | ***** | WITH FED DISCHARGE |
| | | 00419 | SOFT STOOL |
| | | 00420 | SOFT STOOL |
| | | | SOFT STOOL |
| | | | VOMITED-SEMISOLID |
| | | | SOFT STOOL |
| | | ***** | WITH MUCUS |
| | | | VOMITED-SEMISOLID |
| | FEMALE | 00423 | SOFT STOOL |
| | | 00432 | SOFT STOOL |
| | | | VOMITED-SEMISOLID |
| [illegible] | MALE | 00405 | LACERATION : LEAR-PLACEMENT |
| | | ***** | FOOT PADS |
| | | 00415 | VOMITED-LIQUID |
| [illegible] | FEMALE | 00433 | ESTRUS |
| | | | ESTRUS |
| | | | ESTRUS |
| | | | ESTRUS |
| | | | ESTRUS |
| | | | EST US |
| [illegible] | MALE | 00418 | MUCUS IN STOOL |
| | | | MUCUS IN STOOL |
| | | 00419 | VOMITED-LIQUID |
| | | 00420 | MUCUS IN STOOL |
| | | | MUCUS CONTAINING STOOL |
| | | | VOMITED-LIQUID |
| | | | VOMITED-SEMISOLID |
| | | | MUCUS CONTAINING STOOL |

[illegible] OBSERVATIONS [illegible]

TABLE 1 (CONTINUED)

| [illegible] | [illegible] SEX | ANIMAL NUMBER | ***** | OBSERVATIONS : QUALIFIER COMMENTS | ********** |
|---|---|---|---|---|---|
| | FEMALE | 00432 | | SOFT STOOL | |
| [illegible] | MALE | 00411 | | FECES-MUCOID | |
| | | 00417 | | STOOL LIQUID | |
| | | ***** | | RED COLOR | |
| | | | | MUCUS IN STOOL | |
| | FEMALE | 00424 | | SMALL AMOUNT(<10 CC) : LIMB-FORE,RIGHT | |
| [illegible] | MALE | 00408 | | VOMITED-LIQUID | |
| | | ***** | | YELLOW MUCUS | |
| | | 00415 | | VOMITED-SEMISOLID | |
| [illegible] | FEMALE | 00424 | | F-CCS-MUCOID | |
| | | 00427 | | ESTRUS | |
| | | 00433 | | ESTRUS | |
| | | | | MUCUS IN STOOL | |
| | | | | ESTRUS | |
| | | | | MUCUS IN STOOL | |
| [illegible] | MALE | 00416 | | VOMITED-LIQUID | |
| | | | | MUCUS IN STOOL | |
| | | | | FECES-MUCOID | |
| | | ***** | | RED MUCUS | |
| | | | | FECES-MUCOID | |
| | | | | FECES-MUCOID | |
| | | | | VOMITED-SEMISOLID | |
| | | ***** | | RED MUCUS | |
| | | 00419 | | MUCUS IN STOOL | |
| | | | | FEC-S-MUCOID | |
| | | 00420 | | MUCUS FLOATING STOOL | |
| | | | | MUCUS CREATE STOOL | |
| | | | | MUCUS IN STOOL | |
| | | | | VOMITED-SEMISOLID | |
| | | ***** | | WITH MUCUS | |
| | | | | FECES-MUCOID | |
| | | | | VOMITED-SEMISOLID | |
| | | | | FECES-MUCOID | |
| | FEMALE | 00434 | | MUCUS IN STOOL | |
| | | | | SOFT STOOL | |
| | | | | FECES-MUCOID | |
| | | ***** | | YELLOW WITH [illegible] | |
| [illegible] | MALE | 00417 | | STOOL LIQUID | |
| | | ***** | | RED | |
| | | | | STOOL LIQUID | |
| | | ***** | | MUCUS AND BLOOD | |
| | | | | VOMITED-LIQUID | |
| | | ***** | | BLOODY | |
| [illegible] | | 00407 | | VOMITED-SEMISOLID | |
| | | | | FEC-S-MUCOID | |

TABLE II-F-44 (Continued)

TOXICOLOGY OBSERVATION REPORT

TABLE 1 (CONTINUED)

| SEX NO. ** | DOSE GROUP/SEX * | ANIMAL NUMBER ***** | OBSERVATIONS : QUALIFIER COMMENTS ********** |
|---|---|---|---|
| | | 00415 | FECES-MUCOID |
| | FEMALE | 00431 | FECES-MUCOID |
| | 300 PPM MALE | 00404 | FECES-MUCOID |
| | | | FECES-MUCOID |
| | | 00412 | FECES-MUCOID |
| | FEMALE | 00421 | FECES-MUCOID |
| | | 00424 | VOMITED-SEMISOLID |
| | | 00427 | ESTRUS |
| | | 00433 | FECES-MUCOID |
| | | | FECES-MUCOID |
| | 1000 PPM MALE | 00416 | SOFT STOOL |
| | | | VOMITED-SEMISOLID |
| | | | SOFT STOOL |
| | | | FECES-MUCOID |
| | | 00419 | FECES-MUCOID |
| | | 00420 | FECES-MUCOID |
| | | ***** | YELLOW |
| | | | FECES-MUCOID |
| | | | SOFT STOOL |
| | | | STOOL LIQUID |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | | FECES-MUCOID |
| | FEMALE | 00432 | SOFT STOOL |
| | | | SOFT STOOL |
| | | 00436 | EXCESS SHEDDING |
| | | | EXCESS SHEDDING |
| | | | ESTRUS |
| | 0% CONTROL MALE | 00417 | STOOL LIQUID |
| | | ***** | RED |
| | FEMALE | 00434 | ABSCESS : LATERAL-RIGHT |
| | | ***** | FOREARM |
| | 100 PPM MALE | 00407 | SOFT STOOL |
| | | | VOMITED-SEMISOLID |
| | | 00415 | FECES-MUCOID |
| | | | SOFT STOOL |
| | FEMALE | 00422 | FECES-MUCOID |
| | | 00430 | FECES-MUCOID |
| | | 00431 | FECES-MUCOID |
| | 300 PPM MALE | 00412 | FECES-MUCOID |
| | FEMALE | 00427 | VOMITED-LIQUID |
| | | ***** | PHLEGM |
| | | 00433 | FECES-MUCOID |
| | | | VOMITED-SEMISOLID |
| | 1000 PPM MALE | 00416 | FECES-MUCOID |
| | | ***** | RED AND YELLOW |

## TABLE II-F-44 (Continued)

TOXICOLOGY OBSERVATION REPORT

TABLE 1 (CONTINUED)

| WEEK NO. | ** DOSE GROUP/SEX * | ANIMAL NUMBER | ***** OBSERVATIONS : QUALIFIER COMMENTS ********** |
|---|---|---|---|
| | | | FECES-MUCOID |
| | | ***** | YELLOW WITH RED |
| | | | SOFT STOOL |
| | | | FECES-MUCOID |
| | | 00420 | SOFT STOOL |
| | FEMALE | 00423 | FECES-MUCOID |
| | | 00432 | SOFT STOOL |
| | | | SOFT STOOL |
| | | | FECES-MUCOID |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | 00436 | ESTRUS |
| | | 00437 | FECES-MUCOID |
| | | | VOMITED-SEMISOLID |
| 000 CONTROL | MALE | 00411 | STOOL LIQUID |
| | | | FECES-MUCOID |
| | | ***** | YELLOW WITH RED |
| | | 00417 | SOFT STOOL |
| | FEMALE | 00434 | SOFT STOOL |
| | | 00435 | VOMITED-LIQUID |
| | | ***** | PHLEGM |
| 100 PPM | MALE | 00415 | FECES-MUCOID |
| | | | SCAB : PENIS |
| | | ***** | SEVERAL |
| | | | SCAB : LIMB-HIND,RIGHT |
| | | ***** | SEVERAL |
| | | | SCAB : LIMB-HIND,LEFT |
| | | ***** | SEVERAL |
| | FEMALE | 00422 | SOFT STOOL |
| 300 PPM | | 00424 | SOFT STOOL |
| | | 00427 | SOFT STOOL |
| | | 00433 | VOMITED-SEMISOLID |
| | | ***** | MUCUS |
| 1000 PPM | MALE | 00413 | VOMITED-LIQUID |
| | | ***** | PHLEGM |
| | | 00416 | FECES-MUCOID |
| | | | SOFT STOOL |
| | | | FECES-MUCOID |
| | | | STOOL LIQUID |
| | | | FECES-MUCOID |
| | | ***** | YELLOW WITH RED |
| | | | SOFT STOOL |
| | | | VOMITED-LIQUID |
| | | ***** | PHLEGM |
| | | 00419 | FECES-MUCOID |
| | | 00420 | SOFT STOOL |

TOXICOLOGY OBSERVATION REPORT

TABLE 1 (CONTINUED)

| WEEK NO. ** | DOSE GROUP/SEX * | ANIMAL NUMBER | ***** | OBSERVATIONS : QUALIFIER COMMENTS ********** |
|---|---|---|---|---|
| | FEMALE | 00432 | | FECES-MUCOID |
| | | | | VOMITED-SEMISOLID |
| | | | | SOFT STOOL |
| | | | | |
| | | | | |
| | | | |

TABLE II-F-44 (Continued)

TOXICOLOGY OBSERVATION REPORT

TABLE 1 (CONTINUED)

| WEEK NO. ** DOSE GROUP/SEX * | ANIMAL NUMBER | ***** OBSERVATIONS : QUALIFIER COMMENTS ********** |
|---|---|---|
| | | FECES-MUCOID |
| | 00420 | SOFT STOOL |
| | | SOFT STOOL |
| | ***** | WITH MUCUS |
| FEMALE | 00432 | SOFT STOOL |
| | | STOOL LIQUID |
| | | FECES-MUCOID |
| | 00436 | ESTRUS |
| | | LOCAL HAIR LOSS : DORSAL |
| | ***** | EXCESS SHEDDING |
| 000 CONTROL MALE | 00408 | URINE SUBMITTED FOR ANALYSIS |
| | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | 00411 | FECES-MUCOID |
| | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | 00417 | VOMITED-SEMISOLID |
| | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | 00418 | FECES-MUCOID |
| | | URINE SUBMITTED FOR ANALYSIS |
| | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| FEMALE | 00425 | URINE SUBMITTED FOR ANALYSIS |
| | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | 00426 | URINE SUBMITTED FOR ANALYSIS |
| | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | 00434 | MEDIUM ABSCESS(1-5CM) : LIMB-FORE,RIGHT |
| | ***** | SEVERAL ABSCESSES |
| | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | 00435 | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| 100 PPM MALE | 00405 | URINE SUBMITTED FOR ANALYSIS |
| | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | 00406 | URINE SUBMITTED FOR ANALYSIS |
| | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | 00407 | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | 00415 | SMALL SCAB(<1CM) : PENIS |
| | ***** | SEVERAL |
| | | SMALL SCAB(<1CM) : LIMB-HIND,RIGHT |
| | ***** | SEVERAL |
| | | SMALL SCAB(<1CM) : LIMB-HIND,LEFT |
| | ***** | SEVERAL |
| | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| FEMALE | 00422 | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | 00429 | URINE SUBMITTED FOR ANALYSIS |
| | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | 00430 | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | 00431 | FECES-MUCOID |
| | | URINE SUBMITTED FOR ANALYSIS |
| | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |

TABLE II-F-44 (Continued)

TOXICOLOGY OBSERVATION REPORT

TABLE 1 (CONTINUED)

| WEEK NO. ** DOSE GROUP/SEX * | ANIMAL NUMBER | OBSERVATIONS : QUALIFIER COMMENTS ********** |
|---|---|---|
| 300 PPM MALE | 00404 | FECES-MUCOID |
| | | SOFT STOOL |
| | | STOOL LIQUID |
| | | URINE SUBMITTED FOR ANALYSIS |
| | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | 00409 | URINE SUBMITTED FOR ANALYSIS |
| | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | 00412 | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | 00414 | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| FEMALE | 00421 | FECES-MUCOID |
| | | URINE SUBMITTED FOR ANALYSIS |
| | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | 00424 | SOFT STOOL |
| | | FECES-MUCOID |
| | | SOFT STOOL |
| | | SOFT STOOL |
| | | FECES-MUCOID |
| | | SOFT STOOL |
| | | FECES-MUCOID |
| | | SOFT STOOL |
| | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | 00427 | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | 00433 | FECES-MUCOID |
| | | URINE SUBMITTED FOR ANALYSIS |
| | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| 1000 PPM MALE | 00413 | URINE SUBMITTED FOR ANALYSIS |
| | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | 00416 | SOFT STOOL |
| | | SOFT STOOL |
| | | FECES-MUCOID |
| | | VOMITED-LIQUID |
| | | STOOL LIQUID |
| | | FECES-MUCOID |
| | ***** | WITH RED STREAKS |
| | | SOFT STOOL |
| | | SOFT STOOL |
| | | FECES-MUCOID |
| | | URINE SUBMITTED FOR ANALYSIS |
| | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | 00419 | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | 00420 | FECES-MUCOID |
| | | SOFT STOOL |
| | | SOFT STOOL |
| | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| FEMALE | 00423 | FECES-MUCOID |
| | | VOMITED-LIQUID |
| | ***** | PHLEGM |

TABLE II-F-44 (Continued)

TOXICOLOGY OBSERVATION REPORT

TABLE 1 (CONTINUED)

| ECK NO. | ** DOSE GROUP/SEX * | ANIMAL NUMBER | *** OBSERVATIONS : QUALIFIER COMMENTS ********** |
|---|---|---|---|
| | | | URINE SUBMITTED FOR ANALYSIS |
| | | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | | 00432 | SOFT STOOL |
| | | | SOFT STOOL |
| | | | FECES-MUCOID |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | | FECES-MUCOID |
| | | | SOFT STOOL |
| | | | FECES-MUCOID |
| | | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | | 00436 | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | | | EXCESS SHEDDING |
| | | 00437 | URINE SUBMITTED FOR ANALYSIS |
| | | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| 000 CONTROL | MALE | 00411 | URINE SUBMITTED FOR ANALYSIS |
| | | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | | 00417 | URINE SUBMITTED FOR ANALYSIS |
| | | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | | | SOFT STOOL |
| | | | FECES-MUCOID |
| | | | FECES-MUCOID |
| | FEMALE | 00434 | URINE SUBMITTED FOR ANALYSIS |
| | | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | | | FECES-MUCOID |
| | | | LOCAL HAIR LOSS : LIMB-FORE,RIGHT |
| | | | LESION : LIMB-FORE,RIGHT |
| | | ***** | SCM,RED |
| | | 00435 | URINE SUBMITTED FOR ANALYSIS |
| | | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| 100 PPM | MALE | 00406 | SOFT STOOL |
| | | | SOFT STOOL |
| | | 00407 | URINE SUBMITTED FOR ANALYSIS |
| | | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | | | SOFT STOOL |
| | | 00415 | URINE SUBMITTED FOR ANALYSIS |
| | | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | | | SOFT STOOL |
| | | | LOCAL HAIR LOSS : LIMB-HIND,RIGHT |
| | | ***** | INNER THIGH |
| | | | LOCAL HAIR LOSS : LIMB-HIND,LEFT |
| | | ***** | INNER THIGH |
| | | | PENILE DISCHARGE |
| | | ***** | GREENISH |
| | | | PAPILLOMA : PENIS |
| | | ***** | LEFT SIDE |

## TABLE II-F-44 (Continued)

TOXICOLOGY OBSERVATION REPORT

TABLE 1 (CONTINUED)

| WEEK NO. | ** DOSE GROUP/SEX ** | ANIMAL NUMBER | ***** | OBSERVATIONS : QUALIFIER COMMENTS ********** |
|---|---|---|---|---|
| | | | | LESION : PENIS |
| | | | | LESION : LIMB-HIND,RIGHT |
| | | | ***** | INNER THIGH |
| | | | | LESION : LIMB-HIND,LEFT |
| | | | ***** | INNER THIGH |
| | | FEMALE 00427 | | URINE SUBMITTED FOR ANALYSIS |
| | | | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | | | | SWELLING |
| | | | ***** | MAMMARY GLANDS |
| | | 00430 | | URINE SUBMITTED FOR ANALYSIS |
| | | | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | | | | VOMITED-LIQUID |
| | | | ***** | PHLEGM |
| | 300 PPM | MALE 00404 | | SOFT STOOL |
| | | | | FECES-MUCOID |
| | | 00409 | | SOFT STOOL |
| | | 00412 | | URINE SUBMITTED FOR ANALYSIS |
| | | | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | | | | FECES-MUCOID |
| | | | | VOMITED-LIQUID |
| | | | ***** | PHLEGM |
| | | | | FECES-MUCOID |
| | | 00414 | | URINE SUBMITTED FOR ANALYSIS |
| | | | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | | FEMALE 00421 | | SOFT STOOL |
| | | 00424 | | URINE SUBMITTED FOR ANALYSIS |
| | | | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | | 00427 | | URINE SUBMITTED FOR ANALYSIS |
| | | | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | | | | FECES-MUCOID |
| | | | | VOMITED-LIQUID |
| | | | ***** | PHLEGM |
| | | | | SWELLING |
| | | | ***** | MAMMARY GLANDS |
| | | 00433 | | FECES-MUCOID |
| | | | | SOFT STOOL |
| | | | | SWELLING |
| | | | ***** | MAMMARY GLANDS |
| | 1000 PPM | MALE 00416 | | FECES-MUCOID |
| | | | | FECES-MUCOID |
| | | | ***** | RED STREAKS |
| | | 00419 | | URINE SUBMITTED FOR ANALYSIS |
| | | | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | | | | LESION : LIMB-HIND,RIGHT |
| | | | ***** | INNER THIGH, RED |
| | | 00420 | | URINE SUBMITTED FOR ANALYSIS |
| | | | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |

TABLE II-F-44 (Continued)

TOXICOLOGY OBSERVATION REPORT

TABLE 1 (CONTINUED)

| WEEK NO. ** | DOSE GROUP/SEX * | ANIMAL NUMBER | ***** | OBSERVATIONS : QUALIFIER COMMENTS ********** |
|---|---|---|---|---|
| | | | | SOFT STOOL |
| | FEMALE | 00432 | | STOOL LIQUID |
| | | | | FECES-MUCOID |
| | | | | URINE SUBMITTED FOR ANALYSIS |
| | | | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | | | | SOFT STOOL |
| | | | | SOFT STOOL |
| | | | | STOOL LIQUID |
| | | | | SOFT STOOL |
| | | | | SOFT STOOL |
| | | 00436 | | URINE SUBMITTED FOR ANALYSIS |
| | | | | BLOOD SUBMITTED FOR CHEM AND HEMOGRAM |
| | | | | FECES-MUCOID |
| | | | | EXCESS SHEDDING |
| | | 00437 | | SOFT STOOL |
| 010 CONTROL | MALE | 00408 | | FECES-MUCOID |
| | | | | FECES-MUCOID |
| | | 00417 | | SOFT STOOL |
| | | | | FECES-MUCOID |
| | | | | SOFT STOOL |
| | | 00418 | | PENILE DISCHARGE |
| | | ***** | | CLEANED W/PEROXIDE |
| | FEMALE | 00426 | | FECES-MUCOID |
| | | | | VOMITED-LIQUID |
| | | ***** | | PHLEGM |
| | | | | VOMITED-LIQUID |
| | | ***** | | PHLEGM |
| | | 00434 | | LESION : LIMB-FORE,RIGHT |
| | | ***** | | CLEANED W/PEROXIDE |
| | | | | LESION : LIMB-FORE,RIGHT |
| | | ***** | | CLEANED W/PEROXIDE |
| | | | | LESION : LIMB-FORE,RIGHT |
| | | ***** | | CLEANED W/PEROXIDE |
| | | | | LESION : LIMB-FORE,RIGHT |
| | | ***** | | CLEANED W/PEROXIDE |
| | | | | LESION : LIMB-FORE,RIGHT |
| | | ***** | | CLEANED W/PEROXIDE |
| | | | | LESION |
| | | | | LESION : LIMB-FORE,RIGHT |
| | | ***** | | CLEANED W/PEROXIDE |
| | | 00435 | | VOMITED-LIQUID |
| | | ***** | | PHLEGM |
| 100 PPM | MALE | 00407 | | SOFT STOOL |
| | | | | SOFT STOOL |
| | | | | VOMITED-LIQUID |
| | | ***** | | PHLEGM |

## TABLE II-F-44 (Continued)

TOXICOLOGY OBSERVATION REPORT

TABLE 1 (CONTINUED)

| WEEK NO. ** | DOSE GROUP/SEX * | ANIMAL NUMBER | ***** OBSERVATIONS : QUALIFIER COMMENTS ********** |
|---|---|---|---|
| | | | VOMITED-LIQUID |
| | | ***** | PHLEGM |
| | | | SOFT STOOL |
| | | | VOMITED-LIQUID |
| | | ***** | PHLEGM |
| | | 00415 | PENILE DISCHARGE |
| | | ***** | CLEANED W/PEROXIDE |
| | | | PENILE DISCHARGE |
| | | ***** | CLEANED W/PEROXIDE |
| | | | PENILE DISCHARGE |
| | | ***** | CLEANED W/PEROXIDE |
| | | | PENILE DISCHARGE |
| | | ***** | CLEANED W/PEROXIDE |
| | | | SOFT STOOL |
| | | | PENILE DISCHARGE |
| | | ***** | CLEANED W/PEROXIDE |
| | FEMALE | 00422 | SWELLING |
| | | ***** | MAMMARY GLANDS |
| | | | SWELLING |
| | | ***** | MAMMARY GLANDS |
| | | | SWELLING |
| | | ***** | MAMMARY GLANDS |
| | | | SWELLING |
| | | ***** | MAMMARY GLANDS |
| | | | SOFT STOOL |
| | | | SWELLING |
| | | ***** | MAMMARY |
| | | | SWELLING |
| | | ***** | MAMMARY GLANDS |
| | | 00429 | SWELLING |
| | | ***** | MAMMARY GLANDS |
| | | | SWELLING |
| | | ***** | MAMMARY GLANDS |
| | | 00430 | FECES-MUCOID |
| | | | VOMITED-LIQUID |
| | | ***** | PHLEGM |
| | | 00431 | SOFT STOOL |
| | | | FECES-MUCOID |
| | | | FECES-MUCOID |
| 300 PPM | MALE | 00404 | FECES-MUCOID |
| | | | STOOL LIQUID |
| | | | FECES-MUCOID |
| | | ***** | W/RED SPOTS |
| | | | FECES-MUCOID |
| | | | VOMITED-LIQUID |
| | | ***** | PHLEGM |
| | FEMALE | 00424 | SOFT STOOL |

TABLE II-F-44 (Continued)

TOXICOLOGY OBSERVATION REPORT

TABLE 1 (CONTINUED)

| WEEK NO. ** | DOSE GROUP/SEX * | ANIMAL NUMBER ***** | OBSERVATIONS : QUALIFIER COMMENTS ********** |
|---|---|---|---|
| | | 00427 | SWELLING |
| | | ***** | MAMMARY GLANDS SWELLING |
| | | ***** | MAMMARY GLANDS SWELLING |
| | | ***** | MAMMARY GLANDS SWELLING |
| | | ***** | MAMMARY SWELLING |
| | | ***** | MAMMARY GLANDS SWELLING |
| | | ***** | MAMMARY GLANDS |
| | | 00433 | SWELLING |
| | | ***** | MAMMARY GLANDS STOOL LIQUID FECES-MUCOID SWELLING |
| | | ***** | MAMMARY GLANDS SWELLING |
| | | ***** | MAMMARY GLANDS SWELLING |
| | | ***** | MAMMARY GLANDS VOMITED-LIQUID |
| | | ***** | PHLEGM SWELLING |
| | | ***** | MAMMARY GLANDS SWELLING |
| | | ***** | MAMMARY GLANDS SWELLING |
| | | ***** | MAMMARY GLANDS |
| 1000 PPM | MALE | 00416 | SOFT STOOL FECES-MUCOID SOFT STOOL SOFT STOOL SOFT STOOL FECES-MUCOID |
| | | 00420 | SOFT STOOL VOMITED-LIQUID |
| | | ***** | PHLEGM SOFT STOOL VOMITED-LIQUID |
| | | ***** | PHLEGM |
| | FEMALE | 00423 | FECES-MUCOID |
| | | ***** | WITH RED STREAKS VOMITED-LIQUID |
| | | ***** | PHLEGM |
| | | 00432 | SOFT STOOL |

TABLE II-F-44 (Continued)

TOXICOLOGY OBSERVATION REPORT

TABLE 1 (CONTINUED)

| WEEK NO. ** DOSE GROUP/SEX * | ANIMAL NUMBER | OBSERVATIONS : QUALIFIER ***** COMMENTS ********** |
|---|---|---|
| | | SOFT STOOL |
| | | FECES-MUCOID |
| | | SOFT STOOL |
| | | FECES-MUCOID |
| | ***** | W/RED SPOTS |
| | | SOFT STOOL |
| | | FECES-MUCOID |
| | | SOFT STOOL |
| | | FECES-MUCOID |
| | | SOFT STOOL |
| | 00436 | VOMITED-LIQUID |
| | ***** | PHLEGM |
| | 00437 | VOMITED-LIQUID |
| | ***** | PHLEGM |
| | | SOFT STOOL |
| 011 CONTROL MALE | 00408 | STOOL LIQUID |
| | 00411 | SOFT STOOL |
| | 00417 | VOMITED-SEMISOLID |
| | | SOFT STOOL |
| | | STOOL LIQUID |
| | | STOOL LIQUID |
| | 00419 | PENILE DISCHARGE |
| | ***** | CLEANED W/PEROXIDE |
| | | PENILE DISCHARGE |
| | ***** | CLEANED W/PEROXIDE |
| | | PENILE DISCHARGE |
| | ***** | CLEANED W/PEROXIDE |
| | | VOMITED-SEMISOLID |
| FEMALE | 00425 | VOMITED-LIQUID |
| | ***** | PHLEGM |
| | | EYE ABNORMAL : EYE-RIGHT |
| | ***** | RED |
| | | EYE ABNORMAL : EYE-LEFT |
| | ***** | RED |
| | | EYE ABNORMAL : EYE-RIGHT |
| | ***** | RED |
| | | SOFT STOOL |
| | | SOFT STOOL |
| | | STOOL LIQUID |
| | | SOFT STOOL |
| | 00426 | SOFT STOOL |
| | 00434 | LESION : LIMB-FORE,RIGHT |
| | ***** | CLEANED W/PEROXIDE |
| | | SOFT STOOL |
| | | SOFT STOOL |
| | | SOFT STOOL |

TOXICOLOGY OBSERVATION REPORT

TABLE 1 (CONTINUED)

| WEEK NO. | DOSE GROUP/SEX | ANIMAL NUMBER | OBSERVATIONS : QUALIFIER ***** COMMENTS ********** |
|---|---|---|---|
| | | 00420 | SOFT STOOL |
| | | | SOFT STOOL |
| | | | STOOL LIQUID |
| | | | STOOL LIQUID |
| | | | STOOL LIQUID |
| | | | STOOL LIQUID |
| | | | STOOL LIQUID |
| | FEMALE | 00423 | SOFT STOOL |
| | | | VOMITED-LIQUID |
| | | ***** | PHLEGM |
| | | | SOFT STOOL |
| | | 00432 | STOOL LIQUID |
| | | | STOOL LIQUID |
| | | | FECES-MUCOID |
| | | | SOFT STOOL |
| | | | STOOL LIQUID |
| | | | STOOL LIQUID |
| | | | SOFT STOOL |
| | | | STOOL LIQUID |
| | | | APPEARS SKINNY |
| | | 00436 | SOFT STOOL |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | | SMALL MASS(<1CM) : LIMB-HIND,LEFT |
| | | ***** | CLEANED W/ PEROXIDE |
| | | 00437 | SOFT STOOL |
| | | | VOMITED-SEMISOLID |
| | | | STOOL LIQUID |
| | | | FECES-MUCOID |
| | | ***** | W/RED SPOTS |
| | | | STOOL LIQUID |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| 013 | CONTROL MALE | 00408 | SOFT STOOL |
| | | | VOMITED-LIQUID |
| | | ***** | PHLEGM |
| | | 00411 | FECES-MUCOID |
| | | 00417 | SOFT STOOL |
| | | | VOMITED-LIQUID |
| | | ***** | PHLEGM |
| | | | APPEARS SKINNY |
| | | | SOFT STOOL |
| | | | APPEARS SKINNY |
| | | | SOFT STOOL |
| | | | APPEARS SKINNY |

TABLE II-F-44 (Continued)

TOXICOLOGY OBSERVATION REPORT

TABLE 1 (CONTINUED)

| WEEK NO. | ** DOSE GROUP/SEX * | ANIMAL NUMBER | ***** | OBSERVATIONS : QUALIFIER COMMENTS ********** |
|---|---|---|---|---|
| | | | | LESION : LIMB-FORE,RIGHT |
| | | | ***** | CLEANED W/PEROXIDE |
| | 100 PPM MALE | | 00405 | SOFT STOOL |
| | | | | FECES-MUCOID |
| | | | ***** | COVERING STOOL |
| | | | 00406 | VOMITED-LIQUID |
| | | | ***** | PHLEGM |
| | | | | SOFT STOOL |
| | | | ***** | STOOL SOFT W/MUCUS |
| | | | 00407 | SOFT STOOL |
| | | | | STOOL LIQUID |
| | | | 00415 | PENILE DISCHARGE |
| | | | ***** | CLEANED W/PEROXIDE |
| | | | | SOFT STOOL |
| | | | | FECES-MUCOID |
| | | | ***** | W/RED STREAKS |
| | | | | PENILE DISCHARGE |
| | | | ***** | CLEANED W/PEROXIDE |
| | | | | SOFT STOOL |
| | | | | PENILE DISCHARGE |
| | | | ***** | CLEANED W/PEROXIDE |
| | | | | PENILE DISCHARGE |
| | | | ***** | CLEANED W/PEROXIDE |
| | | | | PENILE DISCHARGE |
| | | | ***** | CLEANED W/PEROXIDE |
| | | | | PAPILLOMA : PENIS |
| | | | ***** | LEFT SIDE |
| | | | | LESION : LIMBS-HIND |
| | | | ***** | BOTH LEFTSRT THIGHS |
| | | | | SMALL SCAB(<1CM) : PENIS |
| | | | ***** | SEVERAL |
| | FEMALE | 00422 | | SOFT STOOL |
| | | | | FECES-MUCOID |
| | | | | SOFT STOOL |
| | | | | SWELLING : VENTRAL-MID |
| | | | ***** | MAMMARY GLANDS |
| | | | 00430 | VOMITED-SEMISOLID |
| | | | ***** | ESTRUS |
| | | | | SOFT STOOL |
| | | | | STOOL LIQUID |
| | | | | SOFT STOOL |
| | | | 00431 | FECES-MUCOID |
| | 300 PPM MALE | | 00404 | FECES-MUCOID |
| | | | | SOFT STOOL |
| | | | | SOFT STOOL |
| | | | | FECES-MUCOID |
| | | | 00409 | VOMITED-LIQUID |
| | | | ***** | PHLEGM |

TOXICOLOGY OBSERVATION REPORT

TABLE 1 (CONTINUED)

| WEEK NO. | ** DOSE GROUP/SEX * | ANIMAL NUMBER | ***** OBSERVATIONS : QUALIFIER COMMENTS ********** |
|---|---|---|---|
| | | | PENILE DISCHARGE |
| | | ***** | CLEANED W/PEROXIDE |
| | | | PENILE DISCHARGE |
| | | ***** | CLEANED W/PEROXIDE |
| | | 00412 | VOMITED-LIQUID |
| | | ***** | PHLEGM |
| | | | STOOL LIQUID |
| | FEMALE | 00421 | SOFT STOOL |
| | | | FECES-MUCOID |
| | | ***** | LIQUID MUCUS IN STOO |
| | | 00424 | VOMITED-LIQUID |
| | | ***** | PHLEGM |
| | | | FECES-MUCOID |
| | | 00427 | STOOL LIQUID |
| | | ***** | STOOL W/MUCUS |
| | | 00433 | STOOL LIQUID |
| | | | FECES-MUCOID |
| | | | SWELLING |
| | | ***** | MAMMARY GLANDS |
| | | | SWELLING : VENTRAL-MID |
| | | ***** | MAMMARY GLANDS |
| | | | SWELLING : VENTRAL-MID |
| | | ***** | MAMMARY GLANDS |
| | | | SWELLING : VENTRAL-MID |
| | | ***** | MAMMARY GLANDS |
| | | | SWELLING : VENTRAL-MID |
| | | ***** | MAMMARY GLANDS |
| | | | SWELLING : VENTRAL-MID |
| | | ***** | MAMMARY GLANDS |
| 1000 PPM | MALE | 00413 | SOFT STOOL |
| | | | PENILE DISCHARGE |
| | | ***** | CLEANED W/PEROXIDE |
| | | 00416 | STOOL LIQUID |
| | | | FECES-MUCOID |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | | PENILE DISCHARGE |
| | | ***** | CLEANED W/PEROXIDE |
| | | 00419 | FECES-MUCOID |
| | | | SOFT STOOL |
| | | | LOCAL HAIR LOSS : LIMB-HIND,RIGHT |
| | | ***** | INNER THIGH |
| | | | PAPILLOMA : PENIS |
| | | ***** | LEFT SIDE |
| | | | LESION : LIMB-HIND,RIGHT |
| | | ***** | SMALL/SEVERAL |

TABLE II-F-44 (Continued)

TOXICOLOGY OBSERVATION REPORT

TABLE 1 (CONTINUED)

| WEEK NO. | ** DOSE GROUP/SEX * | ANIMAL NUMBER | ***** OBSERVATIONS : QUALIFIER COMMENTS ********** |
|---|---|---|---|
| | | 00420 | FECES-MUCOID |
| | | | SOFT STOOL |
| | | | FECES-MUCOID |
| | | ***** | IN SOFT STOOL |
| | | | VOMITED-LIQUID |
| | | ***** | PHLEGM |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | ***** | COVERED W/MUCUS |
| | | | STOOL LIQUID |
| | | ***** | W/MUCUS |
| | | | SOFT STOOL |
| | FEMALE | 00423 | SOFT STOOL |
| | | 00432 | SOFT STOOL |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | | STOOL LIQUID |
| | | | SOFT STOOL |
| | | 00437 | SOFT STOOL |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| 012 | CONTROL | MALE | 00408 | SOFT STOOL |
| | | | | VOMITED-LIQUID |
| | | ***** | PHLEGM |
| | | 00411 | SOFT STOOL |
| | | 00417 | STOOL LIQUID |
| | | | STOOL LIQUID |
| | | | STOOL LIQUID |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | | FECES-MUCOID |
| | | | SOFT STOOL |
| | | | APPEARS SKINNY |
| | | 00418 | SOFT STOOL |
| | FEMALE | 00425 | STOOL LIQUID |
| | | 00426 | VOMITED-LIQUID |
| | | ***** | PHLEGM |
| | | 00434 | SOFT STOOL |
| | | | LOCAL HAIR LOSS : LIMB-FORE,RIGHT |
| | | | SOFT STOOL |
| | | | LESION : LIMB-FORE,RIGHT |

TABLE II-F-44 (Continued)

TOXICOLOGY OBSERVATION REPORT

TABLE 1 (CONTINUED)

| WEEK NO. ** | DOSE GROUP/SEX * | ANIMAL NUMBER | ***** | OBSERVATIONS : QUALIFIER COMMENTS | ********** |
|---|---|---|---|---|---|
| | 100 PPM | MALE | 00405 | VOMITED-LIQUID | |
| | | | ***** | PHLEGM | |
| | | | | SOFT STOOL | |
| | | | | SOFT STOOL | |
| | | | | PAPILLOMA : NOSE:ABOVE | |
| | | | 00406 | STOOL LIQUID | |
| | | | | VOMITED-SEMISOLID | |
| | | | | VOMITED-SEMISOLID | |
| | | | | SOFT STOOL | |
| | | | 00407 | SWELLING : LIMB-HIND,LEFT | |
| | | | ***** | ON FOOT | |
| | | | | LESION : LIMB-HIND,LEFT | |
| | | | ***** | CLEANED W/PEROXIDE | |
| | | | 00415 | SOFT STOOL | |
| | | | | FECES-MUCOID | |
| | | | | PENILE DISCHARGE | |
| | | | ***** | CLEANED W/PEROXIDE | |
| | | | | STOOL LIQUID | |
| | | | | STOOL LIQUID | |
| | | | | LOCAL HAIR LOSS : PENIS | |
| | | | | LOCAL HAIR LOSS : LIMB-HIND,RIGHT | |
| | | | ***** | VENTRAL SIDE | |
| | | | | LOCAL HAIR LOSS : LIMB-HIND,LEFT | |
| | | | ***** | VENTRAL SIDE | |
| | | | | PENILE DISCHARGE | |
| | | | | SOFT STOOL | |
| | | | | PAPILLOMA : PENIS | |
| | | | ***** | LEFT AND RIGHT SIDES | |
| | | FEMALE | 00422 | SWELLING : VENTRAL-MID | |
| | | | ***** | MAMMARY GLANDS | |
| | | | | SOFT STOOL | |
| | | | | SWELLING : VENTRAL-MID | |
| | | | ***** | MAMMARY GLANDS | |
| | | | | SWELLING : VENTRAL-MID | |
| | | | ***** | MAMMARY GLANDS | |
| | | | | SWELLING : VENTRAL-MID | |
| | | | ***** | MAMMARY GLANDS | |
| | | | | SWELLING : VENTRAL-MID | |
| | | | ***** | MAMMARY GLANDS | |
| | | | | SWELLING : VENTRAL-MID | |
| | | | ***** | MAMMARY GLANDS | |
| | | | 00429 | SOFT STOOL | |
| | | | | SOFT STOOL | |
| | | | 00430 | STOOL LIQUID | |
| | | | | STOOL LIQUID | |

TOXICOLOGY OBSERVATION REPORT

TABLE 1 (CONTINUED)

| SEX NO. OF DOSE GROUP/SEX * | | ANIMAL NUMBER | ***** | OBSERVATIONS : QUALIFIER COMMENTS ********** |
|---|---|---|---|---|
| | | | | FECES-MUCOID |
| | | | | SOFT STOOL |
| | | | 00431 | SOFT STOOL |
| 300 PPM | MALE | | 00404 | SOFT STOOL |
| | | | | VOMITED-SEMISOLID |
| | | | | STOOL LIQUID |
| | | | | FECES-MUCOID |
| | | | 00409 | PENILE DISCHARGE |
| | | | ***** | CLEANED W/PEROXIDE |
| | | | | SOFT STOOL |
| | | | | SOFT STOOL |
| | | | | PENILE DISCHARGE |
| | | | | SOFT STOOL |
| | | | 00412 | SOFT STOOL |
| | | | | STOOL LIQUID |
| | FEMALE | | 00421 | SOFT STOOL |
| | | | | SOFT STOOL |
| | | | | SOFT STOOL |
| | | | | SCARRED TISSUE : EAR-LEFT:INSIDE |
| | | | ***** | ON FLAP-RED AREA-1.5 |
| | | | 00424 | SOFT STOOL |
| | | | | SOFT STOOL |
| | | | | SOFT STOOL |
| | | | | FECES-MUCOID |
| | | | 00427 | SOFT STOOL |
| | | | | VOMITED-SEMISOLID |
| | | | 00433 | SWELLING : VENTRAL-MID |
| | | | ***** | MAMMARY GLANDS |
| | | | | SWELLING : VENTRAL-MID |
| | | | ***** | MAMMARY GLANDS |
| | | | | SOFT STOOL |
| | | | | SOFT STOOL |
| | | | | VOMITED-LIQUID |
| | | | ***** | PHLEGM |
| | | | | SOFT STOOL |
| 1000 PPM | MALE | | 00413 | SOFT STOOL |
| | | | | STOOL LIQUID |
| | | | 00416 | SOFT STOOL |
| | | | | FECES-MUCOID |
| | | | | SOFT STOOL |
| | | | | STOOL LIQUID |
| | | | | STOOL LIQUID |
| | | | | SOFT STOOL |
| | | | 00419 | STOOL LIQUID |
| | | | | FECES-MUCOID |
| | | | | FECES-MUCOID |
| | | | | LOCAL HAIR LOSS : LIMB-HIND,RIGHT |
| | | | ***** | INNER THIGH |

TABLE II-F-44 (Continued)

TOXICOLOGY OBSERVATION REPORT

TABLE 1 (CONTINUED)

| SEX NO. ** DOSE GROUP/SEX * | ANIMAL NUMBER | ***** OBSERVATIONS : QUALIFIER COMMENTS ********** |
|---|---|---|
| | | SOFT STOOL |
| | | APPEARS SKINNY |
| | | SOFT STOOL |
| | | APPEARS SKINNY |
| | | SOFT STOOL |
| | | APPEARS SKINNY |
| | | SOFT STOOL |
| FEMALE | 00425 | SOFT STOOL |
| | | SOFT STOOL |
| | 00426 | SOFT STOOL |
| | | SOFT STOOL |
| | 00434 | SOFT STOOL |
| | | SOFT STOOL |
| 100 PPM MALE | 00405 | SOFT STOOL |
| | | SOFT STOOL |
| | | SOFT STOOL |
| | | SOFT STOOL |
| | | SOFT STOOL |
| | | SOFT STOOL |
| | 00406 | SOFT STOOL |
| | | FECES-MUCOID |
| | 00407 | LESION : LIMB-HIND,LEFT |
| | ***** | CLEANED W/PEROXIDE |
| | | SOFT STOOL |
| | | SOFT STOOL |
| | | VOMITED-LIQUID |
| | ***** | PHLEGM |
| | 00415 | STOOL LIQUID |
| | | FECES-MUCOID |
| | | SOFT STOOL |
| | | SOFT STOOL |
| | | SOFT STOOL |
| FEMALE | 00422 | SWELLING : VENTRAL-MID |
| | ***** | MAMMARY GLANDS |
| | | SWELLING : VENTRAL-MID |
| | | SOFT STOOL |
| | | SWELLING : VENTRAL-MID |
| | ***** | MAMMARY GLANDS |
| | | SOFT STOOL |
| | | SWELLING : VENTRAL-MID |
| | | SWELLING : VENTRAL-MID |
| | ***** | MAMMARY GLANDS |
| | | SWELLING : VENTRAL-MID |
| | ***** | MAMMARY GLANDS |
| | | SWELLING : VENTRAL-MID |
| | ***** | MAMMARY GLANDS |
| | 00429 | SOFT STOOL |

TOXICOLOGY OBSERVATION REPORT

TABLE 1 (CONTINUED)

| WEEK NO. ** | DOSE GROUP/SEX * | ANIMAL NUMBER | ***** OBSERVATIONS : QUALIFIER COMMENTS ********** |
|---|---|---|---|
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | 00430 | STOOL LIQUID |
| | | | VOMITED-SEMISOLID |
| | | | SOFT STOOL |
| | | | STOOL LIQUID |
| | | | STOOL LIQUID |
| | 300 PPM MALE | 00404 | SOFT STOOL |
| | | 00409 | STOOL LIQUID |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | 00412 | STOOL LIQUID |
| | | | SOFT STOOL |
| | | 00414 | SOFT STOOL |
| | | | VOMITED-SEMISOLID |
| | | | SOFT STOOL |
| | FEMALE | 00421 | SOFT STOOL |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | 00424 | SOFT STOOL |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | 00433 | STOOL LIQUID |
| | | | SOFT STOOL |
| | | | FECES-MUCOID |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | 1000 PPM MALE | 00416 | SOFT STOOL |
| | | | SOFT STOOL |
| | | 00420 | SOFT STOOL |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | | VOMITED-LIQUID |
| | | ***** | PHLEGM |
| | | | SOFT STOOL |
| | FEMALE | 00423 | SOFT STOOL |
| | | 00432 | SOFT STOOL |
| | | | APPEARS SKINNY |
| | | | STOOL LIQUID |
| | | | APPEARS SKINNY |
| | | | STOOL LIQUID |
| | | | FECES-MUCOID |

TABLE II-F-44 (Continued)

TOXICOLOGY OBSERVATION REPORT

TABLE 1 (CONTINUED)

| WEEK NO. ** | DOSE GROUP/SEX * | ANIMAL NUMBER | OBSERVATIONS : QUALIFIER ***** COMMENTS ********** |
|---|---|---|---|
| | | | APPEARS SKINNY |
| | | | STOOL LIQUID |
| | | | FECES-MUCOID |
| | | | APPEARS SKINNY |
| | | | STOOL LIQUID |
| | | | APPEARS SKINNY |
| | | | STOOL LIQUID |
| | | | APPEARS SKINNY |
| | | | STOOL LIQUID |
| | | | SKINNY |
| | | 00436 | SOFT STOOL |
| | | 00437 | SOFT STOOL |
| | | | SOFT STOOL |
| | | | STOOL LIQUID |
| | | | SOFT STOOL |
| | | | FECES-MUCOID |
| | | ***** | LIQUID MUCUS |
| | | | SOFT STOOL |
| 014 | CONTROL MALE | 00408 | SOFT STOOL |
| | | | VOMITED-LIQUID |
| | | ***** | PHLEGM |
| | | | VOMITED-LIQUID |
| | | ***** | PHLEGM |
| | | | TERMINAL KILL |
| | | 00411 | TERMINAL KILL |
| | | 00417 | SOFT STOOL |
| | | | SKINNY |
| | | | SOFT STOOL |
| | | | SKINNY |
| | | | SOFT STOOL |
| | | | VOMITED-LIQUID |
| | | ***** | PHLEGM |
| | | | SOFT STOOL |
| | | | SKINNY APPEARANCE |
| | | | STOOL LIQUID |
| | | | SKINNY |
| | | | TERMINAL KILL |
| | | 00418 | TERMINAL KILL |
| | FEMALE | 00425 | SOFT STOOL |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | | TERMINAL KILL |
| | | | TERMINAL KILL |
| | | | SOFT STOOL |

TOXICOLOGY OBSERVATION REPORT

TABLE 1 (CONTINUED)

| WEEK NO. ** | DOSE GROUP/SEX * | ANIMAL NUMBER | ***** | OBSERVATIONS : QUALIFIER COMMENTS | ********** |
|---|---|---|---|---|---|
| | | 00426 | | SOFT STOOL | |
| | | | | TERMINAL KILL | |
| | | 00434 | | SOFT STOOL | |
| | 100 PPM MALE | 00405 | | SOFT STOOL | |
| | | | | SOFT STOOL | |
| | | | | SOFT STOOL | |
| | | | | SOFT STOOL | |
| | | | | SOFT STOOL | |
| | | | | TERMINAL KILL | |
| | | | | TERMINAL KILL | |
| | | 00406 | | SOFT STOOL | |
| | | | | SOFT STOOL | |
| | | | | STOOL LIQUID | |
| | | | | TERMINAL KILL | |
| | | 00407 | | SOFT STOOL | |
| | | | | FECES-MUCOID | |
| | | 00415 | | SOFT STOOL | |
| | FEMALE | 00422 | | SWELLING : VENTRAL-MID | |
| | | ***** | | MAMMARY GLANDS | |
| | | | | SWELLING : VENTRAL-MID | |
| | | ***** | | MAMMARY GLANDS | |
| | | | | SWELLING : VENTRAL-MID | |
| | | ***** | | MAMMARY GLANDS | |
| | | | | SOFT STOOL | |
| | | | | SWELLING : VENTRAL-MID | |
| | | ***** | | MAMMARY GLANDS | |
| | | | | SOFT STOOL | |
| | | | | SWELLING : VENTRAL-MID | |
| | | ***** | | MAMMARY GLANDS | |
| | | | | TERMINAL KILL | |
| | | | | SOFT STOOL | |
| | | | | SWELLING : VENTRAL-MID | |
| | | ***** | | MAMMARY GLANDS | |
| | | 00429 | | VOMITED-SEMISOLID | |
| | | | | SOFT STOOL | |
| | | | | SOFT STOOL | |
| | | | | TERMINAL KILL | |
| | | | | SOFT STOOL | |
| | | 00430 | | SOFT STOOL | |
| | | | | TERMINAL KILL | |
| | | 00431 | | SOFT STOOL | |
| | | | | TERMINAL KILL | |
| | 300 PPM MALE | 00404 | | TERMINAL KILL | |
| | | | | STOOL LIQUID | |
| | | 00409 | | SOFT STOOL | |
| | | | | SOFT STOOL | |
| | | | | SOFT STOOL | |

TABLE II-F-44 (Continued)

TOXICOLOGY OBSERVATION REPORT

TABLE 1 (CONTINUED)

| WEEK NO. ** | DOSE GROUP/SEX * | ANIMAL NUMBER | ***** OBSERVATIONS : QUALIFIER COMMENTS ********** |
|---|---|---|---|
| | | | TERMINAL KILL |
| | | 00412 | SOFT STOOL |
| | | | TERMINAL KILL |
| | | 00414 | TERMINAL KILL |
| | FEMALE | 00421 | STOOL LIQUID |
| | | | ESTRUS |
| | | | TERMINAL KILL |
| | | 00424 | SOFT STOOL |
| | | | SOFT STOOL |
| | | | STOOL LIQUID |
| | | | TERMINAL KILL |
| | | 00433 | SOFT STOOL |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | | FECES-MUCOID |
| 1000 PPM | MALE | 00413 | VOMITED-LIQUID |
| | | ***** | PHLEGM |
| | | | VOMITED-LIQUID |
| | | ***** | PHLEGM |
| | | | TERMINAL KILL |
| | | 00416 | SOFT STOOL |
| | | | STOOL LIQUID |
| | | | SOFT STOOL |
| | | | TERMINAL KILL |
| | | 00419 | FECES-MUCOID |
| | | 00420 | SOFT STOOL |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | | VOMITED-SEMISOLID |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | FEMALE | 00423 | SOFT STOOL |
| | | | VOMITED-LIQUID |
| | | ***** | PHLEGM |
| | | | STOOL LIQUID |
| | | | SOFT STOOL |
| | | | TERMINAL KILL |
| | | 00432 | STOOL LIQUID |
| | | | SKINNY |
| | | | STOOL LIQUID |
| | | | SKINNY |
| | | | STOOL LIQUID |
| | | | SKINNY APPEARANCE |
| | | | STOOL LIQUID |
| | | | SKINNY APPEARANCE |
| | | | STOOL LIQUID |
| | | | SKINNY APPEARANCE |

TABLE II-F-44 (Continued)

TOXICOLOGY OBSERVATION REPORT

TABLE 1 (CONTINUED)

| WEEK NO. ** DOSE GROUP/SEX ** | | ANIMAL NUMBER | ***** OBSERVATIONS : QUALIFIER COMMENTS ********** |
|---|---|---|---|
| | | | TERMINAL KILL |
| | | | STOOL LIQUID |
| | | | SKINNY APPEARANCE |
| | | 00436 | VOMITED-SEMISOLID |
| | | | RED SPOTS IN STOOL |
| | | | TERMINAL KILL |
| | | 00437 | STOOL LIQUID |
| | | | STOOL LIQUID |
| | | | SOFT STOOL |
| | | | SOFT STOOL |
| | | | TERMINAL KILL |
| 015 CONTROL | FEMALE | 00434 | TERMINAL KILL |
| | | 00435 | TERMINAL KILL |
| 100 PPM | MALE | 00407 | TERMINAL KILL |
| | | 00415 | TERMINAL KILL |
| 300 PPM | FEMALE | 00427 | TERMINAL KILL |
| | | 00433 | TERMINAL KILL |
| 1000 PPM | MALE | 00419 | TERMINAL KILL |
| | | 00420 | TERMINAL KILL |

# TABLE II-F-45

PROJECT NO. 1073409
COMPUTER GROUP NO: 301A
LITTON BIONETICS, INC.
BODY WEIGHT DATA
GROUP 1 MALES DOSE: CONTROL

TABLE 2

| ANML NO. | DATES OF TESTING (1978) 5/10 | 5/17 | 5/24 | 5/31 | 6/ 7 | 6/14 | 6/21 | 6/28 | 7/ 5 | 7/12 | 7/19 | 7/26 | 8/ 2 | 8/ 9 | TERMINATION |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| 408 | 13.6 | 13.6 | 13.5 | 14.0 | 14.1 | 13.8 | 14.3 | 14.4 | 14.5 | 15.3 | 15.4 | 15.5 | 16.0 | 15.5 | 15.8 |
| 411 | 9.8 | 9.7 | 9.5 | 9.8 | 10.4 | 9.8 | 9.8 | 9.9 | 9.8 | 9.9 | 10.0 | 10.1 | 10.5 | 9.8 | 9.8 |
| 417 | 10.0 | 9.8 | 9.7 | 9.6 | 10.2 | 9.4 | 9.4 | 9.5 | 9.5 | 9.3 | 9.6 | 9.2 | 10.0 | 9.3 | 9.2 |
| 418 | 9.6 | 9.8 | 9.7 | 9.8 | 9.5 | 9.4 | 9.5 | 9.4 | 8.9 | 9.9 | 9.8 | 9.8 | 9.8 | 9.5 | 8.7 |
| SAMPLE | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| MEAN | 10.8 | 10.7 | 10.6 | 10.8 | 11.0 | 10.6 | 10.8 | 10.8 | 10.7 | 11.1 | 11.2 | 11.1 | 11.6 | 11.0 | 10.9 |
| S.D. | 1.9 | 1.9 | 1.9 | 2.1 | 2.1 | 2.1 | 2.4 | 2.4 | 2.6 | 2.8 | 2.8 | 2.9 | 3.0 | 3.0 | 3.3 |
| S.E. | 1.0 | 1.0 | 1.0 | 1.1 | 1.0 | 1.1 | 1.2 | 1.2 | 1.3 | 1.4 | 1.4 | 1.5 | 1.5 | 1.5 | 1.7 |

TABLE II-F-45 (Continued)

PROJECT NO. 1073409
COMPUTER GROUP NO: 3018
LITTON BIONETICS, INC.
BODY WEIGHT DATA
GROUP 1 FEMALES DOSE: CONTROL

TABLE 2 (CONTINUED)

| ANML NO. | DATES OF TESTING (1978) 5/10 | 5/17 | 5/24 | 5/31 | 6/ 7 | 6/14 | 6/21 | 6/28 | 7/ 5 | 7/12 | 7/19 | 7/26 | 8/ 2 | 8/ 9 | TERMINATION |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| 425 | 8.6 | 8.4 | 8.1 | 8.5 | 8.2 | 7.8 | 8.3 | 8.3 | 8.2 | 8.3 | 8.6 | 8.6 | 8.6 | 8.3 | 8.3 |
| 426 | 8.8 | 7.9 | 7.9 | 8.1 | 8.1 | 7.7 | 7.6 | 7.6 | 7.5 | 7.9 | 8.1 | 7.7 | 8.1 | 7.7 | 7.6 |
| 434 | 8.1 | 7.8 | 7.7 | 7.9 | 8.3 | 8.0 | 7.9 | 7.9 | 7.9 | 8.1 | 8.5 | 8.5 | 8.4 | 7.9 | 7.9 |
| 435 | 7.0 | 6.9 | 6.7 | 6.9 | 6.9 | 6.4 | 6.6 | 6.7 | 6.9 | 6.9 | 6.9 | 6.9 | 6.8 | 6.4 | 6.4 |
| SAMPLE | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| MEAN | 8.1 | 7.7 | 7.6 | 7.8 | 7.9 | 7.5 | 7.6 | 7.6 | 7.6 | 7.8 | 8.0 | 7.9 | 8.0 | 7.6 | 7.5 |
| S.D. | 0.8 | 0.6 | 0.6 | 0.7 | 0.7 | 0.7 | 0.7 | 0.7 | 0.6 | 0.6 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 |
| S.E. | 0.4 | 0.3 | 0.3 | 0.3 | 0.3 | 0.4 | 0.4 | 0.3 | 0.3 | 0.3 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 |

TABLE II-F-45 (Continued)

PROJECT NO. 1073409
COMPUTER GROUP NO: 301C
LITTON BIONETICS, INC.
BODY WEIGHT DATA
GROUP 2 MALES DOSE: 100 PPM
TABLE 2 (CONTINUED)

| ANML NO. | DATES OF TESTING (1978) 5/10 | 5/17 | 5/24 | 5/31 | 6/ 7 | 6/14 | 6/21 | 6/28 | 7/ 5 | 7/12 | 7/19 | 7/26 | 8/ 2 | 8/ 9 | TERMINATION |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| 405 | 12.4 | 11.7 | 11.5 | 11.9 | 12.7 | 11.0 | 11.5 | 11.9 | 12.0 | 12.3 | 12.1 | 12.7 | 12.6 | 11.8 | 12.0 |
| 406 | 12.8 | 12.7 | 12.6 | 13.0 | 12.7 | 12.7 | 13.1 | 13.4 | 12.9 | 11.8 | 13.4 | 13.6 | 14.1 | 13.6 | 12.4 |
| 407 | 11.8 | 11.5 | 11.7 | 11.3 | 11.8 | 11.7 | 11.5 | 11.8 | 12.1 | 13.4 | 11.6 | 11.8 | 11.1 | 11.0 | 10.9 |
| 415 | 11.4 | 11.4 | 11.4 | 11.7 | 11.5 | 11.7 | 11.8 | 11.7 | 11.7 | 11.8 | 11.9 | 11.9 | 12.0 | 11.3 | 11.2 |
| SAMPLE | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| MEAN | 12.1 | 11.8 | 11.8 | 12.0 | 12.2 | 11.8 | 12.0 | 12.2 | 12.2 | 12.3 | 12.3 | 12.5 | 12.4 | 11.9 | 11.6 |
| S.D. | 0.6 | 0.6 | 0.5 | 0.7 | 0.6 | 0.7 | 0.8 | 0.8 | 0.5 | 0.8 | 0.8 | 0.8 | 1.3 | 1.2 | 0.7 |
| S.E. | 0.3 | 0.3 | 0.3 | 0.4 | 0.3 | 0.3 | 0.4 | 0.4 | 0.3 | 0.4 | 0.4 | 0.4 | 0.6 | 0.6 | 0.3 |

# TABLE II-F-45 (Continued)

PROJECT NO. 1073409
COMPUTER GROUP NO: 3010
LITTON BIONETICS, INC.
BODY WEIGHT DATA
GROUP 2 FEMALES DOSE: 100 PPM

TABLE2 (CONTINUED)

| ANML NO. | DATES OF TESTING (1978) 5/10 | 5/17 | 5/24 | 5/31 | 6/ 7 | 6/14 | 6/21 | 6/28 | 7/ 5 | 7/12 | 7/19 | 7/26 | 8/ 2 | 8/ 9 | TERMINATION |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| 422 | 9.0 | 8.7 | 8.5 | 8.7 | 8.7 | 8.5 | 8.6 | 9.0 | 8.8 | 9.1 | 8.8 | 8.9 | 9.1 | 8.6 | 8.7 |
| 429 | 9.0 | 9.0 | 8.8 | 8.9 | 9.1 | 9.1 | 9.3 | 8.9 | 9.0 | 9.1 | 9.3 | 9.2 | 9.4 | 9.6 | 9.6 |
| 430 | 9.9 | 9.7 | 9.9 | 9.9 | 10.0 | 9.4 | 9.9 | 10.1 | 10.0 | 10.2 | 10.1 | 9.8 | 10.3 | 9.7 | 9.1 |
| 431 | 8.0 | 7.9 | 7.8 | 7.9 | 8.4 | 7.6 | 7.9 | 8.2 | 8.1 | 8.6 | 8.6 | 8.5 | 8.5 | 8.3 | 7.8 |
| SAMPLE | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| MEAN | 9.0 | 8.8 | 8.8 | 8.8 | 9.0 | 8.6 | 8.9 | 9.0 | 9.0 | 9.3 | 9.2 | 9.1 | 9.3 | 9.1 | 8.8 |
| S.D. | 0.8 | 0.7 | 0.9 | 0.8 | 0.7 | 0.8 | 0.9 | 0.8 | 0.8 | 0.7 | 0.7 | 0.5 | 0.8 | 0.7 | 0.8 |
| S.E. | 0.4 | 0.4 | 0.4 | 0.4 | 0.3 | 0.4 | 0.4 | 0.4 | 0.4 | 0.3 | 0.3 | 0.3 | 0.4 | 0.4 | 0.4 |

TABLE II-F-45 (Continued)

PROJECT NO. 1073409
COMPUTER GROUP NO: 301E
LITTON BIONETICS, INC.
BODY WEIGHT DATA
GROUP 3 MALES DOSE: 300 PPM

TABLE 2 (CONTINUED)

| ANML NO. | DATES OF TESTING (1978) 5/10 | 5/17 | 5/24 | 5/31 | 6/ 7 | 6/14 | 6/21 | 6/28 | 7/ 5 | 7/12 | 7/19 | 7/26 | 8/ 2 | 8/ 9 | TERMINATION |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| 404 | 10.6 | 10.4 | 10.2 | 10.3 | 10.9 | 10.0 | 10.7 | 10.9 | 10.4 | 10.5 | 10.9 | 10.9 | 11.1 | 10.4 | 10.8 |
| 409 | 9.4 | 9.5 | 9.1 | 9.4 | 9.7 | 9.7 | 9.7 | 9.5 | 9.4 | 9.8 | 9.8 | 9.8 | 10.0 | 9.2 | 9.4 |
| 412 | 9.2 | 9.0 | 9.0 | 9.2 | 9.1 | 8.9 | 9.0 | 9.4 | 9.5 | 9.5 | 9.5 | 9.2 | 8.9 | 9.1 | 8.7 |
| 414 | 10.7 | 10.5 | 10.5 | 10.9 | 10.6 | 10.5 | 10.7 | 11.1 | 11.2 | 11.3 | 11.4 | 11.5 | 11.5 | 10.8 | 10.4 |
| SAMPLE | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| MEAN | 10.0 | 9.8 | 9.7 | 9.9 | 10.1 | 9.8 | 10.0 | 10.2 | 10.1 | 10.3 | 10.4 | 10.3 | 10.4 | 9.9 | 9.8 |
| S.D. | 0.8 | 0.7 | 0.8 | 0.8 | 0.8 | 0.7 | 0.8 | 0.9 | 0.8 | 0.8 | 0.9 | 1.0 | 1.2 | 0.9 | 1.0 |
| S.E. | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.3 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.5 | 0.6 | 0.4 | 0.5 |

# TABLE II-F-45 (Continued)

PROJECT NO. 1073409
COMPUTER GROUP NO: 301F
LITTON BIONETICS, INC.
BODY WEIGHT DATA
GROUP 3 FEMALES DOSE: 300 PPM
TABLE 2 (CONTINUED)

| ANML NO. | DATES OF TESTING (1978) 5/10 | 5/17 | 5/24 | 5/31 | 6/ 7 | 6/14 | 6/21 | 6/28 | 7/ 5 | 7/12 | 7/19 | 7/26 | 8/ 2 | 8/ 9 | TERMINATION |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| 421 | 10.6 | 10.5 | 10.1 | 10.4 | 10.5 | 10.4 | 10.6 | 10.8 | 10.3 | 11.0 | 10.8 | 10.9 | 11.1 | 10.5 | 10.9 |
| 424 | 8.5 | 8.1 | 8.3 | 8.6 | 9.0 | 8.5 | 8.3 | 8.4 | 8.9 | 8.7 | 8.7 | 9.1 | 8.6 | 8.4 | 7.8 |
| 427 | 7.3 | 7.3 | 7.2 | 7.5 | 7.6 | 7.6 | 7.5 | 7.6 | 7.5 | 7.5 | 7.7 | 7.7 | 7.6 | 7.4 | 7.3 |
| 433 | 8.9 | 9.3 | 9.3 | 9.2 | 10.1 | 9.8 | 9.6 | 9.8 | 9.5 | 10.3 | 10.3 | 10.4 | 9.9 | 9.4 | 9.4 |
| SAMPLE | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| MEAN | 8.8 | 8.8 | 8.7 | 8.9 | 9.3 | 9.1 | 9.0 | 9.1 | 9.0 | 9.4 | 9.4 | 9.5 | 9.3 | 8.9 | 8.8 |
| S.D. | 1.4 | 1.4 | 1.3 | 1.2 | 1.3 | 1.3 | 1.4 | 1.4 | 1.2 | 1.6 | 1.4 | 1.4 | 1.5 | 1.3 | 1.6 |
| S.E. | 0.7 | 0.7 | 0.6 | 0.6 | 0.6 | 0.6 | 0.7 | 0.7 | 0.6 | 0.8 | 0.7 | 0.7 | 0.8 | 0.7 | 0.8 |

TABLE II-F-45 (Continued)

PROJECT NO. 1073409
COMPUTER GROUP NO: 301G
LITTON BIONETICS, INC.
BODY WEIGHT DATA
GROUP 4 MALES DOSE: 1000 PPM
TABLE 2 (CONTINUED)

| ANML NO. | DATES OF TESTING (1978) 5/10 | 5/17 | 5/24 | 5/31 | 6/ 7 | 6/14 | 6/21 | 6/28 | 7/ 5 | 7/12 | 7/19 | 7/26 | 8/ 2 | 8/ 9 | TERMINATION |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| 413 | 10.9 | 10.6 | 10.6 | 9.9 | 10.5 | 10.2 | 10.5 | 10.5 | 10.5 | 10.8 | 10.9 | 10.8 | 10.9 | 10.3 | 10.7 |
| 416 | 10.0 | 9.9 | 10.2 | 9.9 | 9.8 | 9.7 | 9.7 | 10.0 | 9.6 | 10.3 | 10.2 | 10.2 | 10.6 | 9.8 | 9.4 |
| 419 | 11.0 | 10.8 | 10.9 | 11.1 | 11.1 | 10.7 | 11.0 | 11.3 | 10.7 | 10.5 | 10.2 | 10.3 | 11.1 | 10.6 | 10.6 |
| 420 | 11.4 | 10.9 | 11.4 | 11.5 | 12.3 | 11.7 | 11.5 | 11.1 | 11.2 | 10.9 | 11.2 | 11.5 | 11.2 | 11.0 | 10.9 |
| SAMPLE | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| MEAN | 10.8 | 10.5 | 10.8 | 10.6 | 10.9 | 10.6 | 10.7 | 10.7 | 10.5 | 10.6 | 10.6 | 10.7 | 10.9 | 10.4 | 10.4 |
| S.D. | 0.6 | 0.5 | 0.5 | 0.8 | 1.1 | 0.9 | 0.8 | 0.6 | 0.7 | 0.3 | 0.5 | 0.6 | 0.3 | 0.5 | 0.7 |
| S.E. | 0.3 | 0.2 | 0.3 | 0.4 | 0.5 | 0.4 | 0.4 | 0.3 | 0.3 | 0.1 | 0.3 | 0.3 | 0.1 | 0.3 | 0.3 |

TABLE II-F-45 (Continued)

PROJECT NO.: 107340?
COMPUTER GROUP NO: 301H
LITTON BIONETICS, INC.
BODY WEIGHT DATA
GROUP 4 FEMALES DOSE: 1000 PPM
TABLE 2 (CONTINUED)

| ANML NO. | DATES OF TESTING (1978) 5/10 | 5/17 | 5/24 | 5/31 | 6/ 7 | 6/14 | 6/21 | 6/28 | 7/ 5 | 7/12 | 7/19 | 7/26 | 8/ 2 | 8/ 9 | TERMINATION |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| 423 | 7.8 | 7.6 | 7.5 | 7.7 | 10.2 | 7.4 | 7.7 | 7.9 | 7.5 | 8.0 | 7.8 | 7.9 | 8.0 | 7.3 | 7.6 |
| 432 | 8.0 | 7.9 | 7.8 | 7.8 | 7.8 | 7.6 | 7.6 | 7.9 | 7.8 | 7.9 | 7.8 | 7.9 | 7.9 | 7.4 | 7.4 |
| 436 | 8.4 | 8.0 | 7.9 | 7.9 | 8.2 | 8.2 | 8.4 | 8.5 | 8.8 | 8.3 | 8.2 | 8.0 | 8.1 | 8.0 | 7.9 |
| 437 | 9.0 | 8.8 | 8.9 | 8.9 | 9.3 | 9.2 | 9.0 | 9.2 | 9.0 | 9.2 | 9.4 | 9.6 | 9.8 | 8.9 | 8.8 |
| SAMPLE | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| MEAN | 8.3 | 8.1 | 8.0 | 8.1 | 8.9 | 8.1 | 8.2 | 8.4 | 8.3 | 8.3 | 8.3 | 8.3 | 8.4 | 7.9 | 7.9 |
| S.D. | 0.5 | 0.5 | 0.6 | 0.6 | 1.1 | 0.8 | 0.7 | 0.6 | 0.7 | 0.6 | 0.8 | 0.8 | 0.9 | 0.7 | 0.6 |
| S.E. | 0.3 | 0.3 | 0.3 | 0.3 | 0.5 | 0.4 | 0.3 | 0.3 | 0.4 | 0.3 | 0.4 | 0.4 | 0.5 | 0.4 | 0.3 |

# TABLE II-F-46

PROJECT NO. 1073409
COMPUTER GROUP NO: 301A
LITTON BIONETICS, INC.
DAILY FOOD INTAKE IN GRAMS
GROUP 1 MALES DOSE: CONTROL
TABLE 3

| ANML NO. | DATES OF TESTING (1978) 5/17 | 5/24 | 5/31 | 6/ 7 | 6/14 | 6/21 | 6/28 | 7/ 5 | 7/12 | 7/19 | 7/26 | 8/ 2 | 8/ 9 | 8/16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| 408 | 382.3 | 337.3 | 433.7 | - | - | - | - | 479.7 | 447.6 | 395.1 | - | 388.1 | 368.3 | 411.1 |
| 411 | - | - | - | - | - | - | - | - | - | - | - | - | 261.1 | 302.2 |
| 417 | 310.8 | 290.6 | 289.5 | 289.0 | 371.4 | - | 300.4 | 333.5 | 240.1 | 314.9 | 251.3 | 360.4 | 285.9 | 350.4 |
| 418 | 346.1 | 345.6 | 376.3 | 266.9 | 316.8 | 297.2 | 294.4 | 288.7 | 371.2 | 325.2 | 340.9 | 340.8 | 345.3 | 324.2 |
| SAMPLE | 3 | 3 | 3 | 2 | 2 | 1 | 2 | 3 | 3 | 3 | 2 | 3 | 4 | 4 |
| MEAN | 346.4 | 324.5 | 366.5 | 278.0 | 344.1 | 297.2 | 297.4 | 367.3 | 353.0 | 345.1 | 296.1 | 363.1 | 315.2 | 347.0 |
| S.D. | 35.8 | 29.6 | 72.6 | 15.6 | 38.6 | 0.0 | 4.2 | 99.9 | 104.9 | 43.7 | 63.4 | 23.8 | 50.0 | 47.0 |
| S.E. | 20.7 | 17.1 | 41.9 | 11.0 | 27.3 | 0.0 | 3.0 | 57.7 | 60.6 | 25.2 | 44.8 | 13.7 | 25.0 | 23.5 |

## TABLE II-F-46 (Continued)

PROJECT NO. 1073409
COMPUTER GROUP NO: 3018
LITTON BIONETICS, INC.
DAILY FOOD INTAKE IN GRAMS
GROUP 1 FEMALES DOSE: CONTROL
TABLE3 (CONTINUED)

| ANML NO. | DATES OF TESTING (1978) 5/17 | 5/24 | 5/31 | 6/ 7 | 6/14 | 6/21 | 6/28 | 7/ 5 | 7/12 | 7/19 | 7/26 | 8/ 2 | 8/ 9 | 8/16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| 425 | 348.2 | - | - | - | 309.4 | -[a] | - | 263.5 | - | 266.8 | - | - | 297.3 | 263.4 |
| 426 | 226.6 | 247.1 | 283.7 | 264.6 | - | - | - | - | 300.1 | 271.8 | - | 259.0 | 288.1 | 274.9 |
| 434 | 262.0 | 271.6 | 320.2 | 283.7 | 424.2 | - | 304.9 | 326.5 | 328.5 | 324.1 | 350.2 | 299.1 | - | 368.8 |
| 435 | 214.4 | 208.0 | 199.0 | 191.9 | 302.4 | - | - | 215.5 | 216.0 | - | - | 197.2 | 220.5 | 265.7 |
| SAMPLE | 4 | 3 | 3 | 3 | 3 | 0.0 | 1 | 3 | 3 | 3 | 1 | 3 | 3 | 4 |
| MEAN | 262.8 | 242.2 | 267.7 | 246.7 | 345.3 | 0.0 | 304.9 | 268.5 | 281.5 | 287.6 | 350.2 | 251.8 | 268.6 | 293.2 |
| S.D. | 60.4 | 32.1 | 62.2 | 48.5 | 68.4 | 0.0 | 0.0 | 55.7 | 58.5 | 31.7 | 0.0 | 51.4 | 42.0 | 50.6 |
| S.E. | 30.2 | 18.5 | 35.9 | 28.0 | 39.5 | 0.0 | 0.0 | 32.1 | 33.8 | 18.3 | 0.0 | 29.6 | 24.2 | 25.3 |

[a]All spilled food.

TABLE II-F-46 (Continued)

PROJECT NO. 1073-09
COMPUTER GROUP NO: 301C
LITTON BIONETICS, INC.
DAILY FOOD INTAKE IN GRAMS
GROUP 2 MALES DOSE: 100 PPM
TABLE 3 (CONTINUED)

| ANML NO. | DATES OF TESTING (1978) 5/17 | 5/24 | 5/31 | 6/ 7 | 6/14 | 6/21 | 6/28 | 7/ 5 | 7/12 | 7/19 | 7/26 | 8/ 2 | 8/ 9 | 8/16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| 405 | 411.4 | 387.9 | - | - | - | - | - | - | 383.8 | 326.0 | 357.8 | 365.7 | 354.9 | 317.0 |
| 406 | 309.1 | - | - | - | 414.4 | 312.5 | 361.5 | 265.3 | 338.6 | 314.9 | 300.6 | 304.8 | 340.3 | 450.7 |
| 407 | 304.4 | 355.6 | 302.3 | 361.3 | 313.2 | 386.0 | 348.5 | 349.8 | - | - | - | - | 358.6 | 252.5 |
| 415 | 327.1 | 317.9 | 337.6 | - | - | - | 278.8 | 265.0 | 306.8 | 308.2 | 271.9 | 258.5 | 225.5 | 311.0 |
| SAMPLE | 4 | 3 | 2 | 1 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 4 | 4 |
| MEAN | 338.0 | 353.8 | 319.9 | 361.3 | 363.8 | 349.2 | 329.6 | 293.4 | 343.1 | 316.4 | 310.1 | 309.7 | 319.8 | 332.8 |
| S.D. | 49.9 | 35.0 | 25.0 | 0.0 | 71.6 | 52.0 | 44.5 | 48.9 | 38.7 | 9.0 | 43.7 | 53.7 | 63.4 | 83.8 |
| S.E. | 24.9 | 20.2 | 17.6 | 0.0 | 50.6 | 36.8 | 25.7 | 28.2 | 22.3 | 5.2 | 25.2 | 31.0 | 31.7 | 41.9 |

## TABLE II-F-46 (Continued)

PROJECT NO. 107340
COMPUTER GROUP NO: 301D
LITTON BIONETICS, INC.
DAILY FOOD INTAKE IN GRAMS
GROUP 2 FEMALES DOSE: 100 PPM
TABLE 3 (CONTINUED)

| ANML NO. | DATES OF TESTING (1976) 5/17 | 5/24 | 5/31 | 6/ 7 | 6/14 | 6/21 | 6/28 | 7/ 5 | 7/12 | 7/19 | 7/26 | 8/ 2 | 8/ 9 | 8/16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| 422 | 213.4 | 201.9 | 238.0 | 207.3 | 201.1 | 215.6 | 246.4 | 213.9 | 198.4 | 161.5 | 218.4 | 203.4 | 180.5 | 210.6 |
| 429 | 262.9 | - | 285.6 | - | 309.4 | 304.5 | 272.5 | 291.8 | 268.3 | 239.0 | 279.9 | 270.1 | - | 257.8 |
| 430 | 275.6 | 253.4 | 287.6 | 277.5 | 252.2 | 267.6 | 283.9 | 220.1 | 277.1 | 249.7 | 205.5 | 236.6 | 251.0 | 253.7 |
| 431 | 276.6 | 236.1 | 255.8 | 264.9 | 219.6 | 249.3 | 253.6 | - | 229.1 | 275.7 | 268.2 | 172.4 | 170.5 | 156.1 |
| SAMPLE | 4 | 3 | 4 | 3 | 4 | 4 | 4 | 3 | 4 | 4 | 4 | 4 | 3 | 4 |
| MEAN | 244.6 | 230.5 | 266.8 | 249.9 | 245.6 | 259.1 | 264.1 | 241.9 | 243.2 | 231.5 | 243.0 | 220.6 | 200.7 | 219.5 |
| S.D. | 29.4 | 26.2 | 24.1 | 37.4 | 47.5 | 37.1 | 17.2 | 43.3 | 36.4 | 49.2 | 36.5 | 42.1 | 43.9 | 47.4 |
| S.E. | 14.7 | 15.1 | 12.0 | 21.6 | 23.8 | 18.5 | 8.6 | 25.0 | 18.2 | 24.6 | 18.3 | 21.1 | 25.3 | 23.7 |

## TABLE II-F-46 (Continued)

PROJECT NO. 1073409
COMPUTER GROUP NO: 301E
LITTON BIONETICS, INC.
DAILY FOOD INTAKE IN GRAMS
GROUP 3 MALES DOSE: 300 PPM
TABLE 3 (CONTINUED)

| ANML NO. | DATES OF TESTING (1978) 5/17 | 5/24 | 5/31 | 6/ 7 | 6/14 | 6/21 | 6/28 | 7/ 5 | 7/12 | 7/19 | 7/26 | 8/ 2 | 8/ 9 | 8/16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| 404 | 215.5 | 266.0 | 274.6 | 335.1 | 294.1 | 306.6 | 328.4 | 267.4 | 275.3 | 323.8 | 313.9 | 298.9 | 292.7 | 319.6 |
| 409 | 342.0 | 277.4 | 305.8 | 302.5 | 331.2 | 289.5 | 258.1 | 227.9 | - | - | 284.2 | 271.2 | 270.4 | 336.1 |
| 412 | 239.5 | 248.0 | 246.6 | - | 228.2 | 222.0 | 325.2 | 228.9 | 251.3 | - | - | 188.5 | 337.5 | 190.7 |
| 414 | - | 308.1 | 339.3 | 300.9 | 286.2 | - | 304.1 | - | - | 275.7 | 315.4 | 291.6 | 306.6 | 244.7 |
| SAMPLE | 3 | 4 | 4 | 3 | 4 | 3 | 4 | 3 | 2 | 2 | 3 | 4 * | 4 | 4 |
| MEAN | 265.6 | 274.9 | 291.6 | 312.8 | 284.9 | 272.7 | 303.9 | 241.4 | 263.3 | 299.7 | 304.5 | 262.5 | 301.8 | 272.8 |
| S.D. | 67.2 | 25.3 | 40.0 | 19.3 | 42.6 | 44.8 | 32.4 | 22.5 | 17.0 | 34.0 | 17.6 | 50.8 | 28.1 | 67.6 |
| S.E. | 38.8 | 12.6 | 20.0 | 11.1 | 21.3 | 25.8 | 16.2 | 13.0 | 12.0 | 24.0 | 10.2 | 25.4 | 14.0 | 33.8 |

*p<0.05 as compared to controls: Dunnett's t-test.

## TABLE II-F-46 (Continued)

PROJECT NO. 107-3409
COMPUTER GROUP NO: 3011
LITTON BIONETICS, INC.
DAILY FOOD INTAKE IN GRAMS
GROUP 3 FEMALES DOSE: 300 PPM
TABLE 3 (CONTINUED)

| ANML NO. | DATES OF TESTING (1978) 5/17 | 5/24 | 5/31 | 6/ 7 | 6/14 | 6/21 | 6/28 | 7/ 5 | 7/12 | 7/19 | 7/26 | 8/ 2 | 8/ 9 | 8/16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| 421 | - | 273.5 | 353.7 | - | 313.3 | - | 318.7 | 277.6 | 316.8 | 275.2 | 270.6 | 307.8 | 276.8 | 303.9 |
| 424 | 232.3 | 276.9 | 289.0 | 245.1 | 205.8 | 219.1 | 305.5 | 247.8 | - | - | 278.7 | 246.6 | 292.4 | 273.1 |
| 427 | 244.4 | 221.5 | 244.5 | 231.1 | 196.7 | 207.9 | 224.7 | 196.3 | - | - | 205.6 | 204.4 | 211.7 | 214.1 |
| 433 | 330.5 | - | - | - | - | 262.7 | 343.6 | - | - | - | - | - | - | - |
| SAMPLE | 3 | 3 | 3 | 2 | 3 | 3 | 4 | 3 | 1 | 1 | 3 | 3 | 3 | 3 |
| MEAN | 269.1 | 257.3 | 295.7 | 238.1 | 238.6 | 229.9 | 298.1 | 227.2 | 316.8 | 275.2 | 251.6 | 252.9 | 260.3 | 263.7 |
| S.D. | 53.6 | 31.0 | 54.9 | 9.9 | 64.8 | 28.9 | 51.4 | 63.2 | 0.0 | 0.0 | 40.1 | 52.0 | 42.8 | 45.7 |
| S.E. | 30.9 | 17.9 | 31.7 | 7.0 | 37.4 | 16.7 | 25.7 | 36.5 | 0.0 | 0.0 | 23.2 | 30.0 | 24.7 | 26.4 |

TABLE II-F-46 (Continued)

PROJECT NO. 1073409
COMPUTER GROUP NO: 3016
LITTON BIONETICS, INC.
DAILY FOOD INTAKE IN GRAMS
GROUP 4 MALES DOSE: 1000 PPM
TABLE 3 (CONTINUED)

| ANML NO. | DATES OF TESTING (1978) 5/17 | 5/24 | 5/31 | 6/ 7 | 6/14 | 6/21 | 6/28 | 7/ 5 | 7/12 | 7/19 | 7/26 | 8/ 2 | 8/ 9 | 8/16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| 413 | - | 301.8 | 201.3 | 379.4 | 222.1 | 324.2 | - | - | 330.1 | 321.0 | 294.3 | - | 224.5 | 292.3 |
| 416 | - | 402.3 | 264.7 | - | 266.6 | 242.3 | 274.8 | 260.0 | 323.3 | 271.5 | 306.3 | 341.7 | 261.6 | 282.2 |
| 419 | 317.9 | 293.6 | 293.1 | 267.2 | 324.5 | 280.1 | 308.7 | 250.8 | 248.6 | 272.9 | 200.8 | - | - | 339.7 |
| 420 | 339.8 | - | 411.9 | 442.1 | - | - | - | - | 260.6 | - | 354.5 | 406.8 | - | 358.1 |
| SAMPLE | 2 | 3 | 4 | 3 | 3 | 3 | 2 | 2 | 4 | 3 | 4 | 2 | 2 | 4 |
| MEAN | 328.9 | 332.6 | 292.8 | 362.9 | 271.1 | 282.2 | 291.8 | 255.4 | 290.7 | 288.5 | 289.0 | 374.2 | 243.1 | 318.1 |
| S.D. | 15.4 | 60.5 | 88.2 | 88.6 | 51.4 | 41.0 | 24.0 | 6.5 | 42.0 | 28.2 | 64.3 | 46.0 | 26.3 | 36.6 |
| S.E. | 10.9 | 34.9 | 44.1 | 51.2 | 29.7 | 23.7 | 17.0 | 4.6 | 21.0 | 16.3 | 32.1 | 32.5 | 18.6 | 18.3 |

## TABLE II-F-46 (Continued)

PROJECT NO. 107340
COMPUTER GROUP NO: 3011
LITTON BIONETICS, INC.
DAILY FOOD INTAKE IN GRAMS
GROUP 4 FEMALES DOSE: 1000 PPM
TABLE 3 (CONTINUED)

| ANML NO. | DATES OF TESTING (1978) 5/17 | 5/24 | 5/31 | 6/ 7 | 6/14 | 6/21 | 6/28 | 7/ 5 | 7/12 | 7/19 | 7/26 | 8/ 2 | 8/ 9 | 8/16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| 423 | 273.4 | - | 288.4 | 232.4 | 199.1 | - | 260.1 | - | 253.8 | 188.6 | 236.3 | - | - | 307.5 |
| 432 | - | - | - | - | - | - | - | - | - | - | - | - | - | 0.0 |
| 436 | 181.3 | 205.2 | 202.0 | 359.2 | 195.1 | 220.3 | - | 204.4 | 200.9 | 157.9 | 181.8 | 248.7 | 262.1 | 177.0 |
| 437 | 216.9 | 233.8 | 247.9 | 273.0 | 274.2 | 244.8 | 244.1 | 218.4 | 232.4 | 252.5 | 250.2 | 277.5 | 228.8 | 251.5 |
| SAMPLE | 3 | 2 | 3 | 3 | 3 | 2 | 2 | 2 | 3 | 3 | 3 | 2 | 2 | 4 |
| MEAN | 223.8 | 219.5 | 246.1 | 288.2 | 222.8 | 232.6 | 252.1 | 241.4 | 229.0 | 199.7 | 222.7* | 263.1 | 245.5 | 184.0 |
| S.D. | 46.4 | 20.2 | 43.2 | 64.8 | 44.6 | 17.4 | 11.3 | 32.5 | 26.6 | 48.2 | 36.2 | 20.4 | 23.5 | 133.8 |
| S.E. | 26.8 | 14.3 | 25.0 | 37.4 | 25.7 | 12.3 | 8.0 | 23.0 | 15.4 | 27.9 | 20.9 | 14.4 | 16.7 | 66.9 |

*$p<0.05$ as compared to controls: Dunnett's t-test.

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE 4

CLINICAL HEMATOLOGY

KEY

| | | | |
|---|---|---|---|
| WBC | = | Leukocyte Count | $10^3/mm^3$ |
| RBC | = | Erythrocyte Count | $10^6/mm^3$ |
| HGB | = | Hemoglobin | g% |
| HCT | = | Hematocrit | vol % |
| BN | = | Band Neutrophils | % |
| SG | = | Segmented Neutrophils | % |
| LY | = | Lymphocytes | % |
| MO | = | Monocytes | % |
| EO | = | Eosinophils | % |
| BS | = | Basophils | % |
| OT | = | Other | |
| R | = | Repeat value | |
| S | = | Repeat attempted without success, first value taken | |

# TABLE II-F-47

CLINICAL HEMATOLOGIES FOR P-1073409

TABLE 4
INDIVIDUAL ANIMAL HEMATOLOGIES-MALES
INTERVAL OF STUDY= INITIAL

| DOSE GROUP | ANIMAL NO | WBC | RBC | HGB | HCT | BN | SG | LY | MO | EO | BS | OT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CONTROL | 408 | 9.9 | 6.03 | 14.8 | 44.0 | . | 27 | 68 | . | 5 | . | . |
| | 411 | 10.1 | 6.03 | 14.9 | 42.0 | . | 34 | 65 | 1 | . | . | . |
| | 417 | 9.1 | 6.22 | 13.0 | 38.5 | . | 33 | 62 | 1 | 4 | . | . |
| | 418 | 9.0 | 6.20 | 14.8 | 43.0 | . | 58 | 41 | . | 1 | . | 2 |
| | MEAN | 9.52 | 6.120 | 14.37 | 41.88 | | | | | | | |
| | SE | 0.28 | 0.052 | 0.46 | 1.20 | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | |
| 100 PPM | 405 | 15.4 | 6.94 | 15.7 | 46.5 | . | 38 | 59 | 3 | 1 | . | . |
| | 406 | 10.7 | 6.79 | 16.4 | 47.0 | . | 35 | 63 | 2 | . | . | . |
| | 407 | 8.6 | 6.42 | 15.3 | 46.0 | . | 53 | 40 | 1 | 6 | . | . |
| | 415 | 10.1 | 7.12 | 15.4 | 44.5 | . | 41 | 58 | 1 | . | . | . |
| | MEAN | 11.20 | 6.817 | 15.70 | 46.00 | | | | | | | |
| | SE | 1.47 | 0.149 | 0.25 | 0.54 | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | |
| 300 PPM | 404 | 7.7 | 7.38 | 16.8 | 49.0 | . | 16 | 83 | 1 | . | . | . |
| | 409 | 7.6 | 6.98 | 15.1 | 44.5 | . | 40 | 54 | 3 | 3 | . | . |
| | 412 | 10.2 | 6.59 | 16.9 | 48.5 | . | 48 | 51 | 1 | . | . | . |
| | 414 | 11.0 | 6.21 | 14.3 | 43.5 | . | 61 | 39 | . | . | . | . |
| | MEAN | 9.12 | 6.790 | 15.77 | 46.36 | | | | | | | |
| | SE | 0.87 | 0.252 | 0.64 | 1.39 | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | |

# TABLE II-F-47 (Continued)

CLINICAL HEMATOLOGIES FOR P-1073409

TABLE 4 (CONTINUED)
INDIVIDUAL ANIMAL HEMATOLOGIES-MALES
INTERVAL OF STUDY= INITIAL

| DOSE GROUP | ANIMAL NO | WBC | RBC | HGB | HCT | BA | SG | LY | MO | EO | BS | OT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1000 PPM | 413 | 11.8 | 5.61 | 14.7 | 42.0 | . | 28 | 66 | 2 | 2 | 2 | . |
| | 416 | 12.0 | 6.53 | 15.1 | 44.5 | . | 55 | 34 | 3 | 8 | . | . |
| | 419 | 9.9 | 6.81 | 15.3 | 47.0 | . | 44 | 55 | . | 1 | 1 | 11 |
| | 420 | 9.7 | 6.90 | 15.7 | 45.0 | . | 13 | 86 | 1 | . | . | 8 |
| | MEAN | 10.85 | 6.462 | 15.20 | 44.63 | | | | | | | |
| | SE | 0.61 | 0.295 | 0.21 | 1.03 | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | |

# TABLE II-F-47 (Continued)

CLINICAL HEMATOLOGIES FOR P-1073409

TABLE 4 (CONTINUED)
INDIVIDUAL ANIMAL HEMATOLOGIES-FEMALES
INTERVAL OF STUDY= INITIAL

| DOSE GROUP | ANIMAL NO | WBC | RBC | HGB | HCT | BN | SG | LY | MO | EO | BS | GT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CONTROL | 425 | 10.1 | 7.90 | 17.0 | 50.5 | . | 31 | 65 | . | 2 | . | 1 |
| | 426 | 7.7 | 7.23 | 18.2 | 54.0 | . | 61 | 35 | . | 4 | . | 1 |
| | 434 | 14.9 | 6.76 | 14.9 | 43.0 | 1 | 39 | 60 | . | . | . | . |
| | 435 | 8.6 | 6.91 | 17.0 | 50.0 | . | 38 | 62 | . | . | . | . |
| | MEAN | 10.32 | 7.200 | 16.77 | 49.38 | | | | | | | |
| | SE | 1.60 | 0.253 | 0.69 | 2.30 | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | |
| 100 PPM | 422 | 10.7 | 7.36 | 15.4 | 44.5 | . | 60 | 36 | 2 | 1 | 1 | . |
| | 429 | 10.6 | 6.81 | 17.8 | 51.0 | . | 37 | 59 | 3 | 1 | . | . |
| | 430 | 11.2 | 6.14 | 14.9 | 44.5 | . | 26 | 74 | . | . | . | . |
| | 431 | 9.2 | 6.27 | 16.3 | 47.5 | . | 46 | 51 | 1 | 2 | 0 | . |
| | MEAN | 10.42 | 6.645 | 16.10 | 46.88 | | | | | | | |
| | SE | 0.43 | 0.279 | 0.64 | 1.55 | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | |
| 300 PPM | 421 | 11.3 | 6.92 | 16.5 | 48.5 | . | 22 | 76 | . | 2 | . | . |
| | 424 | 9.8 | 6.59 | 15.1 | 44.0 | . | 35 | 63 | 2 | . | . | 19 |
| | 427 | 8.8 | 7.39 | 17.8 | 53.0 | . | 56 | 42 | 1 | 1 | . | 4 |
| | 433 | 9.1 | 6.88 | 16.3 | 47.5 | . | 35 | 55 | 3 | 7 | . | . |
| | MEAN | 9.75 | 6.945 | 16.42 | 48.25 | | | | | | | |
| | SE | 0.56 | 0.166 | 0.55 | 1.85 | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | |

# TABLE II-F-47 (Continued)

CLINICAL HEMATOLOGIES FOR P-1073409

TABLE 4 (CONTINUED)
INDIVIDUAL ANIMAL HEMATOLOGIES-FEMALES
INTERVAL OF STUDY= INITIAL

| DOSE GROUP | ANIMAL NO | WBC | RBC | HGB | HCT | BN | SG | LY | MO | EO | BS | OT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1000 PPM | 423 | 10.0 | 6.89 | 15.9 | 46.5 | . | 34 | 60 | . | 6 | . | . |
| | 432 | 7.8 | 6.64 | 16.2 | 47.5 | . | 66 | 30 | 2 | 2 | . | 16 |
| | 436 | 8.6 | 6.48 | 16.4 | 49.0 | . | 33 | 65 | 1 | 1 | . | 13 |
| | 437 | 8.4 | 7.63 | 17.2 | 51.5 | 1 | 55 | 43 | 1 | . | . | . |
| | MEAN | 8.70 | 6.910 | 16.42 | 48.63 | | | | | | | |
| | SE | 0.47 | 0.254 | 0.28 | 1.09 | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | |

# TABLE II-F-47 (Continued)

CLINICAL HEMATOLOGIES FOR P-1073409

TABLE 4 (CONTINUED)
INDIVIDUAL ANIMAL HEMATOLOGIES-MALES
INTERVAL OF STUDY= WEEK 4

| DOSE GROUP | ANIMAL NO | WBC | RBC | HGB | HCT | BN | SG | LY | MO | EO | BS | OT | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CONTROL | 408 | 10.6 | 7.03 | 15.5 | 42.5 | . | 41 | 44 | 6 | 9 | . | . | 3 |
| | 411 | 10.6 | 6.27 | 15.1 | 45.0 | . | 57 | 41 | . | 2 | . | . | . |
| | 417 | 8.7 | 7.15 | 15.0 | 41.0 | . | 45 | 51 | 2 | 2 | . | . | . |
| | 418 | 11.9 R | 7.27 R | 16.1 R | 46.5 R | . | 54 | 40 | 1 | 5 | . | . | . |
| | MEAN | 10.45 | 6.930 | 15.42 | 43.75 | | | | | | | | |
| | SE | 0.66 | 0.225 | 0.25 | 1.23 | | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | | |
| 100 PPM | 405 | 12.0 | 6.72 | 15.3 | 45.0 | . | 63 | 36 | . | 1 | . | . | . |
| | 406 | 8.1 | 6.84 | 16.2 | 45.0 | . | 26 | 72 | . | 2 | . | . | . |
| | 407 | 9.9 | 8.37 | 16.4 | 46.0 | . | 42 | 47 | 6 | 5 | . | . | 2 |
| | 415 | 11.6 | 7.63 | 15.1 | 45.0 | . | 48 | 44 | 3 | 4 | 1 | . | 2 |
| | MEAN | 10.40 | 7.390 | 15.75 | 45.25 | | | | | | | | |
| | SE | 0.89 | 0.384 | 0.32 | 0.25 | | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | | |
| 300 PPM | 404 | 9.3 | 6.87 | 15.9 | 45.0 | . | 38 | 60 | 2 | . | . | . | . |
| | 409 | 8.6 | 6.83 | 15.8 | 44.0 | . | 30 | 67 | 2 | . | 1 | . | . |
| | 412 | 10.8 | 6.81 | 15.7 | 44.5 | . | 62 | 25 | 5 | 7 | 1 | . | 1 |
| | 414 | 13.8 | 8.45 | 16.6 | 43.0 | 3 | 71 | 19 | 4 | 2 | 1 | . | . |
| | MEAN | 10.62 | 7.240 | 16.00 | 44.13 | | | | | | | | |
| | SE | 1.15 | 0.404 | 0.20 | 0.43 | | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | | |

# TABLE II-F-47 (Continued)

CLINICAL HEMATOLOGIES FOR P-1073409

TABLE 4 (CONTINUED)
INDIVIDUAL ANIMAL HEMATOLOGIES-MALES
INTERVAL OF STUDY= WEEK 4

| DOSE GROUP | ANIMAL NO | WBC | RBC | HGB | HCT | BN | SG | LY | MO | EO | BS | OT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1000 PPM | 413 | 11.5 | 6.40 | 15.9 | 45.0 | 2 | 42 | 36 | 7 | 13 | . | . . |
| | 416 | 13.1 R | 7.18 R | 15.9 R | 46.0 R | . | 56 | 31 | 2 | 11 | . | . . |
| | 419 | 9.4 | 6.42 | 15.3 | 43.0 | . | 19 | 78 | 1 | 2 | . | . . |
| | 420 | 9.6 | 6.18 | 14.6 | 41.0 | 3 | 42 | 52 | 2 | 1 | . | . . |
| | MEAN | 10.90 | 6.545 | 15.42 | 43.75 | | | | | | | |
| | SE | 0.87 | 0.219 | 0.31 | 1.11 | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | |

# TABLE II-F-47 (Continued)

CLINICAL HEMATOLOGIES FOR P-1073409

TABLE 4 (CONTINUED)
INDIVIDUAL ANIMAL HEMATOLOGIES-FEMALES
INTERVAL OF STUDY= WEEK 4

| DOSE GROUP | ANIMAL NO | WBC | RBC | HGB | HCT | BN | SG | LY | MO | EO | BS | OT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CONTROL | 425 | 9.5 | 8.36 | 16.6 | 49.0 | 3 | 57 | 26 | 7 | 7 | . | . | 1 |
| | 426 | 9.6 | 6.98 | 15.0 | 49.0 | . | 55 | 36 | 3 | 5 | 1 | . | 5 |
| | 434 | 9.0 | 7.15 | 15.7 | 45.0 | . | 28 | 69 | . | 3 | . | . | . |
| | 435 | 8.8 | 7.30 | 17.7 | 50.0 | . | 65 | 33 | 1 | 1 | . | . | . |
| | MEAN | 9.22 | 7.447 | 16.47 | 48.25 | | | | | | | | |
| | SE | 0.19 | 0.311 | 0.45 | 1.11 | | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | | |
| 100 PPM | 422 | 11.6 | 6.81 | 15.5 | 44.0 | 2 | 62 | 20 | 12 | 4 | . | . | . |
| | 429 | 11.0 | 7.62 | 18.9 | 52.0 | . | 45 | 54 | . | . | 1 | . | . |
| | 430 | 9.7 | 7.23 | 16.1 | 45.0 | 1 | 56 | 34 | 6 | 3 | . | . | 2 |
| | 431 | 10.9 | 7.33 | 15.8 | 44.0 | . | 45 | 52 | 2 | 1 | . | . | . |
| | MEAN | 10.80 | 7.247 | 16.57 | 46.25 | | | | | | | | |
| | SE | 0.40 | 0.168 | 0.78 | 1.93 | | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | | |
| 300 PPM | 421 | 12.6 | 7.47 | 17.8 | 50.0 | 1 | 51 | 45 | . | 2 | 1 | . | . |
| | 424 | 11.5 | 6.84 | 16.0 | 47.0 | 2 | 66 | 21 | 6 | 5 | . | . | 2 |
| | 427 | 12.9 | 6.80 | 15.6 | 48.0 | 1 | 67 | 25 | 4 | 2 | 1 | . | 2 |
| | 433 | 15.3 | 6.28 | 15.2 | 42.0 | . | 47 | 46 | 1 | 5 | 1 | . | . |
| | MEAN | 13.07 | 6.847 | 16.15 | 46.75 | | | | | | | | |
| | SE | 0.80 | 0.244 | 0.57 | 1.70 | | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | | |

CLINICAL HEMATOLOGIES FOR P-1073409

TABLE 4 (CONTINUED)
INDIVIDUAL ANIMAL HEMATOLOGIES-FEMALES
INTERVAL OF STUDY= WEEK 4

| DOSE GROUP | ANIMAL NO | WBC | PBC | HGB | HCT | BN | SG | LY | MO | EO | BS | OT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1000 PPM | 423 | 9.2 | 6.96 | 16.2 | 45.0 | . | 27 | 71 | 2 | . | . | . |
| | 432 | 18.0 | 6.85 | 15.8 | 46.0 | . | 67 | 23 | 6 | 4 | . | . |
| | 436 | 11.7 | 6.98 | 16.2 | 46.5 | 1 | 55 | 36 | 2 | 6 | . | 2 |
| | 437 | 11.5 | 7.10 | 17.7 | 49.0 | 4 | 25 | 67 | 1 | 3 | . | . |
| | MEAN | 12.60 | 6.972 | 16.47 | 46.63 | | | | | | | |
| | SE | 1.89 | 0.051 | 0.42 | 0.85 | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | |

# TABLE II-F-47 (Continued)

CLINICAL HEMATOLOGIES FOR P-1073409

TABLE 4 (CONTINUED)
INDIVIDUAL ANIMAL HEMATOLOGIES-MALES
INTERVAL OF STUDY= WEEK 8

| DOSE GROUP | ANIMAL NO | WBC | RBC | HGB | HCT | BN | SG | LY | MO | EO | PS | CT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CONTROL | 408 | 11.3 R | 6.46 R | 14.5 R | 46.0 R | . | 47 | 43 | . | 10 | . | . . |
| | 411 | 10.7 | 5.88 | 15.2 | 44.5 | . | 68 | 29 | 1 | 2 | . | . . |
| | 417 | 6.5 | 5.47 | 12.0 | 38.0 | . | 52 | 26 | 5 | 16 | 1 | . . |
| | 418 | 15.2 | 6.50 | 14.0 | 43.0 | 1 | 66 | 16 | 11 | 5 | 1 | . . |
| | MEAN | 10.92 | 6.077 | 13.92 | 42.88 | | | | | | | |
| | SE | 1.78 | 0.247 | 0.69 | 1.74 | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | |
| 100 PPM | 405 | 13.6 | 7.07 | 15.2 | 45.0 | . | 52 | 25 | 7 | 16 | . | . 1 |
| | 406 | 8.5 | 7.19 | 16.0 | 47.0 | 1 | 53 | 41 | 3 | 2 | . | . . |
| | 407 | 9.0 | 5.93 | 14.4 | 44.0 | 2 | 54 | 30 | 3 | 11 | . | . . |
| | 415 | 9.9 | 7.19 | 15.5 | 48.0 | 1 | 50 | 38 | 4 | 7 | . | . . |
| | MEAN | 10.25 | 6.845 | 15.27 | 46.00 | | | | | | | |
| | SE | 1.15 | 0.306 | 0.34 | 0.91 | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | |
| 300 PPM | 404 | 9.9 R | 7.26 R | 14.6 R | 45.0 R | 2 | 27 | 67 | 1 | 3 | . | . . |
| | 409 | 9.1 S | 6.67 S | 15.0 S | 45.0 S | . | 58 | 33 | 1 | 8 | . | . 1 |
| | 412 | 10.3 | 6.07 | 15.4 | 45.0 | . | 60 | 26 | 6 | 7 | 1 | . . |
| | 414 | 14.0 | 5.84 | 14.1 | 44.0 | . | 63 | 30 | 6 | 1 | . | . . |
| | MEAN | 10.82 | 6.460 | 14.77 | 44.75 | | | | | | | |
| | SE | 1.09 | 0.310 | 0.28 | 0.25 | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | |

# TABLE II-F-47 (Continued)

CLINICAL HEMATOLOGICS FOR P-107340"

TABLE 4 (CONTINUED)
INDIVIDUAL ANIMAL HEMATOLOGIES-MALES
INTERVAL OF STUDY= WEEK 8

| DOSE GROUP | ANIMAL NO | WBC | RBC | HGB | HCT | BN | SG | LY | MO | EO | BS | OT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1000 PPM | 413 | 12.8 | 6.47 | 14.4 | 44.0 | 2 | 48 | 30 | 9 | 10 | 1 | . . |
| | 416 | 12.2 | 6.64 | 14.3 | 44.0 | . | 37 | 37 | 1 | 22 | 3 | . . |
| | 419 | 8.4 | 7.14 | 14.8 | 46.0 | . | 64 | 19 | 9 | 8 | . | . . |
| | 420 | 7.5 | 6.50 | 14.2 | 43.0 | . | 67 | 25 | 4 | 4 | . | . 2 |
| | MEAN | 10.22 | 6.687 | 14.42 | 44.25 | | | | | | | |
| | SE | 1.33 | 0.155 | 0.13 | 0.63 | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | |

# TABLE II-F-47 (Continued)

CLINICAL HEMATOLOGIES FOR B-1073405

TABLE 4 (CONTINUED)
INDIVIDUAL ANIMAL HEMATOLOGIES-FEMALES
INTERVAL OF STUDY= WEEK 8

| DOSE GROUP | ANIMAL NO | WBC | RBC | HGB | HCT | BN | SG | LY | MO | EO | BS | OT | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CONTROL | 425 | 11.9 | 6.54 | 14.6 | 44.0 | . | 64 | 24 | 3 | 9 | . | . | 1 |
| | 426 | 10.5 | 7.10 | 15.2 | 50.0 | . | 81 | 12 | 1 | 3 | 3 | . | . |
| | 434 | 7.3 | 6.25 | 13.9 | 41.0 | . | 61 | 23 | 9 | 5 | 2 | . | 1 |
| | 435 | 7.4 | 6.35 | 15.8 | 48.0 | . | 58 | 24 | 4 | 14 | . | . | . |
| | MEAN | 9.27 | 6.555 | 15.22 | 45.75 | | | | | | | | |
| | SE | 1.15 | 0.191 | 0.60 | 2.02 | | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | | |
| 100 PPM | 422 | 7.6 | 7.22 | 13.9 | 40.5 | . | 40 | 46 | 6 | 8 | . | . | 1 |
| | 429 | 10.6 | 6.67 | 15.8 | 46.0 | 1 | 64 | 22 | 4 | 9 | . | . | 3 |
| | 430 | 10.7 | 6.09 | 14.9 | 47.5 | . | 60 | 29 | 8 | 3 | . | . | . |
| | 431 | 12.7 | 6.14 | 14.0 | 42.0 | 1 | 55 | 34 | 10 | . | . | . | 1 |
| | MEAN | 10.40 | 6.530 | 14.65 | 44.00 | | | | | | | | |
| | SE | 1.05 | 0.265 | 0.44 | 1.65 | | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | | |
| 300 PPM | 421 | 13.3 | 6.92 | 17.0 | 50.0 | . | 59 | 34 | 3 | 2 | 2 | . | 2 |
| | 424 | 10.0 | 7.08 | 16.3 | 47.5 | . | 58 | 29 | 2 | 9 | 2 | . | 1 |
| | 427 | 8.4 | 6.59 | 16.6 | 47.0 | . | 63 | 25 | 5 | 4 | 3 | . | 1 |
| | 433 | 13.4 | 6.92 | 16.4 | 48.0 | . | 58 | 25 | 8 | 9 | . | . | 2 |
| | MEAN | 11.27 | 6.877 | 16.57 | 48.13 | | | | | | | | |
| | SE | 1.24 | 0.103 | 0.15 | 0.66 | | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | | |

# TABLE II-F-47 (Continued)

CLINICAL HEMATOLOGIES FOR P-1073409

TABLE 4 (CONTINUED)
INDIVIDUAL ANIMAL HEMATOLOGIES-FEMALES
INTERVAL OF STUDY= WEEK 8

| DOSE GROUP | ANIMAL NO | WBC | RBC | HGB | HCT | BN | SG | LY | MO | EO | BS | OT | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1000 PPM | 423 | 11.2 | 6.04 | 12.9 | 39.0 | 1 | 50 | 35 | 3 | 8 | 3 | . | . |
| | 432 | 13.7 | 5.97 | 14.6 | 46.0 | . | 67 | 19 | 8 | 6 | . | . | 1 |
| | 436 | 9.4 | 6.53 | 15.1 | 4..5 | . | 61 | 29 | 9 | 1 | . | . | 1 |
| | 437 | 9.0 | 7.22 | 17.1 | 50.0 | . | 38 | 51 | 4 | 7 | . | . | 3 |
| | MEAN | 10.82 | 6.440 | 14.92 | 44.63 | | | | | | | | |
| | SE | 1.07 | 0.288 | 0.86 | 2.30 | | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | | |

# TABLE II-F-47 (Continued)

CLINICAL HEMATOLOGIES FOR P-1073409

TABLE 4 (CONTINUED)
INDIVIDUAL ANIMAL HEMATOLOGIES-MALES
INTERVAL OF STUDY= TERMINAL KILL

| DOSE GROUP | ANIMAL NO | WBC | RBC | HGB | HCT | BN | SG | LY | MO | EO | BS | OT | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CONTROL | 408 | 10.9 | 7.43 | 16.2 | 44.0 | . | 54 | 35 | 4 | 3 | . | . | . |
| | 411 | 8.6 | 6.71 | 16.3 | 46.0 | . | 47 | 33 | 2 | 12 | . | 8 | . |
| | 417 | 8.1 | 5.87 | 12.9 | 37.0 | 5 | 64 | 20 | 3 | 7 | 1 | . | . |
| | 418 | 10.9 | 7.05 | 15.6 | 44.0 | 4 | 57 | 31 | 3 | 5 | . | . | 2 |
| | MEAN | 9.62 | 6.765 | 15.25 | 42.75 | | | | | | | | |
| | SE | 0.74 | 0.333 | 0.80 | 1.97 | | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | | |
| 100 PPM | 405 | 13.7 | 7.36 | 16.6 | 47.0 | 6 | 71 | 12 | 2 | 9 | . | . | . |
| | 406 | 8.4 | 7.72 | 17.2 | 49.0 | 2 | 57 | 30 | 8 | 3 | . | . | . |
| | 407 | 8.8 | 7.03 | 15.7 | 45.0 | . | 39 | 49 | . | 10 | 1 | 6 | . |
| | 415 | 14.9 | 6.52 | 15.7 | 44.0 | 5 | 65 | 24 | 1 | 3 | . | . | . |
| | MEAN | 11.45 | 7.157 | 16.30 | 46.25 | | | | | | | | |
| | SE | 1.67 | 0.255 | 0.37 | 1.11 | | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | | |
| 300 PPM | 404 | 8.0 | 6.80 | 14.8 | 43.5 | . | 63 | 27 | 5 | 4 | . | 11 | . |
| | 409 | 9.6 | 7.24 | 16.7 | 47.0 | . | 46 | 46 | 1 | 7 | . | 13 | . |
| | 412 | 7.5 | 7.30 | 17.4 | 49.0 | . | 52 | 42 | . | 7 | . | . | . |
| | 414 | 12.4 | 6.53 | 15.1 | 43.0 | . | 79 | 20 | . | 1 | . | . | . |
| | MEAN | 9.37 | 6.967 | 16.00 | 45.63 | | | | | | | | |
| | SE | 1.10 | 0.184 | 0.63 | 1.43 | | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | | |

# TABLE II-F-47 (Continued)

CLINICAL HEMATOLOGIES FOR P-1073409

TABLE 4 (CONTINUED)
INDIVIDUAL ANIMAL HEMATOLOGIES-MALES
INTERVAL OF STUDY: TERMINAL KILL

| DOSE GROUP | ANIMAL NO | WBC | RBC | HGB | HCT | BN | SG | LY | MO | EO | BS | OT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1000 PPM | 413 | 11.6 | 7.12 | 14.5 | 43.0 | . | 54 | 34 | 4 | 8 | . | 12 . |
| | 416 | 9.5 | 7.27 | 15.1 | 44.5 | ? | 59 | ?2 | 1 | 6 | . | 25 . |
| | 419 | 8.1 | 6.66 | 15.8 | 45.0 | . | 63 | 28 | 1 | 7 | 1 | . 11 |
| | 420 | 8.7 | 6.38 | 14.8 | 42.0 | . | 58 | 37 | 2 | ? | . | . 8 |
| | MEAN | 9.47 | 6.857 | 15.05 | 43.63 | | | | | | | |
| | SE | 0.76 | 0.205 | 0.28 | 0.69 | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | |

# TABLE II-F-47 (Continued)

CLINICAL HEMATOLOGIES FOR P-1073409

TABLE 4 (CONTINUED)
INDIVIDUAL ANIMAL HEMATOLOGIES-FEMALES
INTERVAL OF STUDY: TERMINAL KILL

| DOSE GROUP | ANIMAL NO | WBC | RBC | HGB | HCT | DN | SG | LY | MO | EO | BS | LT | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CONTROL | 425 | 10.3 | 6.89 | 15.4 | 44.0 | 1 | 53 | 36 | 5 | 5 | . | . | 1 |
| | 426 | 10.9 | 7.22 | 17.0 | 48.0 | 1 | 63 | 20 | 4 | 12 | . | . | 1 |
| | 434 | 9.8 | 6.83 | 14.1 | 40.0 | . | 51 | 39 | 3 | 7 | . | 13 | . |
| | 435 | 9.4 | 7.76 | 17.2 | 49.0 | . | 48 | 46 | 1 | 5 | . | . | . |
| | MEAN | 10.10 | 7.175 | 15.92 | 45.25 | | | | | | | | |
| | SE | 0.32 | 0.213 | 0.73 | 2.06 | | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | | |
| 100 PPM | 422 | 11.3 | 6.13 | 13.6 | 37.0 | 2 | 34 | 54 | . | 10 | . | 17 | . |
| | 429 | 9.9 | 6.25 | 16.0 | 45.0 | . | 67 | 28 | 3 | 2 | . | . | . |
| | 430 | 9.3 | 8.27 | 17.4 | 50.0 | 3 | 44 | 44 | 6 | 3 | . | 11 | . |
| | 431 | 7.0 | 6.83 | 16.9 | 47.0 | . | 35 | 62 | 2 | 1 | . | . | . |
| | MEAN | 9.37 | 6.870 | 15.97 | 44.75 | | | | | | | | |
| | SE | 0.90 | 0.461 | 0.84 | 2.78 | | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | | |
| 300 PPM | 421 | 14.9 | 8.52 | 17.0 | 48.0 | 3 | 63 | 28 | 2 | 4 | . | . | . |
| | 424 | 11.8 | 6.71 | 16.1 | 45.0 | 2 | 64 | 27 | . | 7 | . | . | 19 |
| | 427 | 8.1 | 6.20 | 14.9 | 41.5 | 2 | 64 | 23 | . | 11 | . | . | 4 |
| | 433 | 15.3 | 8.03 | 16.2 | 46.3 | 6 | 56 | 17 | 5 | 14 | 2 | 11 | . |
| | MEAN | 12.52 | 7.366 | 16.05 | 45.13 | | | | | | | | |
| | SE | 1.67 | 0.545 | 0.43 | 1.34 | | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | | |

# TABLE II-F-47 (Continued)

CLINICAL HEMATOLOGIES FOR P-1072409

TABLE 4 (CONTINUED)
INDIVIDUAL ANIMAL HEMATOLOGIES-FEMALES
INTERVAL OF STUDY= TERMINAL KILL

| DOSE GROUP | ANIMAL NO | WBC | RBC | HGB | HCT | BN | SG | LY | MO | EO | BS | CT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1000 PPM | 422 | 10.6 | 7.05 | 15.8 | 45.0 | . | 49 | 38 | 4 | 9 | . | 5 . |
| | 432 | 12.4 | 6.77 | 15.9 | 47.0 | . | 67 | 31 | 1 | 1 | . | . 16 |
| | 436 | 9.2 | 5.87 | 13.0 | 40.0 | 2 | 60 | 30 | 3 | 5 | . | . 13 |
| | 437 | 9.4 | 8.00 | 19.2 | 55.0 | 3 | 41 | 45 | 2 | 9 | . | 0 . |
| | MEAN | 10.45 | 6.922 | 16.20 | 46.75 | | | | | | | |
| | SE | 0.76 | 0.439 | 1.10 | 3.12 | | | | | | | |
| | N | 4 | 4 | 4 | 4 | | | | | | | |

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE 5

CLINICAL CHEMISTRY

KEY

| | | |
|---|---|---|
| BILI | = Bilirubin, total | mg/dl |
| BUN | = Blood Urea Nitrogen | mg/dl |
| ALB | = Albumin | g/dl |
| CA | = Calcium | mg/dl |
| CHOL | = Cholesterol | mg/dl |
| GLCS | = Glucose | mg/dl |
| LDH | = Lactic Dehydrogenase | mU/ml |
| SAP | = Alkaline Phosphatase | mU/ml |
| PHOS | = Phosphorus | mg/dl |
| PROT | = Protein, total | g/dl |
| SGOT | = Serum Glutamic-oxaloacetic Transaminase | mU/ml |
| SGPT | = Serum Glutamic-pyruvic Transaminase | mU/ml |
| URIC | = Uric Acid | mg/dl |
| NA | = Sodium | meg/l |
| K | = Potassium | meg/l |
| CL | = Chloride | meg/l |

A = Test not performed
R = Repeat value
S = Repeat attempted without success, first value taken

* = $p<0.05$ as compared to controls: Dunnett's t-test

# TABLE II-F-48

CLINICAL CHEMISTRIES FOR P-1073409

TABLE 5
INDIVIDUAL ANIMAL CHEMISTRIES-FEMALES
INTERVAL OF STUDY= INITIAL

| DOSE GROUP | ANIMAL NO | BILI | BUN | ALB | CA | CHOL | GLCS | LDH | SAP | PHOS | PROT | SGOT | SGPT | URIC | NA | K | CL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CONTROL | 425 | 0.1 | 15 | 3.3 | 11.1 | 145 | 70 | 96 | 62 | 4.1 | 6.0 | 28 | 22 | 0.2 | 147 | 4.6 | 108 |
| | 426 | 0.1 | 11 | 4.6 | 11.3 | 155 | 88 | 204 | 61 | 3.5 | 6.6 | 33 | 48 | 0.4 | 148 | 4.3 | 110 |
| | 434 | 0.1 | 14 | 3.6 | 11.0 | 135 | 85 | 166 | 34 | 4.7 | 6.1 | 29 | 47 | 0.3 | 149 | 4.8 | 109 |
| | 435 | 0.1 | 13 | 4.7 | 10.9 | 145 | 116 | 165 | 38 | 3.1 | 6.1 | 27 | 7 | 0.4 | 148 | 4.8 | 111 |
| | MEAN | 0.10 | 13.3 | 4.05 | 11.07 | 145.0 | 89.8 | 157.8 | 48.8 | 3.85 | 6.20 | 29.3 | 31.0 | 0.32 | 148.0 | 4.62 | 109.5 |
| | SE | 0.00 | 0.9 | 0.35 | 0.09 | 4.1 | 9.6 | 22.5 | 7.4 | 0.35 | 0.14 | 1.3 | 10.0 | 0.05 | 0.4 | 0.12 | 0.6 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 100 PPM | 422 | 0.1 | 11 | 3.1 | 11.1 | 140 | 73 | 56 | 68 | 4.8 | 5.8 | 26 | 44 | 0.2 | 146 | 4.8 | 108 |
| | 429 | 0.1 | 12 | 3.5 | 11.0 | 138 | 66 | 55 | 68 | 4.7 | 6.1 | 28 | 30 | 0.2 | 146 | 4.5 | 108 |
| | 430 | 0.1 R | 15 R | 3.3 R | 11.4 R | 134 R | 101 R | 175 R | 46 R | 4.3 R | 6.1 R | 37 R | 45 R | 0.3 R | 148 R | 5.7 R | 108 R |
| | 431 | 0.1 | 16 | 3.8 | 11.0 | 125 | 82 | 110 | 63 | 4.6 | 6.1 | 34 | 43 | 0.3 | 148 | 4.7 | 108 |
| | MEAN | 0.10 | 13.5 | 3.42 | 11.12 | 134.3 | 80.5 | 99.0 | 61.3 | 4.60 | 6.02 | 31.3 | 40.5 | 0.25 | 147.0 | 4.92 | 108.0 |
| | SE | 0.00 | 1.2 | 0.15 | 0.09 | 3.3 | 7.6 | 28.4 | 5.2 | 0.11 | 0.08 | 2.6 | 3.5 | 0.03 | 0.6 | 0.27 | 0.0 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 300 PPM | 421 | 0.1 | 20 | 4.5 | 11.3 | 185 | 100 | 160 | 61 | 3.8 | 6.2 | 39 | 34 | 0.5 | 148 | 4.4 | 107 |
| | 424 | 0.1 | 12 | 3.3 | 10.5 | 136 | 78 | 152 | 69 | 4.3 | 6.0 | 31 | 41 | 0.3 | 148 | 4.1 | 109 |
| | 427 | 0.1 R | 10 R | 3.1 R | 11.2 R | 153 R | 85 R | 250 R | 47 R | 3.9 R | 6.7 R | 25 R | 28 R | 0.2 R | 147 R | 5.3 R | 110 R |
| | 433 | 0.1 | 15 | 4.2 | 10.7 | 156 | 100 | 146 | 73 | 3.9 | 5.9 | 27 | 33 | 0.1 | 145 | 4.8 | 108 |
| | MEAN | 0.10 | 14.3 | 3.77 | 10.92 | 157.5 | 90.8 | 177.0 | 62.5 | 3.97 | 6.20 | 30.5 | 34.0 | 0.27 | 147.0 | 4.65 | 108.5 |
| | SE | 0.00 | 2.2 | 0.34 | 0.19 | 10.2 | 5.5 | 24.5 | 5.7 | 0.11 | 0.18 | 3.1 | 2.7 | 0.09 | 0.7 | 0.26 | 0.6 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

# TABLE II-F-48 (Continued)

CLINICAL CHEMISTRIES FOR P-1073409

TABLE 5 (CONTINUED)
INDIVIDUAL ANIMAL CHEMISTRIES-FEMALES
INTERVAL OF STUDY= INITIAL

| DOSE GROUP | ANIMAL NO | BILI | BUN | ALB | CA | CHOL | GLCS | LDH | SAP | PHOS | PROT | SGOT | SGPT | URIC | NA | K | CL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1000 PPM | 423 | 0.0 | 20 | 4.8 | 11.7 | 171 | 101 | 280 | 59 | 5.4 | 6.4 | 40 | 32 | 0.5 | 152 | 5.1 | 112 |
| | 432 | 0.1 | 12 | 3.1 | 10.1 | 133 | 69 | 142 | 70 | 5.8 | 5.3 | 34 | 38 | 0.4 | 145 | 5.0 | 108 |
| | 436 | 0.1 | 10 | 4.6 | 11.0 | 126 | 92 | 110 | 84 | 4.5 | 6.1 | 27 | 53 | 0.4 | 147 | 4.8 | 110 |
| | 437 | 0.1 | 12 | 3.6 | 11.0 | 157 | 72 | 50 | 64 | 5.1 | 5.9 | 26 | 50 | 0.1 | 145 | 5.0 | 109 |
| | MEAN | 0.07 | 13.5 | 4.02 | 10.95 | 146.8 | 83.5 | 145.5 | 69.3 | 5.20 | 5.92 | 31.8 | 43.3 | 0.35 | 147.3 | 4.97 | 109.8 |
| | SE | 0.02 | 2.2 | 0.40 | 0.33 | 10.5 | 7.8 | 48.7 | 5.4 | 0.27 | 0.23 | 3.3 | 5.0 | 0.09 | 1.7 | 0.06 | 0.9 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

# TABLE II-F-48 (Continued)

CLINICAL CHEMISTRIES FOR P-1073409

TABLE 5 (CONTINUED)
INDIVIDUAL ANIMAL CHEMISTRIES-MALES
INTERVAL OF STUDY= INITIAL

| DOSE GROUP | ANIMAL NO | BILI | BUN | ALB | CA | CHOL | GLCS | LDH | SAP | PHOS | PROT | SGOT | SGPT | URIC | NA | K | CL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CONTROL | 408 | 0.1 R | 10 R | 3.2 R | 10.8 R | 136 R | 97 R | 192 R | 94 R | 5.2 R | 6.1 R | 37 R | 40 R | 0.4 R | 145 R | 5.2 R | 108 R |
| | 411 | 0.0 | 16 | 4.4 | 11.6 | 151 | 90 | 239 | 62 | 5.0 | 6.9 | 31 | 25 | 0.4 | 147 | 5.3 | 105 |
| | 417 | 0.1 R | 14 R | 3.0 R | 10.7 R | 144 R | 97 R | 546 R | 66 R | 5.1 R | 5.5 R | 37 R | 31 R | 0.3 R | 147 R | 5.3 R | 109 R |
| | 418 | 0.1 | 14 | 4.6 | 11.4 | 163 | 102 | 151 | 81 | 4.3 | 6.5 | 34 | 54 | 0.5 | 150 | 4.6 | 112 |
| | MEAN | 0.07 | 13.5 | 3.80 | 11.12 | 148.5 | 96.5 | 282.0 | 75.8 | 4.90 | 6.25 | 34.8 | 37.5 | 0.40 | 147.3 | 5.10 | 108.5 |
| | SE | 0.02 | 1.3 | 0.41 | 0.22 | 5.7 | 2.5 | 89.8 | 7.3 | 0.20 | 0.30 | 1.4 | 6.3 | 0.04 | 1.0 | 0.17 | 1.4 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 100 PPM | 405 | 0.0 | 18 | 4.0 | 11.4 | 148 | 91 | 240 | 162 | 5.3 | 6.7 | 31 | 39 | 0.4 | 147 | 4.8 | 106 |
| | 406 | 0.0 | 18 | 4.7 | 11.7 | 184 | 87 | 93 | 63 | 5.2 | 6.6 | 26 | 31 | 0.4 | 147 | 4.9 | 108 |
| | 407 | 0.1 R | 14 R | 3.3 R | 10.8 R | 172 R | 87 R | 164 R | 62 R | 4.6 R | 6.2 R | 33 R | 31 R | 0.4 R | 144 R | 4.9 R | 108 R |
| | 415 | 0.1 | 13 | 3.1 | 10.6 | 145 | 72 | 82 | 65 | 5.2 | 5.8 | 36 | 49 | 0.4 | 147 | 4.2 | 110 |
| | MEAN | 0.05 | 15.8 | 3.77 | 11.12 | 162.3 | 84.3 | 144.8 | 88.0 | 5.07 | 6.32 | 31.5 | 37.5 | 0.40 | 146.3 | 4.70 | 108.0 |
| | SE | 0.03 | 1.3 | 0.36 | 0.26 | 9.4 | 4.2 | 36.6 | 24.7 | 0.16 | 0.21 | 2.1 | 4.3 | 0.00 | 0.8 | 0.17 | 0.8 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 300 PPM | 404 | 0.1 | 13 | 4.7 | 11.4 | 180 | 101 | 188 | 67 | 4.4 | 6.7 | 31 | 36 | 0.4 | 147 | 4.7 | 108 |
| | 409 | 0.1 | 11 | 3.3 | 10.7 | 144 | 72 | 123 | 61 | 4.9 | 6.3 | 30 | 38 | 0.4 | 143 | 4.8 | 108 |
| | 412 | 0.0 | 10 | 4.7 | 11.2 | 193 | 92 | 262 | 69 | 3.5 | 6.4 | 32 | 47 | 0.5 | 146 | 4.9 | 108 |
| | 414 | 0.1 | 12 | 4.1 | 11.0 | 179 | 97 | 94 | 79 | 5.1 | 6.8 | 29 | 35 | 0.5 | 144 | 4.9 | 106 |
| | MEAN | 0.07 | 11.5 | 4.20 | 11.07 | 174.0 | 90.5 | 166.8 | 69.0 | 4.47 | 6.55 | 30.5 | 39.0 | 0.45 | 145.0 | 4.82 | 107.5 |
| | SE | 0.02 | 0.6 | 0.33 | 0.15 | 10.5 | 6.4 | 37.3 | 3.7 | 0.36 | 0.12 | 0.6 | 2.7 | 0.03 | 0.9 | 0.05 | 0.5 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

TABLE 5 (CONTINUED)
INDIVIDUAL ANIMAL CHEMISTRIES-MALES
INTERVAL OF STUDY= INITIAL

| DOSE GROUP | ANIMAL NO | BILI | BUN | ALB | CA | CHOL | GLCS | LDH | SAP | PHOS | PROT | SGOT | SGPT | URIC | NA | K | CL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1000 PPM | 413 | 0.1 | 11 | 3.3 | 10.7 | 144 | 81 | 68 | 145 | 4.1 | 5.8 | 28 | 34 | 0.5 | 145 | 4.4 | 108 |
| | 416 | 0.1 | 16 | 4.5 | 11.0 | 120 | 100 | 174 | 52 | 4.0 | 5.8 | 34 | 53 | 0.6 | 148 | 4.7 | 109 |
| | 419 | 0.0 | 14 | 4.2 | 11.2 | 150 | 91 | 244 | 77 | 4.7 | 6.2 | 41 | 60 | 0.4 | 146 | 4.9 | 107 |
| | 420 | 0.1 R | 8 P | 3.3 R | 11.0 R | 149 R | 92 R | 170 F | 67 R | 4.8 R | 6.0 R | 32 R | 76 R | 0.3 R | 146 R | 5.0 R | 113 R |
| | MEAN | 0.07 | 12.3 | 3.82 | 10.97 | 140.8 | 91.0 | 164.0 | 85.3 | 4.40 | 5.95 | 33.8 | 55.8 | 0.45 | 146.3 | 4.75 | 109.3 |
| | SE | 0.02 | 1.8 | 0.31 | 0.10 | 7.0 | 3.9 | 36.2 | 20.6 | 0.20 | 0.10 | 2.7 | 8.7 | 0.06 | 0.6 | 0.13 | 1.3 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

# TABLE II-F-48 (Continued)

CLINICAL CHEMISTRIES FOR P-1073409

TABLE 5 (CONTINUED)
INDIVIDUAL ANIMAL CHEMISTRIES-MALES
INTERVAL OF STUDY= WEEK 4

| DOSE GROUP | ANIMAL NO | BILI | BUN | ALB | CA | CHOL | GLCS | LDH | SAP | PHOS | PROT | SGOT | SGPT | URIC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CONTROL | 408 | 0.1 | 14 | 3.2 | 10.5 | 131 | 89 | 123 | 83 | 4.9 | 6.5 | 72 | 52 | 0.4 |
| | 411 | 0.1 | 20 | 3.2 | 11.6 | 155 | 78 | 463 | 55 | 4.5 | 6.8 | 40 | 29 | 0.2 |
| | 417 | 0.1 | 14 | 2.8 | 10.4 | 121 | 87 | 332 | 57 | 4.1 | 5.5 | 39 | 34 | 0.1 |
| | 418 | 0.1 | 14 | 3.2 | 10.8 | 134 | 90 | 243 | 37 | 4.1 | 6.0 | 66 | 39 | 0.5 |
| | MEAN | 0.10 | 15.5 | 3.10 | 10.82 | 135.3 | 86.0 | 290.3 | 58.0 | 4.40 | 6.20 | 54.3 | 38.5 | 0.30 |
| | SE | 0.00 | 1.5 | 0.10 | 0.27 | 7.1 | 2.7 | 71.8 | 9.5 | 0.19 | 0.29 | 8.6 | 4.9 | 0.09 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 100 PPM | 405 | 0.0 | 19 | 3.0 | 11.1 | 152 | 81 | 351 | 105 | 4.2 | 6.6 | 45 | 44 | 0.0 |
| | 406 | 0.1 | 15 | 3.0 | 11.3 | 176 | 81 | 205 | 45 | 4.4 | 6.4 | 32 | 27 | 0.0 |
| | 407 | 0.1 | 15 | 3.0 | 10.6 | 187 | 92 | 174 | 55 | 4.6 | 6.1 | 106 | 32 | 0.4 |
| | 415 | 0.1 | 17 | 3.1 | 10.7 | 143 | 80 | 299 | 54 | 3.6 | 5.8 | 72 | 32 | 0.3 |
| | MEAN | 0.07 | 16.5 | 3.02 | 10.92 | 164.5 | 83.5 | 257.3 | 64.8 | 4.20 | 6.22 | 63.8 | 33.8 | 0.17 |
| | SE | 0.02 | 1.0 | 0.02 | 0.17 | 10.2 | 2.8 | 41.0 | 13.6 | 0.22 | 0.18 | 16.4 | 3.6 | 0.10 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 300 PPM | 404 | 0.1 | 13 | 2.7 | 10.5 | 156 | 81 | 279 | 56 | 4.0 | 6.2 | 40 | 32 | 0.0 |
| | 409 | 0.1 | 16 | 2.6 | 10.6 | 121 | 86 | 284 | 58 | 4.4 | 6.1 | 38 | 39 | 0.0 |
| | 412 | 0.1 | 16 | 3.2 | 10.8 | 154 | 82 | 134 | 56 | 4.1 | 5.6 | 47 | 42 | 0.4 |
| | 414 | 0.1 | 16 | 3.1 | 11.2 | 165 | 89 | 129 | 76 | 4.7 | 6.9 | 80 | 28 | 0.4 |
| | MEAN | 0.10 | 15.3 | 2.90 | 10.77 | 149.0 | 84.5 | 206.5 | 61.5 | 4.30 | 6.20 | 51.3 | 35.3 | 0.20 |
| | SE | 0.00 | 0.8 | 0.15 | 0.15 | 9.6 | 1.8 | 43.3 | 4.9 | 0.16 | 0.27 | 9.8 | 3.2 | 0.12 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

# TABLE II-F-48 (Continued)

CLINICAL CHEMISTRIES FOR P-1073409

TABLE 5 (CONTINUED)
INDIVIDUAL ANIMAL CHEMISTRIES-MALES
INTERVAL OF STUDY= WEEK 4

| DOSE GROUP | ANIMAL NO | BILI | BUN | ALB | CA | CHOL | GLCS | LDH | SAP | PHOS | PROT | SGOT | SGPT | URIC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1000 PPM | 413 | 0.1 | 14 | 3.0 | 10.4 | 148 | 88 | 247 | 137 | 3.8 | 5.9 | 67 | 26 | 0.6 |
| | 416 | 0.1 | 14 | 2.9 | 10.7 | 157 | 98 | 95 | 92 | 4.1 | 6.3 | 51 | 39 | 0.4 |
| | 419 | 0.1 | 15 | 2.7 | 10.8 | 137 | 80 | 286 | 56 | 4.4 | 6.2 | 40 | 42 | 0.9 |
| | 420 | 0.1 | 18 | 2.9 | 10.6 | 132 | 90 | 298 | 65 | 4.2 | 6.1 | 56 | 62 | 0.3 |
| | MEAN | 0.10 | 15.3 | 2.87 | 10.62 | 143.5 | 89.0 | 231.5 | 87.5 | 4.12 | 6.12 | 53.5 | 42.3 | 0.55 |
| | SE | 0.00 | 0.9 | 0.06 | 0.09 | 5.6 | 3.7 | 46.8 | 18.2 | 0.13 | 0.09 | 5.6 | 7.4 | 0.13 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

# TABLE II-F-48 (Continued)

CLINICAL CHEMISTRIES FOR P-1073409

TABLE 5 (CONTINUED)
INDIVIDUAL ANIMAL CHEMISTRIES-FEMALES
INTERVAL OF STUDY= WEEK 4

| DOSE GROUP | ANIMAL NO | BILI | BUN | ALB | CA | CHOL | GLCS | LDH | SAP | PHOS | PROT | SGOT | SGPT | URIC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CONTROL | 425 | 0.1 | 12 | 3.6 | 11.0 | 138 | 84 | 164 | 55 | 3.6 | 5.9 | 65 | 28 | 0.4 |
| | 426 | 0.2 | 13 | 3.3 | 10.9 | 127 | 81 | 124 | 52 | 4.0 | 6.3 | 67 | 37 | 0.3 |
| | 434 | 0.1 | 13 | 3.0 | 11.0 | 114 | 81 | 975 | 32 | 3.9 | 6.3 | 48 | 32 | 0.1 |
| | 435 | 0.1 | 12 | 3.2 | 10.9 | 138 | 88 | 483 | 31 | 3.2 | 6.0 | 49 | 39 | 0.0 |
| | MEAN | 0.12 | 12.5 | 3.27 | 10.95 | 129.3 | 83.5 | 436.5 | 42.5 | 3.67 | 6.12 | 57.3 | 34.0 | 0.20 |
| | SE | 0.02 | 0.3 | 0.12 | 0.03 | 5.7 | 1.7 | 196.7 | 6.4 | 0.18 | 0.10 | 5.1 | 2.5 | 0.09 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 100 PPM | 422 | 0.1 | 10 | 2.9 | 11.1 | 128 | 86 | 117 | 87 | 4.7 | 5.6 | 55 | 31 | 0.4 |
| | 429 | 0.1 | 11 | 3.2 | 10.9 | 165 | 75 | 371 | 81 | 3.2 | 6.4 | 43 | 27 | 0.0 |
| | 430 | 0.1 | 18 | 3.3 | 11.3 | 131 | 83 | 316 | 43 | 4.2 | 5.8 | 87 | 34 | 0.4 |
| | 431 | 0.1 | 19 | 3.4 | 11.1 | 113 | 93 | 355 | 50 | 4.0 | 6.1 | 37 | 33 | 0.1 |
| | MEAN | 0.10 | 14.5 | 3.20 | 11.10 | 134.3 | 84.3 | 289.8 | 65.3 | 4.02 | 5.97 | 55.5 | 31.3 | 0.22 |
| | SE | 0.00 | 2.3 | 0.11 | 0.08 | 11.0 | 3.7 | 58.7 | 11.0 | 0.31 | 0.18 | 11.1 | 1.5 | 0.10 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 300 PPM | 421 | 0.1 | 26 | 2.9 | 11.0 | 197 | 79 | 320 | 64 | 3.6 | 6.2 | 48 | 40 | 0.3 |
| | 424 | 0.1 | 13 | 3.1 | 10.7 | 146 | 87 | 127 | 72 | 5.0 | 5.9 | 69 | 79 | 0.5 |
| | 427 | 0.1 | 11 | 3.3 | 11.1 | 183 | 81 | 261 | 44 | 3.4 | 6.6 | 71 | 24 | 0.3 |
| | 433 | 0.1 | 14 | 1.4 | 10.5 | 163 | 85 | 231 | 82 | 4.4 | 6.0 | 36 | 27 | 0.5 |
| | MEAN | 0.10 | 16.0 | 2.67 | 10.82 | 172.3 | 83.0 | 234.8 | 65.5 | 4.10 | 6.17 | 56.0 | 42.5 | 0.40 |
| | SE | 0.00 | 3.4 | 0.43 | 0.14 | 11.2 | 1.8 | 40.4 | 8.1 | 0.37 | 0.15 | 8.5 | 12.7 | 0.06 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

TABLE II-F-48 (Continued)

CLINICAL CHEMISTRIES FOR P-1073409

TABLE 5 (CONTINUED)
INDIVIDUAL ANIMAL CHEMISTRIES-FEMALES
INTERVAL OF STUDY= WEEK 4

| DOSE GROUP | ANIMAL NO | BILI | BUN | ALB | CA | CHOL | GLUS | LDH | SAP | PHOS | PROT | SGOT | SGPT | URIC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1000 PPM | 423 | 0.1 | 25 | 3.2 | 11.7 | 231 | 80 | 473 | 54 | 4.4 | 6.7 | 45 | 23 | 0.4 |
| | 432 | 0.1 | 16 | 2.8 | 10.2 | 112 | 76 | 222 | 80 | 4.7 | 5.5 | 72 | 36 | 0.5 |
| | 436 | 0.1 | 11 | 3.2 | 10.7 | 134 | 82 | 213 | 72 | 3.8 | 6.0 | 68 | 29 | 0.3 |
| | 437 | 0.1 | 15 | 2.9 | 11.4 | 176 | 72 | 479 | 70 | 3.6 | 6.0 | 50 | 35 | 0.3 |
| | MEAN | 0.10 | 16.8 | 3.02 | 11.00 | 163.3 | 77.5 | 346.8 | 69.0 | 4.12 | 6.05 | 58.8 | 30.8 | 0.37 |
| | SE | 0.00 | 3.0 | 0.10 | 0.34 | 26.2 | 2.2 | 74.7 | 5.4 | 0.26 | 0.25 | 6.6 | 3.0 | 0.05 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

CLINICAL CHEMISTRIES FOR P-1073409

TABLE 5 (CONTINUED)
INDIVIDUAL ANIMAL CHEMISTRIES-MALES
INTERVAL OF STUDY= WEEK 8

| DOSE GROUP | ANIMAL NO | BILI | BUN | ALB | CA | CHOL | GLCS | LDH | SAP | PHOS | PROT | SGOT | SGPT | URIC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CONTROL | 408 | 0.1 | 14 | 3.3 | 11.1 | 131 | 90 | 97 | 61 | 4.7 | 6.6 | 54 | 82 | 0.1 |
| | 411 | 0.1 | 19 | 3.1 | 11.1 | 152 | 87 | 257 | 47 | 4.1 | 6.7 | 34 | 25 | 0.3 |
| | 417 | 0.0 | 17 | 2.9 | 10.1 | 120 | 95 | 227 | 59 | 4.3 | 5.4 | 37 | 33 | 0.2 |
| | 418 | 0.1 | 11 | 3.2 | 11.2 | 143 | 83 | 86 | 66 | 4.0 | 6.4 | 25 | 46 | 0.0 |
| | MEAN | 0.07 | 15.3 | 3.12 | 10.87 | 136.5 | 88.8 | 166.8 | 58.3 | 4.27 | 6.27 | 37.5 | 46.5 | 0.15 |
| | SE | 0.02 | 1.8 | 0.09 | 0.26 | 7.0 | 2.5 | 43.9 | 4.0 | 0.15 | 0.30 | 6.1 | 12.6 | 0.06 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 100 PPM | 405 | 0.0 | 18 | 3.0 | 10.8 | 123 | 94 | 139 | 78 | 4.4 | 6.2 | 35 | 41 | 0.0 |
| | 406 | 0.0 | 15 | 3.4 | 11.6 | 166 | 84 | 170 | 36 | 4.5 | 6.4 | 37 | 26 | 0.0 |
| | 407 | 0.1 | 16 | 3.0 | 10.5 | 173 | 96 | 111 | 46 | 4.4 | 6.1 | 29 | 33 | 0.2 |
| | 415 | 0.1 | 16 | 3.1 | 10.5 | 139 | 94 | 258 | 44 | 4.0 | 5.7 | 36 | 29 | 0.2 |
| | MEAN | 0.05 | 16.3 | 3.12 | 10.85 | 150.3 | 92.0 | 169.5 | 51.0 | 4.32 | 6.10 | 34.3 | 32.3 | 0.10 |
| | SE | 0.03 | 0.6 | 0.09 | 0.26 | 11.7 | 2.7 | 31.9 | 9.3 | 0.11 | 0.15 | 1.8 | 3.3 | 0.06 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 300 PPM | 404 | 0.1 | 12 | 3.4 | 10.9 | 168 | 99 | 149 | 47 | 4.1 | 6.5 | 43 | 45 | 0.0 |
| | 409 | 0.0 | 11 | 3.0 | 10.5 | 116 | 93 | 86 | 34 | 4.1 | 5.8 | 30 | 26 | 0.0 |
| | 412 | 0.1 | 15 | 3.2 | 10.9 | 165 | 92 | 123 | 50 | 3.8 | 5.9 | 23 | 39 | 0.4 |
| | 414 | 0.1 | 12 | 3.4 | 10.9 | 152 | 104 | 88 | 72 | 4.6 | 6.9 | 26 | 19 | 0.2 |
| | MEAN | 0.07 | 12.5 | 3.25 | 10.80 | 150.3 | 97.0 | 111.5 | 50.8 | 4.15 | 6..7 | 30.5 | 32.3 | 0.15 |
| | SE | 0.02 | 0.9 | 0.10 | 0.10 | 11.9 | 2.8 | 15.1 | 7.9 | 0.17 | 0.26 | 4.4 | 5.9 | 0.10 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

# TABLE II-F-48 (Continued)

CLINICAL CHEMISTRIES FOR P-1073409

TABLE 5 (CONTINUED)
INDIVIDUAL ANIMAL CHEMISTRIES-MALES
INTERVAL OF STUDY= WEEK 8

| DOSE GROUP | ANIMAL NO | BILI | BUN | ALB | CA | CHOL | GLCS | LDH | SAP | PHOS | PROT | SGOT | SGPT | URIC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1000 PPM | 413 | 0.1 | 11 | 3.1 | 10.2 | 130 | 91 | 138 | 110 | 3.5 | 5.5 | 36 | 29 | 0.0 |
| | 416 | 0.1 | 11 | 3.2 | 10.7 | 93 | 88 | 170 | 28 | 4.1 | 5.4 | 35 | 41 | 0.0 |
| | 419 | 0.1 | 15 | 3.1 | 10.6 | 123 | 86 | 132 | 49 | 4.5 | 6.6 | 33 | 36 | 0.0 |
| | 420 | 0.1 | 11 | 2.9 | 10.3 | 113 | 84 | 150 | 43 | 4.4 | 6.0 | 42 | 72 | 0.1 |
| | MEAN | 0.10 | 12.0 | 3.07 | 10.45 | 114.8 | 87.3 | 147.5 | 57.5 | 4.12 | 5.87 | 36.5 | 44.5 | 0.02 |
| | SE | 0.00 | 1.0 | 0.06 | 0.12 | 8.0 | 1.5 | 8.4 | 18.0 | 0.23 | 0.28 | 1.9 | 9.5 | 0.02 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

# TABLE II-F-48 (Continued)

CLINICAL CHEMISTRIES FOR P-1073409

TABLE 5 (CONTINUED)
INDIVIDUAL ANIMAL CHEMISTRIES-FEMALES
INTERVAL OF STUDY= WEEK 8

| DOSE GROUP | ANIMAL NO | BILI | BUN | ALB | CA | CHOL | GLCS | LDH | SAP | PHOS | PROT | SGOT | SGPT | URIC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CONTROL | 425 | 0.1 | 17 | 3.2 | 10.8 | 116 | 81 | 92 | 54 | 3.8 | 5.7 | 34 | 23 | 0.1 |
| | 426 | 0.1 | 12 | 3.4 | 11.1 | 144 | 99 | 161 | 62 | 3.5 | 6.8 | 38 | 39 | 0.3 |
| | 434 | 0.1 | 16 | 3.0 | 10.6 | 111 | 105 | 206 | 27 | 4.1 | 6.1 | 32 | 27 | 0.1 |
| | 435 | 0.1 | 13 | 3.2 | 10.4 | 129 | 75 | 220 | 29 | 4.0 | 5.8 | 36 | 38 | 0.0 |
| | MEAN | 0.10 | 14.5 | 3.20 | 10.72 | 125.0 | 90.0 | 169.8 | 43.0 | 3.85 | 6.10 | 35.0 | 31.8 | 0.12 |
| | SE | 0.00 | 1.2 | 0.08 | 0.15 | 7.4 | 7.1 | 28.8 | 8.8 | 0.13 | 0.25 | 1.3 | 4.0 | 0.06 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 100 PPM | 422 | 0.1 | 13 | 3.0 | 10.7 | 147 | 80 | 131 | 58 | 4.5 | 5.7 | 23 | 31 | 0.2 |
| | 429 | 0.1 | 15 | 3.0 | 10.9 | 165 | 76 | 173 | 78 | 3.9 | 6.1 | 39 | 28 | 1.2 |
| | 430 | 0.1 | 17 | 2.9 | 10.7 | 99 | 75 | 204 | 37 | 4.3 | 5.5 | 37 | 35 | 0.1 |
| | 431 | 0.1 | 16 | 3.4 | 10.6 | 106 | 86 | 133 | 45 | 4.0 | 5.8 | 26 | 27 | 0.2 |
| | MEAN | 0.10 | 15.3 | 3.07 | 10.72 | 129.3 | 79.3 | 160.3 | 54.5 | 4.17 | 5.77 | 31.3 | 30.3 | 0.42 |
| | SE | 0.00 | 0.9 | 0.11 | 0.06 | 15.9 | 2.5 | 17.5 | 8.9 | 0.14 | 0.13 | 4.0 | 1.8 | 0.26 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 300 PPM | 421 | 0.0 | 23 | 3.5 | 11.0 | 200 | 93 | 137 | 58 | 3.8 | 6.6 | 38 | 38 | 0.0 |
| | 424 | 0.1 | 12 | 3.3 | 10.8 | 145 | 88 | 153 | 63 | 4.2 | 6.3 | 31 | 37 | 0.2 |
| | 427 | 0.1 R | 14 R | 4.4 R | 10.8 | 189 R | 99 S | 328 R | 68 R | 3.7 R | 6.5 R | 42 R | 29 R | 0.4 R |
| | 433 | 0.0 | 18 | 3.0 | 10.8 | 220 | 93 | 129 | 76 | 4.7 | 6.4 | 32 | 27 | 0.5 |
| | MEAN | 0.05 | 16.8 | 3.55 | 10.85 | 188.5 | 93.3 | 186.8 | 66.3 | 4.10 | 6.45 | 35.8 | 32.8 | 0.27 |
| | SE | 0.03 | 2.4 | 0.30 | 0.05 | 15.9 | 2.3 | 47.3 | 3 | 0.23 | 0.06 | 2.6 | 2.8 | 0.11 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

# TABLE II-F-48 (Continued)

CLINICAL CHEMISTRIES FOR P-1073409

TABLE 5 (CONTINUED)
INDIVIDUAL ANIMAL CHEMISTRIES-FEMALES
INTERVAL OF STUDY= WEEK 8

| DOSE GROUP | ANIMAL NO | BILI | BUN | ALB | CA | CHOL | GLCS | LDH | SAP | PHOS | PROT | SGOT | SGPT | URIC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1000 PPM | 423 | 0.1 | 23 | 3.0 | 11.1 | 248 | 93 | 237 | 70 | 4.1 | 6.4 | 40 | 25 | 0.5 |
| | 432 | 0.1 | 13 | 2.9 | 9.7 | 102 | 80 | 263 | 62 | 4.6 | 5.5 | 41 | 30 | 0.1 |
| | 436 | 0.2 | 14 | 3.2 | 10.2 | 137 | 84 | 123 | 54 | 3.8 | 5.7 | 28 | 22 | 0.0 |
| | 437 | 0.1 | 17 | 3.5 | 11.4 | 180 | 72 | 126 | 61 | 4.3 | 6.0 | 32 | 36 | 0.4 |
| | MEAN | 0.12 | 16.8 | 3.15 | 10.60 | 166.8 | 82.3 | 187.3 | 61.8 | 4.20 | 5.90 | 35.3 | 28.3 | 0.25 |
| | SE | 0.02 | 2.3 | 0.13 | 0.39 | 31.4 | 4.4 | 36.6 | 3.3 | 0.17 | 0.20 | 3.1 | 3.1 | 0.12 |
| | N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

CLINICAL CHEMISTRIES FOR P-1073409

TABLE 5 (CONTINUED)
INDIVIDUAL ANIMAL CHEMISTRIES-MALES
INTERVAL OF STUDY= TERMINAL KILL

| DOSE GROUP | ANIMAL NO | BILI | BUN | ALB | CA | CHOL | GLCS | LDH | SAP | PHOS | PROT | SGOT | SGPT | URIC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CONTROL | 408 | 0.1 | 12 | 4.1 | 10.8 | 107 | . A | 125 | 67 | 4.1 | 6.6 | 30 | 56 | 0.6 |
| | 411 | 0.1 | 20 | 3.9 | 11.9 | 103 | 77 | 243 | 43 | 3.5 | 6.8 | 31 | 24 | 0.5 |
| | 417 | 0.1 | 20 | 3.2 | 10.2 | 81 | 71 | 411 | 45 | 3.0 | 5.3 | 41 | 42 | 0.4 |
| | 418 | 0.1 | 13 | 4.2 | 11.0 | 108 | . A | 175 | 65 | 3.8 | 6.4 | 24 | 46 | 0.6 |
| | MEAN | 0.10 | 16.3 | 3.85 | 10.97 | 98.5 | 74.0 | 238.5 | 55.0 | 3.75 | 6.27 | 31.5 | 42.0 | 0.52 |
| | SE | 0.00 | 2.2 | 0.23 | 0.35 | 6.0 | 3.0 | 62.4 | 6.4 | 0.13 | 0.34 | 3.5 | 6.7 | 0.05 |
| | N | 4 | 4 | 4 | 4 | 4 | 2 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 100 PPM | 405 | 0.1 | 18 | 4.0 | 10.7 | 105 | . A | 259 | 63 | 3.7 | 6.5 | 29 | 39 | 0.4 |
| | 406 | 0.1 | 16 | 4.3 | 11.2 | 122 | . A | 243 | 35 | 3.6 | 6.5 | 29 | 30 | 0.5 |
| | 407 | 0.1 | 19 | 3.5 | 10.6 | 125 | 74 | 215 | 42 | 4.4 | 6.0 | 31 | 31 | 0.6 |
| | 415 | 0.1 | 14 | 3.4 | 10.1 | 104 | 74 | 337 | 45 | 3.2 | 5.4 | 36 | 37 | 0.4 |
| | MEAN | 0.10 | 16.8 | 3.80 | 10.65 | 114.0 | 74.0 | 263.5 | 46.3 | 3.72 | 6.10 | 31.3 | 34.3 | 0.47 |
| | SE | 0.00 | 1.1 | 0.21 | 0.23 | 5.5 | 0.0 | 26.1 | 6.0 | 0.25 | 0.26 | 1.7 | 2.2 | 0.05 |
| | N | 4 | 4 | 4 | 4 | 4 | 2 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 300 PPM | 404 | 0.1 | 18 | 3.6 | 10.6 | 116 | 86 | 161 | 51 | 3.9 | 6.0 | 31 | 37 | 0.5 |
| | 409 | 0.1 | 19 | 3.3 | 10.8 | 96 | 79 | 230 | 36 | 4.0 | 6.5 | 29 | 31 | 0.5 |
| | 412 | 0.1 | 17 | 4.5 | 11.1 | 102 | . A | 263 | 41 | 2.9 | 6.2 | 24 | 41 | 1.1 |
| | 414 | 0.1 | 12 | 4.3 | 10.8 | 109 | . A | 113 | 53 | 3.2 | 6.8 | 24 | 23 | 1.1 |
| | MEAN | 0.10 | 16.5 | 3.92 | 10.82 | 105.8 | 82.5 | 191.8 | 45.3 | 3.50 | 6.37 | 27.0 | 33.0 | 0.80 |
| | SE | 0.00 | 1.6 | 0.28 | 0.10 | 4.3 | 3.5 | 33.8 | 4.0 | 0.27 | 0.18 | 1.8 | 3.9 | 0.17 |
| | N | 4 | 4 | 4 | 4 | 4 | 2 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

# TABLE II-F-48 (Continued)

CLINICAL CHEMISTRIES FOR P-1073409

TABLE 5 (CONTINUED)
INDIVIDUAL ANIMAL CHEMISTRIES-MALES
INTERVAL OF STUDY= TERMINAL KILL

| DOSE GROUP | ANIMAL NO | BILI | BUN | ALB | CA | CHOL | GLCS | LDH | SAP | PHOS | PROT | SGOT | SGPT | URIC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1000 PPM | 413 | 0.1 | 16 | 2.9 | 10.0 | 105 | 88 | 268 | 81 | 3.0 | 5.3 | 30 | 29 | 0.9 |
| | 416 | 0.1 | 17 | 3.7 | 10.8 | 75 | 87 | 184 | 40 | 3.0 | 5.7 | 29 | 43 | 0.5 |
| | 419 | 0.1 | 14 | 4.1 | 11.0 | 90 | . A | 226 | 50 | 4.0 | 6.4 | 39 | 62 | 0.9 |
| | 420 | 0.1 | 15 | 4.3 | 10.9 | 101 | . A | 238 | 55 | 3.5 | 6.3 | 41 | 63 | 1.0 |
| | MEAN | 0.10 | 15.5 | 3.75 | 10.67 | 92.8 | 87.5* | 229.0 | 56.5 | 3.38 | 5.92 | 34.8 | 49.3 | 0.82 |
| | SE | 0.00 | 0.6 | 0.31 | 0.23 | 6.7 | 0.5 | 17.4 | 8.7 | 0.24 | 0.26 | 3.1 | 8.2 | 0.11 |
| | N | 4 | 4 | 4 | 4 | 4 | 2 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

# TABLE II-F-48 (Continued)

CLINICAL CHEMISTRIES FOR P-1073409

TABLE 5 (CONTINUED)
INDIVIDUAL ANIMAL CHEMISTRIES-FEMALES
INTERVAL OF STUDY= TERMINAL KILL

| DOSE GROUP | ANIMAL NO | BILI | BUN | ALB | CA | CHOL | GLCS | LDH | SAP | PHOS | PROT | SGOT | SGPT | URIC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CONTROL | 425 | 0.1 | 15 | 4.3 | 10.8 | 102 | .A | 322 | 55 | 3.2 | 5.9 | 34 | 27 | 0.5 |
| | 426 | 0.2 | 13 | 4.2 | 11.0 | 110 | .A | 239 | 49 | 3.2 | 6.4 | 29 | 37 | 0.6 |
| | 434 | 0.1 | 19 | 3.4 | 10.9 | 78 | 75 | 225 | 28 | 3.7 | 6.0 | 34 | 45 | 0.5 |
| | 435 | 0.1 | 16 | 3.4 | 10.8 | 105 | 81 | 211 | 31 | 3.1 | 5.8 | 32 | 31 | 0.5 |
| | MEAN | 0.12 | 15.8 | 3.82 | 10.87 | 98.8 | 78.0 | 249.3 | 40.8 | 3.30 | 6.02 | 32.3 | 35.0 | 0.52 |
| | SE | 0.02 | 1.3 | 0.25 | 0.05 | 7.1 | 3.0 | 24.9 | 6.6 | 0.14 | 0.13 | 1.2 | 3.9 | 0.03 |
| | N | 4 | 4 | 4 | 4 | 4 | 2 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 100 PPM | 422 | 0.1 | 18 | 3.3 | 11.0 | 129 | 70 | 241 | 49 | 3.7 | 5.4 | 27 | 28 | 0.5 |
| | 429 | 0.1 | 14 | 3.9 | 10.4 | 154 | . A | 240 | 80 | 2.9 | 5.9 | 32 | 33 | 0.4 |
| | 430 | 0.1 | 16 | 3.4 | 10.9 | 82 | 79 | 434 | 26 | 3.7 | 8.7 | 44 | 40 | 0.3 |
| | 431 | 0.1 | 19 | 4.3 | 10.7 | 96 | . A | 175 | 33 | 3.4 | 5.7 | 21 | 35 | 0.5 |
| | MEAN | 0.10 | 16.8 | 3.72 | 10.75 | 115.3 | 74.5 | 272.5 | 47.0 | 3.42 | 6.42 | 31.0 | 34.0 | 0.42 |
| | SE | 0.00 | 1.1 | 0.23 | 0.13 | 16.2 | 4.5 | 56.0 | 12.0 | 0.19 | 0.77 | 4.9 | 2.5 | 0.05 |
| | N | 4 | 4 | 4 | 4 | 4 | 2 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 300 PPM | 421 | 0.1 | 25 | 3.4 | 10.8 | 157 | 80 | 364 | 45 | 3.3 | 6.4 | 38 | 35 | 0.7 |
| | 424 | 0.1 | 12 | 4.1 | 10.5 | 114 | . A | 200 | 61 | 2.9 | 5.7 | 21 | 32 | 1.2 |
| | 427 | 0.1 | 15 | 4.0 | 10.9 | 159 | . A | 236 | 49 | 3.3 | 5.8 | 17 | 25 | 0.9 |
| | 433 | 0.1 | 20 | 3.4 | 11.1 | 137 | 73 | 315 | 66 | 5.0 | 5.8 | 35 | 39 | 0.5 |
| | MEAN | 0.10 | 18.0 | 3.72 | 10.82 | 140.5 | 76.5 | 278.8 | 55.3 | 3.62 | 5.92 | 27.8 | 32.8 | 0.82 |
| | SE | 0.00 | 2.9 | 0.19 | 0.13 | 10.8 | 3.5 | 37.2 | 4.9 | 0.47 | 0.16 | 4.2 | 3.0 | 0.15 |
| | N | 4 | 4 | 4 | 4 | 4 | 2 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

# TABLE II-F-48 (Continued)

CLINICAL CHEMISTRIES FOR P-1073409

TABLE 5 (CONTINUED)
INDIVIDUAL ANIMAL CHEMISTRIES-FEMALES
INTERVAL OF STUDY= TERMINAL KILL

| DOSE GROUP | ANIMAL NO | BILI | BUN | ALB | CA | CHOL | GLCS | LDH | SAP | PHOS | PROT | SGOT | SGPT | URIC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1000 PPM | 423 | 0.2 | 24 | 3.4 | 11.4 | 120 | 81 | 340 | 48 | 3.8 | 6.2 | 39 | 29 | 0.6 |
| | 432 | 0.1 | 15 | 4.0 | 10.2 | 86 | . A | 241 | 59 | 3.8 | 5.5 | 29 | 32 | 1.1 |
| | 436 | 0.1 | 16 | 4.1 | 10.3 | 138 | . A | 171 | 54 | 3.2 | 5.6 | 19 | 19 | 0.8 |
| | 437 | 0.1 | 15 | 3.7 | 11.5 | 136 | 68 | 274 | 55 | 3.6 | 6.0 | 32 | 38 | 0.3 |
| | MEAN | 0.12 | 17.5 | 3.80 | 10.85 | 120.0 | 74.5 | 256.5 | 54.0 | 3.60 | 5.82 | 29.8 | 29.5 | 0.70 |
| | SE | 0.02 | 2.2 | 0.16 | 0.35 | 12.0 | 6.5 | 35.2 | 2.3 | 0.14 | 0.17 | 4.2 | 4.0 | 0.17 |
| | N | 4 | 4 | 4 | 4 | 4 | 2 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE 6

KEY TO URINALYSIS

| | |
|---|---|
| Color: | Y = Yellow<br>Str = Straw<br>Amb = Amber<br>Br = Brown<br>Or = Orange<br>Ply = Pale Yellow<br>PlOr = Pale Orange<br>None = Colorless |
| Appearance: | Cldy = Cloudy<br>Sl Cldy = Slightly Cloudy |
| Albumin: | 0 = Negative<br>+ = Positive<br>± = Trace<br>1+ = 30 mg<br>2+ = 100 mg<br>3+ = 300 mg<br>4+ = 100 mg or greater |
| Other: | - or 0 = None seen or Negative<br>± = Trace, Rare, Occasional<br>1+ = Slight, Small, Little<br>2+ = Moderate, Frequent<br>3+ = Severe, Heavy, Large, Many<br>4+ = Maximal |
| Microscopic Examination: | HPF = High power field |
| Crystals: | UA = Uric Acid<br>TP = Triple Phosphate<br>CaOx = Calcium Oxalate |
| Other: | Yst = Yeast<br>Mu = Mucous Threads<br>Sp = Sperm<br>HA = Hippuric Acid |

# TABLE II-F-49

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE 6

URINALYSIS

INITIAL

MALES

| DOSE LEVEL (PPM) | ANIMAL NUMBER | COLOR | APPEARANCE | SPEC. GRAV. | pH | ALBUMIN | GLUCOSE | KETONES | BILIRUBIN | OCCULT BLOOD | WBC | RBC | CASTS | EPITH | AMORPH | BACT | CRYSTALS | OTHER | MUCOUS THREADS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 408 | Y | Hazy | 1.017 | 7 | 0 | 0 | 0 | ± | 0 | 0 | - | - | 2+ | 3+ | 3+ | TP 2+ | - | - |
| | 411 | Y | Hazy | 1.040 | 7 | 0 | 0 | 0 | ± | 0 | 0-5 | - | - | 1+ | - | 3+ | - | Ha ±, Sp 2+ | |
| | 417 | Amb | Cldy | 1.045 | 7 | 1+ | 0 | 0 | 1+ | 2+ | - | - | - | 2+ | 2+ | 2+ | TP 2+ | - | - |
| | 418 | Amb | Hazy | 1.040 | 9 | 3+ | 0 | 0 | 2+ | 0 | 0-1 | - | - | 1+ | 1+ | 4+ | UA 2+, TP 2+ | Ha ±, Sp 1+ | - |
| 100 | 405 | Amb | Cldy | >1.045 | 8 | 3+ | 0 | 0 | 3+ | 0 | - | - | - | 1+ | 1+ | ± | TP 3+ | - | - |
| | 406 | Y | Cldy | 1.017 | 8 | 0 | 0 | 0 | 1+ | 0 | - | - | - | 1+ | 1+ | 3+ | TP 1+ | Ha 1+ | - |
| | 407 | Y | Cldy | 1.030 | 8 | 0 | 0 | 0 | ± | 0 | - | - | - | 2+ | 2+ | 4+ | - | - | - |
| | 415 | Str | Hazy | 1.007 | 7 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 2+ | ± | - | - | - |
| 300 | 404 | Amb | Hazy | 1.025 | 8 | 1+ | 0 | 0 | 1+ | 0 | 0-1 | - | - | 1+ | 1+ | 3+ | TP 3+ | Ha + | |
| | 409 | Y | Cldy | 1.035 | 8 | 1+ | 0 | 0 | + | 0 | 0-1 | 0-1 | - | 1+ | 2+ | 4+ | TP 2+ | Ha 1+ | - |
| | 412 | Amb | Turbid | >1.045 | 9 | ± | 0 | 0 | 0 | 0 | ± | ± | 0 | 2+ | ± | 2+ | TP 3+ | - | - |
| | 414 | Amb | Hazy | 1.040 | 6 | 1+ | 0 | 0 | 0 | 0 | - | - | - | ± | 1+ | 2+ | UA ±, TP ± | - | - |
| 1000 | 413 | Amb | Cldy | >1.045 | 7 | 2+ | 0 | 0 | 2+ | 0 | 0-2 | 0-1 | - | 1+ | 1+ | 1+ | TP 3+ | Ha 1+, Sp 1+ | - |
| | 416 | Y | Cldy | >1.045 | 9 | 1+ | 0 | 0 | ± | 0 | - | - | - | ± | 1+ | 4+ | UA 1+, TP 2+ | - | - |
| | 419 | Y | Hazy | 1.030 | 6 | 0 | 0 | 0 | 1+ | 0 | - | - | - | 3+ | ± | ± | UA ± | - | - |
| | 420 | Y | Cldy | 1.010 | 6 | ± | 0 | 0 | 0 | 0 | - | - | - | 2+ | 2+ | 3+ | UA ±, TP 1+ | - | - |

## TABLE II-F-49 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE 6 (CONTINUED)

URINALYSIS

INITIAL

FEMALES

| DOSE LEVEL (PPM) | ANIMAL NUMBER | COLOR | APPEAR-ANCE | SPEC. GRAV. | pH | AL-BUMIN | GLU-COSE | KE-TONES | BILI-RUBIN | OCCULT BLOOD | WBC | RBC | CASTS | EPITH | AMORPH | BACT | CRYSTALS | OTHER | MUCOUS THREADS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 425 | Amb | Cldy | 1.035 | 7 | 1+ | 0 | 0 | 0 | 0 | - | - | - | ± | 2+ | 3+ | TP 3+ | - | - |
| | 426 | Amb | Hazy | 1.030 | 8 | 0 | 0 | 0 | 0 | 0 | 2-8 | - | - | 3+ | 1+ | 1+ | UA 1+, TP 1+ | Ha 1+ | - |
| | 434 | Y | Hazy | 1.017 | 8 | 0 | 0 | 0 | 0 | 0 | 0-1 | - | - | 1+ | 2+ | 4+ | TP 3+ | Ha 1+ | - |
| | 435 | Amb | Cldy | >1.045 | 7 | 0 | 0 | 0 | 0 | 0 | 0-1 | 0-1 | - | 2+ | 2+ | 2+ | UA ±, TP 4+ | - | - |
| 100 | 422 | Y | Hazy | >1.045 | 7 | ± | 0 | 0 | 0 | 0 | 0-1 | - | - | 2+ | 2+ | ± | TP 2+ | Ha 2+ | - |
| | 429 | Y | Cldy | 1.010 | 8 | ± | 0 | 0 | 0 | 0 | - | - | - | ± | 1+ | 4+ | TP ± | Ha 2+ | - |
| | 430 | Y | Cldy | >1.045 | 6 | 0 | 0 | 0 | 0 | 0 | - | - | - | 1+ | 1+ | 1+ | TP ± | Ha + | |
| | 431 | Amb | Cldy | 1.025 | 7 | ± | 0 | 0 | 0 | 0 | - | - | - | - | 1+ | 3+ | TP 1+ | - | - |
| 300 | 421 | Y | Hazy | 1.040 | 6 | 0 | 0 | 0 | 0 | 0 | 0-1 | 0-1 | - | 3+ | ± | ± | - | - | - |
| | 424 | Y | Cldy | 1.045 | 7 | 0 | 0 | 0 | 0 | 0 | - | 0-2 | - | ± | 2+ | 1+ | TP 2+ | - | - |
| | 427 | Amb | Hazy | >1.045 | 6 | 1+ | 0 | 0 | 0 | 0 | 0-1 | - | - | 2+ | 1+ | 1+ | UA 1+, TP 2+ | Ha + | - |
| | 433 | Amb | Cldy | 1.035 | 6 | 1+ | 0 | 0 | 3+ | 2+ | - | - | - | 1+ | 3+ | 2+ | UA ± | - | - |
| 1000 | 423 | Y | Hazy | 1.018 | 7 | ± | 0 | 0 | 0 | ± | - | - | - | ± | 2+ | 4+ | UA 1+, TP 1+ | - | - |
| | 432 | Br | Cldy | 1.035 | 7 | ± | 0 | 0 | 0 | 1+ | 0-1 | - | - | 1+ | 2+ | 4+ | TP 1+ | - | - |
| | 436 | Amb | Hazy | 1.044 | 8 | 1+ | 0 | 0 | 0 | 0 | 0-2 | 0-4 | - | 2+ | 1+ | 1+ | TP 2+ | - | - |
| | 437 | Y | Cldy | 1.030 | 9 | ± | 0 | 0 | 0 | 0 | - | - | - | 1+ | 1+ | 2+ | TP 1+ | Ha 3+ | - |

# TABLE II-F-49 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE 6 (CONTINUED)

URINALYSIS

WEEK 8

MALES

| DOSE LEVEL (PPM) | ANIMAL NUMBER | COLOR | APPEARANCE | SPEC. GRAV. | pH | ALBUMIN | GLUCOSE | KETONES | BILIRUBIN | OCCULT BLOOD | WBC | RBC | CASTS | EPITH | AMORPH | BACT | CRYSTALS | OTHER | MUCOUS THREADS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 425 | Y | Cldy | 1.024 | 9 | 2+ | 0 | 0 | 1+ | 0 | - | - | - | - | - | 4+ | TP 2+ | - | - |
| | 426 | Y | Cldy | 1.027 | 9 | 1+ | 0 | 0 | 2+ | 0 | - | - | - | - | - | 4+ | TP 4+ | - | - |
| | 434 | Str | Hazy | 1.045 | 9 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 1+ | 2+ | TP ± | - | - |
| | 435 | Y | Cldy | 1.027 | 6 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | ± | 1+ | TP ± | - | - |
| 100 | 405 | Y | Cldy | 1.030 | 9 | 1+ | 0 | 0 | 2+ | 0 | 3-5 | - | - | - | - | 4+ | TP 4+ | - | - |
| | 406 | Y | Cldy | 1.016 | 9 | 1+ | 0 | 0 | 2+ | 0 | - | - | - | - | - | 4+ | TP 4+ | - | - |
| | 407 | Str | Turbid | 1.050 | 9 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 1+ | 3+ | TP ± | Sp + | - |
| | 415 | Br | Turbid | 1.062 | 9 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | - | 2+ | - | - | - |
| 300 | 404 | Y | Cldy | 1.022 | 7 | 0 | 0 | 0 | 0 | 0 | 2-3 | - | - | 6-8 | - | 4+ | TP 4+ | - | - |
| | 409 | Y | Cldy | 1.058 | 8 | 1+ | 0 | 0 | 1+ | 0 | 3-5 | - | - | - | 2+ | 2+ | TP 4+ | - | - |
| | 412 | Y | Hazy | 1.010 | 9 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | ± | 3+ | TP 1+ | - | - |
| | 414 | Y | Hazy | 1.014 | 8 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | ± | 2+ | TP 1+ | - | - |
| 1000 | 413 | Y | Cldy | 1.032 | 9 | 1+ | 0 | 0 | 2+ | 0 | - | - | - | - | - | 4+ | TP 4+ | - | - |
| | 416 | Y | Cldy | 1.030 | 9 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | - | 4+ | TP 4+ | - | - |
| | 419 | Str | Turbid | 1.050 | 6 | 0 | 0 | 0 | 0 | 0 | 5-10 | - | - | 1-2 | 1+ | ± | - | Sp ± | - |
| | 420 | Y | Hazy | 1.026 | 7 | ± | 0 | 0 | 0 | 0 | - | - | - | 5-10 | 1+ | 1+ | TP 1+ | Sp + | - |

# TABLE II-F-49 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE 6 (CONTINUED)

URINALYSIS

WEEK 8

FEMALES

| DOSE LEVEL (PPM) | ANIMAL NUMBER | COLOR | APPEARANCE | SPEC. GRAV. | pH | ALBUMIN | GLUCOSE | KETONES | BILIRUBIN | OCCULT BLOOD | WBC | RBC | CASTS | EPITH | AMORPH | BACT | CRYSTALS | OTHER | MUCOUS THREADS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 408 | Y | Cldy | 1.010 | 9 | 2+ | 0 | 0 | 1+ | 0 | - | - | - | - | - | 4+ | TP 1+ | - | - |
| | 411 | Str | Hazy | 1.057 | 6 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 1+ | - | TP 3+ | Sp 1+ | - |
| | 417 | Y | Turbid | 1.045 | 6 | ± | 0 | 0 | 0 | 2+ | - | - | - | - | 3+ | 1+ | TP ± | Sp + | - |
| | 418 | Y | Cldy | 1.042 | 9 | ± | 0 | 0 | 4+ | 0 | 3-5 | - | - | - | - | 4+ | TP 2+ | - | - |
| 100 | 422 | Str | Hazy | 1.047 | 6 | 0 | 0 | 0 | 0 | 0 | 6-12 | - | - | 6-8 | ± | - | - | - | - |
| | 429 | Y | Cldy | 1.029 | 8 | 1+ | 0 | 0 | 0 | 0 | - | - | - | - | - | 4+ | TP 4+ | - | - |
| | 430 | Br | Hazy | 1.062 | 8 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 3+ | - | TP 3+ | - | - |
| | 431 | Y | Cldy | 1.034 | 9 | 2+ | 0 | 0 | 4+ | 0 | - | - | - | - | - | 4+ | TP 4+ | - | - |
| 300 | 421 | Y | Cldy | 1.047 | 9 | 1+ | 0 | 0 | 4+ | 0 | - | - | - | - | - | 4+ | TP 4+ | - | - |
| | 424 | Str | Hazy | 1.055 | 9 | 0 | 0 | 0 | 0 | 0 | 0-1 | - | - | 0-1 | 1+ | - | TP 1+ | - | - |
| | 427 | Str | Hazy | 1.037 | 8 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 1+ | 2+ | TP 2+ | - | - |
| | 433 | Y | Cldy | 1.031 | 9 | 1+ | 0 | 0 | 3+ | 0 | - | - | - | - | - | 4+ | TP 4+ | - | - |
| 1000 | 423 | Y | Hazy | 1.021 | 9 | 1+ | 0 | 0 | 2+ | 0 | - | - | - | - | - | 4+ | TP 1+ | - | - |
| | 432 | Str | Hazy | 1.025 | 9 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 2+ | 2+ | TP ± | - | - |
| | 436 | Str | Hazy | 1.040 | 7 | 0 | 0 | 0 | 0 | 0 | - | - | - | 3-6 | + | - | - | - | - |
| | 437 | Y | Cldy | 1.023 | 9 | 3+ | 0 | 0 | 3+ | 0 | - | - | - | - | - | 4+ | TP 4+ | - | - |

# TABLE II-F-49 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE 6 (CONTINUED)

URINALYSIS

WEEK 13

MALES

| DOSE LEVEL (PPM) | ANIMAL NUMBER | COLOR | APPEARANCE | SPEC. GRAV. | pH | ALBUMIN | GLUCOSE | KETONES | BILIRUBIN | OCCULT BLOOD | WBC | RBC | CASTS | EPITH | AMORPH | BACT | CRYSTALS | OTHER | THREADS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 425 | Y | Hazy | 1.024 | 9 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 3+ | 2+ | TP 1+ | - | - |
| | 426 | Y | Hazy | 1.012 | 9 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 2+ | 2+ | TP ± | - | - |
| | 434 | Y | Turbid | 1.019 | 9 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 3+ | - | TP ± | - | - |
| | 435 | Br | Turbid | 1.038 | 8 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 2+ | - | TP 3+ | - | - |
| 100 | 405 | Y | Hazy | 1.019 | 8 | 0 | 0 | 0 | 0 | 0 | 0-1 | - | - | - | 1+ | 2+ | TP ± | - | - |
| | 406 | Y | Hazy | 1.018 | 8 | 0 | 0 | 0 | 0 | 0 | - | | | | 2+ | 2+ | TP ± | - | - |
| | 407 | Y | Turbid | 1.023 | 6 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 3+ | - | - | - | - |
| | 415 | Y | Turbid | 1.019 | 9 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 3+ | - | TP 1+ | - | - |
| 300 | 404 | Y | Turbid | 1.028 | 9 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 3+ | 2+ | TP ± | - | - |
| | 409 | Str | Turbid | 1.053 | 9 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 3+ | 2+ | TP 1+ | - | - |
| | 412 | Str | Turbid | 1.058 | 9 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 3+ | - | TP ± | - | - |
| | 414 | Str | Turbid | 1.023 | 9 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 3+ | - | TP 1+ | - | - |
| 1000 | 413 | Str | Hazy | 1.030 | 8 | 0 | 0 | 0 | 0 | 0 | 0-3 | - | - | - | 2+ | - | TP 1+ | Sp 2+ | 2+ |
| | 416 | Str | Hazy | 1.032 | 7 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 2+ | - | TP 1+ | Sp 2+ | ± |
| | 419 | Str | Turbid | 1.040 | 7 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 3+ | 3+ | TP 2+ | - | 1+ |
| | 420 | Y | Turbid | 1.027 | 9 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 3+ | - | TP 1+ | - | - |

# TABLE II-F-49 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE 6 (CONTINUED)

URINALYSIS

WEEK 13

FEMALES

| DOSE LEVEL (PPM) | ANIMAL NUMBER | COLOR | APPEARANCE | SPEC. GRAV | pH | ALBUMIN | GLUCOSE | KETONES | BILIRUBIN | OCCULT BLOOD | WBC | RBC | CASTS | EPITH | AMORPH | BACT | CRYSTALS | OTHER | MUCOUS THREADS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 408 | Ctr | Hazy | 1.011 | 9 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 2+ | 2+ | TP 1+ | - | - |
| | 411 | Str | Hazy | 1.041 | 8 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 2+ | ± | TP 3+ | Sp | - |
| | 417 | Str | Turbid | 1.037 | 8 | ± | 0 | 0 | 0 | 0 | - | - | - | - | 3+ | 3+ | TP 2+ | - | - |
| | 418 | Y | Hazy | 1.008 | 9 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 2+ | 1+ | TP 1+ | - | - |
| 100 | 422 | Y | Turbid | 1.026 | 9 | ± | 0 | 0 | 0 | 0 | - | - | - | - | 3+ | - | TP 1+ | - | - |
| | 429 | Str | Turbid | 1.055 | 9 | 0 | 0 | 0 | 0 | 0 | 0-1 | - | - | - | 2+ | 2+ | TP + | - | 1+ |
| | 430 | Y | Turbid | 1.032 | 8 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 3+ | - | TP 2+ | - | - |
| | 431 | Y | Turbid | 1.034 | 9 | 0 | 0 | 0 | 0 | 0 | 0-3 | - | - | 0-6 | 3+ | 2+ | TP 2+ | - | ± |
| 300 | 421 | Br | Turbid | 1.027 | 9 | ± | 0 | 0 | 0 | ± | - | - | - | - | 3+ | - | TP 2+ | - | - |
| | 424 | Y | Turbid | 1.022 | 9 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 3+ | - | TP 1+ | - | - |
| | 427 | Br | Turbid | 1.098 | 9 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 2+ | 2+ | TP 1+ | - | 2+ |
| | 433 | Str | Turbid | 1.048 | 9 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 3+ | - | - | - | - |
| 1000 | 423 | Y | Cldy | 1.016 | 9 | ± | 0 | 0 | 0 | 0 | - | - | - | - | 2+ | 2+ | TP 1+ | - | - |
| | 432 | Str | Hazy | 1.034 | 8 | 0 | 0 | 0 | 0 | 0 | 0-3 | - | - | - | 2+ | 2+ | TP 1+ | - | 2+ |
| | 436 | Y | Hazy | 1.004 | 9 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 3+ | 2+ | TP + | - | - |
| | 437 | Y | Hazy | 1.016 | 9 | 0 | 0 | 0 | 0 | 0 | - | - | - | - | 1+ | 3+ | TP + | - | - |

# TABLE II-F-50

TABLE 7

PROJECT NO. 1073409
ORGAN WEIGHTS IN MALE DOGS (GRAMS)
DOSE - 0 PPM
GROUP - 1
TERMINAL KILL

| ANIMAL NUMBER | BODY WEIGHT | BRAIN | THYROID | HEART | LIVER | SPLEEN | KIDNEYS | ADRENALS | TESTES |
|---|---|---|---|---|---|---|---|---|---|
| 0408 | 15800.0 | 77.2990 | 0.0[a] | 112.2260 | 446.8350 | 74.6140 | 81.7960 | 1.1300 | 23.1770 |
| 0411 | 9800.0 | 80.9100 | 1.0340 | 71.8120 | 301.4540 | 58.4590 | 49.0490 | 0.7170 | 15.8160 |
| 0417 | 9200.0 | 76.6100 | 0.6700 | 85.3400 | 267.0000 | 73.5400 | 57.5000 | 0.8200 | 19.3100 |
| 0418 | 8700.0 | 79.4800 | 0.9200 | 77.9500 | 270.7800 | 104.3000 | 58.8500 | 1.9000 | 22.7600 |
| N | 4 | 4 | 3 | 4 | 4 | 4 | 4 | 4 | 4 |
| MEAN | 10875.0 | 78.5747 | 0.8747 | 86.8325 | 322.0172 | 77.7282 | 61.7987 | 1.1417 | 20.2657 |
| S.D. | 3314.0 | 1.9800 | 0.1862 | 17.8108 | 85.9413 | 19.1886 | 14.0193 | 0.5351 | 3.4356 |
| S.E. | 1657.0 | 0.9900 | 0.1075 | 8.9054 | 42.9707 | 9.5943 | 7.0096 | 0.2676 | 1.7178 |

[a]Left thyroid not located.

## TABLE II-F-50 (Continued)

TABLE 7 (CONTINUED)
PROJECT NO. 1073409
ORGAN WEIGHTS IN MALE DOGS (GRAMS)
DOSE - 100 PPM
GROUP - 2
TERMINAL KILL

| ANIMAL NUMBER | BODY WEIGHT | BRAIN | THYROID | HEART | LIVER | SPLEEN | KIDNEYS | ADRENALS | TESTES |
|---|---|---|---|---|---|---|---|---|---|
| 0405 | 12000.0 | 79.2890 | 0.6820 | 87.8710 | 327.2300 | 87.3910 | 61.4320 | 0.9310 | 19.2260 |
| 0406 | 12400.0 | 100.3700 | 0.6900 | 91.4000 | 289.9700 | 100.7200 | 63.4200 | 1.1700 | 20.4700 |
| 0407 | 10900.0 | 86.6800 | 0.8100 | 91.9100 | 335.9300 | 66.1100 | 67.2000 | 1.3400 | 24.1400 |
| 0415 | 11200.0 | 89.8100 | 0.9100 | 81.1400 | 258.5300 | 127.7700 | 49.0900 | 0.8100 | 19.9800 |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| MEAN | 11625.0 | 89.0372* | 0.7730 | 88.0802 | 302.9150 | 95.4977 | 60.2855 | 1.0752 | 20.9540 |
| S.D. | 694.6 | 8.7486 | 0.1085 | 4.9632 | 35.6782 | 25.8078 | 7.8377 | 0.2577 | 2.1848 |
| S.E. | 347.3 | 4.3743 | 0.0542 | 2.4816 | 17.8391 | 12.9039 | 3.9189 | 0.1288 | 1.0924 |

*p<0.05 as compared to controls: Dunnett's t-test.

TABLE 7 (CONTINUED)

PROJECT NO. 1073409
ORGAN WEIGHTS IN MALE DOGS (GRAMS)
DOSE - 300 PPM
GROUP - 3
TERMINAL KILL

| ANIMAL NUMBER | BODY WEIGHT | BRAIN | THYROID | HEART | LIVER | SPLEEN | KIDNEYS | ADRENALS | TESTES |
|---|---|---|---|---|---|---|---|---|---|
| 0404 | 10800.0 | 79.9230 | 0.8040 | 90.3000 | 318.4690 | 92.5170 | 49.3080 | 0.8760 | 18.3230 |
| 0409 | 9400.0 | 82.2420 | 0.3350 | 76.7530 | 250.7610 | 87.2330 | 57.9380 | 0.4100 | 15.7750 |
| 0412 | 6700.0 | 84.1800 | 0.5000 | 68.9300 | 233.9900 | 96.8500 | 45.3700 | 1.8500 | 17.0000 |
| 0414 | 10400.0 | 93.2900 | 0.8400 | 93.4000 | 285.1100 | 81.6300 | 62.3300 | 1.3500 | 25.4800 |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| MEAN | 9825.0 | 84.9087 | 0.6197 | 82.3457 | 272.0825 | 89.5575 | 53.7365 | 1.1215 | 19.1445 |
| S.D. | 953.5 | 5.8522 | 0.2435 | 11.4997 | 37.53o9 | 6.5876 | 7.7698 | 0.6190 | 4.3499 |
| S.E. | 476.8 | 2.9261 | 0.1218 | 5.7498 | 18.7685 | 3.2938 | 3.8849 | 0.3095 | 2.1750 |

## TABLE II-F-50 (Continued)

TABLE 7 (CONTINUED)

PROJECT NO. 1073409
ORGAN WEIGHTS IN MALE DOGS (GRAMS)
DOSE - 1000 PPM
GROUP - 4
TERMINAL KILL

| ANIMAL NUMBER | BODY WEIGHT | BRAIN | THYROID | HEART | LIVER | SPLEEN | KIDNEYS | ADRENALS | TESTES |
|---|---|---|---|---|---|---|---|---|---|
| 0419 | 10600.0 | 77.5800 | 0.8200 | 74.0900 | 270.6200 | 85.5100 | 48.6000 | 1.0400 | 14.3700 |
| 0416 | 9400.0 | 79.3500 | 0.4100 | 75.6700 | 305.8500 | 87.4800 | 56.6200 | 1.6500 | 22.3000 |
| 0413 | 10700.0 | 77.4270 | 0.7710 | 95.9420 | 292.5060 | 132.3990 | 63.3780 | 0.9330 | 21.6440 |
| 0420 | 10900.0 | 82.5300 | 0.5900 | 78.5600 | 274.8400 | 84.6500 | 55.0200 | 0.7400 | 16.4300 |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| MEAN | 10400.0 | 79.2218 | 0.6477 | 81.0655 | 285.9540 | 97.5097 | 55.9045 | 1.0907 | 18.6860 |
| S.D. | 678.2 | 2.3719 | 0.1868 | 10.0689 | 16.3037 | 23.2896 | 6.0691 | 0.3930 | 3.8956 |
| S.E. | 339.1 | 1.1859 | 0.0934 | 5.0444 | 8.1518 | 11.6448 | 3.0346 | 0.1965 | 1.9478 |

## TABLE II-F-50 (Continued)

TABLE 7 (CONTINUED)

PROJECT NO. 1073409
ORGAN WEIGHTS IN FEMALE DOGS (GRAMS)
DOSE - 0 PPM
GROUP - 1
TERMINAL KILL

| ANIMAL NUMBER | BODY WEIGHT | BRAIN | THYROID | HEART | LIVER | SPLEEN | KIDNEYS | ADRENALS | OVARIES |
|---|---|---|---|---|---|---|---|---|---|
| 0425 | 8300.0 | 76.0080 | 0.5500 | 65.0220 | 229.6410 | 96.0820 | 41.0390 | 0.9580 | 0.1490 |
| 0426 | 7600.0 | 64.0300 | 0.5800 | 65.2500 | 224.8400 | 88.1400 | 44.7900 | 0.9800 | 0.5300 |
| 0434 | 7900.0 | 73.1700 | 0.5300 | 71.3600 | 210.8000 | 86.1300 | 42.0700 | 0.6400 | 0.5500 |
| 0435 | 6400.0 | 68.6700 | 0.3100 | 68.3700 | 203.3700 | 52.5300 | 28.3400 | 0.9200 | 0.5600 |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| MEAN | 7550.0 | 75.4695 | 0.4940 | 67.5255 | 217.1627 | 80.7205 | 39.0597 | 0.8745 | 0.4472 |
| S.D. | 816.5 | 6.4574 | 0.1244 | 3.2097 | 12.1843 | 19.2786 | 7.3196 | 0.1583 | 0.1992 |
| S.E. | 409.3 | 3.2287 | 0.0622 | 1.6048 | 6.0921 | 9.6393 | 3.6598 | 0.0791 | 0.0996 |

TABLE II-F-50 (Continued)

TABLE 7 (CONTINUED)

PROJECT NO. 1073409
ORGAN WEIGHTS IN FEMALE DOGS (GRAMS)
DOSE - 100 PPM
GROUP - 2
TERMINAL KILL

| ANIMAL NUMBER | BODY WEIGHT | BRAIN | THYROID | HEART | LIVER | SPLEEN | KIDNEYS | ADRENALS | OVARIES |
|---|---|---|---|---|---|---|---|---|---|
| 0422 | 8700.0 | 70.9690 | 0.5450 | 68.4280 | 227.3220 | 63.3320 | 35.0820 | 0.8030 | 1.1070 |
| 0429 | 9600.0 | 84.7690 | 0.6980 | 75.1000 | 303.8470 | 90.0000 | 42.2570 | 0.8880 | 1.3080 |
| 0430 | 9100.0 | 79.7000 | 1.0000 | 69.3300 | 241.8500 | 81.7900 | 47.5600 | 1.2100 | 2.0400 |
| 0431 | 7800.0 | 81.9400 | 0.5400 | 62.7100 | 250.0700 | 71.1300 | 39.0900 | 0.8500 | 1.3000 |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| MEAN | 8800.0 | 79.3445 | 0.6957 | 68.8920 | 255.7722 | 76.5630 | 40.9972 | 0.7627 | 1.4387 |
| S.D. | 761.6 | 5.9564 | 0.2157 | 5.0716 | 33.4013 | 11.7253 | 5.2689 | 0.4241 | 0.4115 |
| S.E. | 380.8 | 2.9782 | 0.1078 | 2.5358 | 16.7007 | 5.8627 | 2.6345 | 0.2121 | 0.2057 |

## TABLE II-F-50 (Continued)

**TABLE 7 (CONTINUED)**

PROJECT NO. [illegible]
[illegible] WEIGHTS [illegible] FEMALE DOGS (GRAMS)
DOSE - [illegible] PPM
[illegible]
TERMINAL KILL

| ANIMAL NUMBER | BODY WEIGHT | BRAIN | THYROID | HEART | LIVER | SPLEEN | KIDNEYS | ADRENALS | OVARIES |
|---|---|---|---|---|---|---|---|---|---|
| 0421 | 10[illegible].0 | 77.2550 | 0.7500 | 72.5550 | 307.5570 | 62.4[illegible] | 48.2370 | 0.9030 | 3.0510 |
| 0424 | 7600.0 | 74.9100 | 0.7200 | 71.3500 | 249.4200 | 110.3400 | 43.4400 | 0.7600 | 0.0100 |
| 0427 | 7300.0 | 70.7000 | 0.6300 | 54.0000 | 223.1300 | 80.9000 | 39.6000 | 0.6900 | 0.9300 |
| 0430 | 9400.0 | 84.4100 | 0.4700 | 60.1200 | 229.8300 | 93.8000 | 39.2100 | 0.6700 | 0.7500 |
| . | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| MEAN | 8650.0 | 76.2765 | 0.6425 | 64.5087 | 252.6592 | 91.7350 | 42.5392 | 0.8057 | 1.4852 |
| S.D. | 1634.0 | 4.[illegible]0 | 0.1250 | 8.4097 | 38.4713 | 13.5750 | 4.2027 | 0.0984 | 1.4496 |
| S.E. | 817.0 | 2.1200 | 0.0625 | 4.4849 | 19.2357 | 6.7693 | 2.1315 | 0.0492 | 0.7249 |

## TABLE II-F-50 (Continued)

TABLE 7 (CONTINUED)
PROJECT NO. 1073409
ORGAN WEIGHTS IN FEMALE DOGS (GRAMS)
DOSE - 1000 PPM
GROUP - 4
TERMINAL KILL

| ANIMAL NUMBER | BODY WEIGHT | BRAIN | THYROID | HEART | LIVER | SPLEEN | KIDNEYS | ADRENALS | OVARIES |
|---|---|---|---|---|---|---|---|---|---|
| 0432 | 7400.0 | 75.6790 | 0.9490 | 81.2840 | 213.0240 | 136.4550 | 46.2180 | 1.0210 | 0.5970 |
| 0436 | 7900.0 | 0.0[b] | 0.5000 | 53.6200 | 199.5000 | 77.0900 | 39.2500 | 0.9800 | 1.0200 |
| 0437 | 8800.0 | 72.4700 | 0.5700 | 72.9500 | 254.5200 | 95.7400 | 41.0700 | 0.7800 | 0.5300 |
| 0423 | 7600.0 | 69.2230 | 0.4360 | 56.0610 | 206.0600 | 57.4130 | 39.1030 | 0.3170 | 0.9450 |
| N | 4 | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| MEAN | 7925.0 | 72.4573 | 0.6137 | 65.9787 | 218.2760 | 91.6745 | 41.4102 | 0.7745 | 0.7730 |
| S.D. | 618.5 | 3.2280 | 0.2301 | 13.3410 | 24.7856 | 33.7065 | 3.3277 | 0.3227 | 0.2454 |
| S.E. | 309.2 | 1.8637 | 0.1151 | 6.6705 | 12.3928 | 16.8532 | 1.6638 | 0.1613 | 0.1227 |

[b] Weight not taken.

# TABLE II-F-51

TABLE 8
PROJECT NO. 1073409
ORGAN WEIGHT-BODY WEIGHT PERCENTAGES IN MALE DOGS
DOSE - 0 PPM
GROUP - 1
TERMINAL KILL

| ANIMAL NUMBER | BRAIN | THYROID | HEART | LIVER | SPLEEN | KIDNEYS | ADRENALS | TESTES |
|---|---|---|---|---|---|---|---|---|
| 0408 | 0.4892 | 0.0[a] | 0.7103 | 2.8407 | 0.4722 | 0.5177 | 0.0072 | 0.1467 |
| 0411 | 0.8256 | 0.0106 | 0.7328 | 3.0761 | 0.5965 | 0.5005 | 0.0073 | 0.1614 |
| 0417 | 0.8327 | 0.0073 | 0.9276 | 2.9022 | 0.7993 | 0.6250 | 0.0089 | 0.2099 |
| 0419 | 0.9136 | 0.0106 | 0.8960 | 3.1124 | 1.1988 | 0.6764 | 0.0218 | 0.2616 |
| N | 4 | 3 | 4 | 4 | 4 | 4 | 4 | 4 |
| MEAN | 0.7653 | 0.0095 | 0.8167 | 2.9828 | 0.7667 | 0.5799 | 0.0113 | 0.1949 |
| S.D. | 0.1883 | 0.0019 | 0.1110 | 0.1319 | 0.3181 | 0.0847 | 0.0071 | 0.0520 |
| S.E. | 0.0942 | 0.0011 | 0.0555 | 0.0659 | 0.1590 | 0.0424 | 0.0035 | 0.0260 |

[a]Left thyroid not located.

# TABLE II-F-51 (Continued)

TABLE 8 (CONTINUED)

PROJECT NO. 1073435
ORGAN WEIGHT-BODY WEIGHT PERCENTAGES IN TABLE 3000
DOSE = 100 PPM
GROUP = 2
TERMINAL KILL

| ANIMAL NUMBER | BRAIN | THYROID | HEART | LIVER | SPLEEN | KIDNEYS | ADRENALS | TESTES |
|---|---|---|---|---|---|---|---|---|
| 0405 | 0.6607 | 0.0057 | 0.7323 | 2.7209 | 0.7283 | 0.5119 | 0.0078 | 0.1602 |
| 0406 | 0.6394 | 0.0056 | 0.7371 | 2.3385 | 0.6123 | 0.5115 | 0.0094 | 0.1651 |
| 0407 | 0.7952 | 0.0074 | 0.8432 | 3.0919 | 0.6263 | 0.6165 | 0.0128 | 0.2215 |
| 0415 | 0.8019 | 0.0051 | 0.7243 | 2.3053 | 1.1406 | 0.4383 | 0.0072 | 0.1784 |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| MEAN | 0.7668 | 0.0047 | 0.7592 | 2.6134 | 0.8220 | 0.5196 | 0.0093 | 0.1813 |
| S.D. | 0.0710 | 0.0013 | 0.0362 | 0.3656 | 0.2257 | 0.0733 | 0.0025 | 0.0279 |
| S.E. | 0.0355 | 0.0006 | 0.0281 | 0.1828 | 0.1144 | 0.0367 | 0.0012 | 0.0139 |

## TABLE II-F-51 (Continued)

**TABLE 8 (CONTINUED)**

PROJECT NO. 1073404

ORGAN WEIGHT-TO-BODY WEIGHT PERCENTAGES IN MALE DOGS

DOSE - 300 PPM

WEEK -

TERMINAL KILL

| ANIMAL NUMBER | BRAIN | THYROID | HEART | LIVER | SPLEEN | KIDNEYS | ADRENALS | TESTES |
|---|---|---|---|---|---|---|---|---|
| 0404 | 0.7400 | 0.0074 | 0.8361 | 2.9448 | 0.8596 | 0.4566 | 0.0091 | 0.1697 |
| 0405 | 0.6749 | 0.0036 | 0.8165 | 2.6677 | 0.9280 | 0.5104 | 0.0044 | 0.1678 |
| 0412 | 0.9470 | 0.0057 | 0.7923 | 2.6895 | 1.1132 | 0.5215 | 0.0213 | 0.1954 |
| 0414 | 0.8970 | 0.0081 | 0.8981 | 2.7414 | 0.7849 | 0.5993 | 0.0130 | 0.2450 |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| MEAN | 0.8647 | 0.0062 | 0.8358 | 2.7614 | 0.9207 | 0.5444 | 0.0117 | 0.1945 |
| S.D. | 0.0954 | 0.0020 | 0.0452 | 0.1284 | 0.1410 | 0.0738 | 0.0073 | 0.0360 |
| S.E. | 0.0477 | 0.0010 | 0.0226 | 0.0642 | 0.0705 | 0.0369 | 0.0036 | 0.0180 |

## TABLE II-F-51 (Continued)

TABLE 8 (CONTINUED)

PROJECT NO. 1073407
ORGAN WEIGHT-BODY WEIGHT PERCENTAGES IN MALE DOGS
DOSE - 1000 PPM
GROUP - 4
TERMINAL KILL

| ANIMAL NUMBER | BRAIN | THYROID | HEART | LIVER | SPLEEN | KIDNEYS | ADRENALS | TESTES |
|---|---|---|---|---|---|---|---|---|
| 0419 | 0.7319 | 0.0077 | 0.6990 | 2.5530 | 0.2067 | 0.4585 | 0.0096 | 0.1350 |
| 0416 | 0.8441 | 0.0044 | 0.8050 | 3.2537 | 0.4830 | 0.6023 | 0.0176 | 0.2372 |
| 0413 | 0.7236 | 0.0072 | 0.8967 | 2.7537 | 1.2374 | 0.5923 | 0.0087 | 0.2023 |
| 0420 | 0.7572 | 0.0054 | 0.7207 | 2.5215 | 0.7705 | 0.5048 | 0.0056 | 0.1507 |
| | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| MEAN | 0.7642 | 0.0062 | 0.7803 | 2.7655 | 0.6744 | 0.5395 | 0.0107 | 0.1815 |
| S.D. | 0.0552 | 0.0016 | 0.0900 | 0.3337 | 0.2105 | 0.0695 | 0.0047 | 0.0464 |
| S.E. | 0.0276 | 0.0008 | 0.0450 | 0.1669 | 0.1053 | 0.0348 | 0.0024 | 0.0234 |

## TABLE II-F-51 (Continued)

**TABLE 8 (CONTINUED)**

[illegible] NO. 107340.
MEAN FINAL-BODY WEIGHT PERCENTAGES FOR FEMALE DOGS
[illegible]
[illegible]
TERMINAL KILL

| ANIMAL NUMBER | BRAIN | THYROID | HEART | LIVER | SPLEEN | KIDNEYS | ADRENALS | OVARIES |
|---|---|---|---|---|---|---|---|---|
| 0425 | 0.9153 | 0.0067 | 0.7434 | 3.7669 | 1.1576 | 0.4944 | 0.0115 | 0.0018 |
| 0426 | 1.1057 | 0.0076 | 0.8546 | 2.9544 | 1.1597 | 0.5893 | 0.0129 | 0.0070 |
| 0434 | 0.8262 | 0.0067 | 0.9096 | 2.4684 | 1.0903 | 0.5325 | 0.0081 | 0.0070 |
| 0435 | 1.0730 | 0.0048 | 1.0083 | 3.1777 | 0.8206 | 0.4426 | 0.0144 | 0.0087 |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| MEAN | 1.0051 | 0.0065 | 0.7053 | 2.9923 | 1.0571 | 0.5148 | 0.0117 | 0.0061 |
| S.D. | 0.0982 | 0.0012 | 0.1206 | 0.2249 | 0.1606 | 0.0618 | 0.0027 | 0.0030 |
| S.E. | 0.0491 | 0.0006 | 0.0603 | 0.1124 | 0.0804 | 0.0309 | 0.0013 | 0.0015 |

## TABLE II-F-51 (Continued)

TABLE 8 (CONTINUED)

PROJECT NO. 1073409
ORGAN WEIGHT-BODY WEIGHT PERCENTAGES IN FEMALE DOGS
DOSE - 100 PPM
GROUP - 2
TERMINAL KILL

| ANIMAL NUMBER | BRAIN | THYROID | HEART | LIVER | SPLEEN | KIDNEYS | ADRENALS | OVARIES |
|---|---|---|---|---|---|---|---|---|
| 0422 | 0.8157 | 0.0063 | 0.7865 | 2.6129 | 0.7280 | 0.4032 | 0.0092 | 0.0127 |
| 0429 | 0.8830 | 0.0073 | 0.7823 | 3.1651 | 0.9375 | 0.4402 | 0.0020 | 0.0136 |
| 0430 | 0.8758 | 0.0110 | 0.7619 | 2.6577 | 0.8988 | 0.5226 | 0.0133 | 0.0224 |
| 0431 | 1.0505 | 0.0069 | 0.8040 | 3.2060 | 0.9119 | 0.5012 | 0.0109 | 0.0167 |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| MEAN | 0.9063 | 0.0079 | 0.7837 | 2.9104 | 0.8690 | 0.4668 | 0.0088 | 0.0164 |
| S.D. | 0.1008 | 0.0021 | 0.0173 | 0.3187 | 0.0954 | 0.0549 | 0.0049 | 0.0044 |
| S.E. | 0.0504 | 0.0011 | 0.0086 | 0.1593 | 0.0477 | 0.0275 | 0.0024 | 0.0022 |

## TABLE II-F-51 (Continued)

TABLE 8 (CONTINUED)

[illegible]

| ANIMAL NUMBER | BRAIN | THYROID | HEART | LIVER | SPLEEN | KIDNEYS | ADRENALS | OVARIES |
|---|---|---|---|---|---|---|---|---|
| 0421 | 0.7100 | 0.0006 | 0.4695 | 3.8916 | 0.7560 | 0.4423 | 0.0083 | 0.0335 |
| 0424 | 0.9960 | 0.0032 | 0.9149 | 5.1577 | 1.4145 | 0.5966 | 0.0047 | 0.0076 |
| 0427 | 1.0507 | 0.0026 | 0.7947 | 5.0561 | 1.1082 | 0.5384 | 0.0059 | 0.0127 |
| 0433 | 0.4961 | 0.0050 | 0.6346 | 2.4527 | 0.9426 | 0.4171 | 0.0093 | 0.0080 |
| | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| MEAN | 0.9031 | 0.0074 | 0.7493 | 4.8759 | 1.0578 | 0.4887 | 0.0092 | 0.0155 |
| S.D. | 0.1437 | 0.0019 | 0.1241 | 0.3314 | 0.2755 | 0.0693 | 0.0020 | 0.0122 |
| S.E. | 0.0719 | 0.0010 | 0.0620 | 0.1657 | 0.1380 | 0.0346 | 0.0003 | 0.0061 |

## TABLE II-F-51 (Continued)

TABLE 8 (CONTINUED)

PROJECT NO. 1073409
ORGAN WEIGHT-BODY WEIGHT PERCENTAGES IN FEMALE DOGS
DOSE - 1000 PPM
GROUP - 4
TERMINAL KILL

| ANIMAL NUMBER | BRAIN | THYROID | HEART | LIVER | SPLEEN | KIDNEYS | ADRE'LS | OVARIES |
|---|---|---|---|---|---|---|---|---|
| 0432 | 1.0227 | 0.0128 | 1.0984 | 2.8787 | 1.8440 | 0.6246 | 0.0138 | 0.0081 |
| 0436 | 0.0 [b] | 0.0063 | 0.6787 | 2.5253 | 0.9758 | 0.4968 | 0.0124 | 0.0129 |
| 0437 | 0.8235 | 0.0065 | 0.8290 | 2.8923 | 1.0880 | 0.4667 | 0.0089 | 0.0060 |
| 0423 | 0.9108 | 0.0057 | 0.7376 | 2.7113 | 0.7554 | 0.5145 | 0.0042 | 0.0124 |
| N | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| MEAN | 0.9190 | 0.0078 | 0.8359 | 2.7519 | 1.1658 | 0.5257 | 0.0098 | 0.0099 |
| S.D. | 0.0998 | 0.0033 | 0.1856 | 0.1720 | 0.4728 | 0.0688 | 0.0043 | 0.0034 |
| S.E. | 0.0576 | 0.0017 | 0.0928 | 0.0860 | 0.2364 | 0.0344 | 0.0021 | 0.0017 |

[b] Weight not taken.

SPONSOR: U.S. Army Medical Bioengineering R&D Laboratory

MATERIAL: Dicyclopentadiene (DCPD)

SUBJECT: CHEMISTRY REPORT
Analysis of Diet Formulations
LBI Project No. 10734-09

## 1. OBJECTIVE

The objective of this study was to analyze DCPD in animal chow with regard to stability and formulation content in diet.

## 2. MATERIALS

This method describes the analytical procedure for the determination of DCPD in dosed feed used by LBI during the course of the study. A 5 g feed subsample is extracted with 20 ml of diethyl ether by shaking for 15 minutes in an automated shaker. The extract is clarified by centrifugation for 10 minutes at 1350 rpm. The extracts are analyzed with a Varian 2100 gas chromatograph equipped with flame ionization detectors. The DCPD content is calculated from a calibration curve obtained by GLC analysis of reference solutions of DCPD in ether. Control and spiked control feed samples are analyzed concurrently to correct for possible feed background and compound recovery.

The following equipment and supplies were used.

a. Graduated conical Falcon tubes, 50 ml, with positive seal caps (available from Becton, Dickinson and Company, Oxnard, CA, 93030; stock number H8292-209811).

b. Volumetric glassware - 1, 4, 5 and 10 ml pipettes; 50 and 100 ml flasks.

c. Graduated cylinder - 25 ml capacity.

d. Graduated glass centrifuge tubes, 15 ml, with ground glass stoppers.

e. Mechanical shaker.

f. Centrifuge.

g. Analytical laboratory balance (accurate to 0.01 mg).

h. Top-loading laboratory balance (accurate to 0.01 g).

2. MATERIALS (Continued)

i. Gas-liquid chromatograph - Varian 2100, equipped with a 1.8 m x 2 mm I.D. glass column packed with 10% FFAP on 80/100 mesh Supelcoport, flame ionization detectors.

j. Diethyl ether (Burdick and Jackson).

k. Dicyclopentadiene.

3. EXPERIMENTAL DESIGN

A stock standard solution of DCPD is prepared by dissolving 50 mg of DCPD in 50 ml of acetone. Take a 5 ml aliquot and dilute to 100 ml with diethyl ether in a volumetric flask. This solution has a concentration of 0.05 mg/ml. Prepare a standard curve by injecting 1, 2 and 3 µl of the standard solution into a Varian 2100 gas chromatograph with the following parameters:

| | |
|---|---|
| Column temperature: | 60°C |
| Injector temperature: | 225°C |
| FID temperature: | 250°C |
| Chart: | 6 min/inch |
| Carrier gas flow: | 40 cc/min nitrogen |
| Attn.: | 8 x $10^{-11}$ |

Then weigh a 5 g sample of the dosed feed to the nearest 0.01 g in a Falcon tube. Extract the sample with 20 ml of diethyl ether by mixing for 15 minutes in a mechanical shaker, followed by centrifugation at 1300 rpm for 10 minutes. Dilute the high dose level (750 ppm) in a 15 ml graduated centrifuge tube by adding a 1 ml aliquot to 4 ml of diethyl ether. Repeat this procedure using undosed animal feed of the same lot used for the preparation of the dosed feed. This extract will be used as a negative control to assure that there are no interfering peaks contributed by the feed itself. Repeat this procedure using undosed animal feed of the same lot which has been spiked in the laboratory with DCPD at corresponding dose levels.

Quantitate the amount of DCPD in solution by comparing to the calibration curve previously prepared.

Calculate the ppm of DCPD in the dosed feed or spiked (recovery) sample as follows:

To determine mg of sample injected:

$$\frac{5 \text{ g feed}}{20 \text{ ml ether}} = \frac{250 \text{ mg feed}}{1.0 \text{ ml ether}}$$

$$\frac{250 \text{ mg feed}}{1.0 \text{ ml ether}} \times \text{Dilution Factor} = \frac{(x) \text{ mg feed}}{1.0 \text{ ml ether}}$$

3. EXPERIMENTAL DESIGN (Continued)

Dilution Factor = 1 for 80 ppm level
= 0.2 for 750 ppm level

$$\frac{(x)\text{ mg feed}}{1.0\text{ ml ether}} \times \frac{\mu\text{l sample}}{1000} = \text{mg of feed injected}$$

Calculate the intercept and slope from standard curve as determined by linear regression correlation.

$$\frac{\text{peak response (peak height) - intercept}}{\text{slope}} = \text{ng of DCPD injected}$$

To determine ppm:

$$\frac{\text{ng of DCPD found}}{\text{mg of feed injected}} = \text{ppm}$$

Determine method of recovery from spiked samples as follows:

$$\text{percent recovery} = \frac{\text{ppm found x 100}}{\text{ppm added}}$$

Correct the result of the dosed feed sample for method recovery of its corresponding spiked sample.

$$\text{corrected ppm} = \frac{\text{sample ppm x 100}}{\text{percent recovery}}$$

4. RESULTS

DCPD samples were analyzed on a weekly basis by the method previously described. Samples were received by the analytical laboratory and frozen until day of analysis. This action was required due to the volatile nature of the compound. Results of the analysis are indicated in Table 1.

For the 100 ppm level, the average value obtained was 97.7±7.2 ppm, which corresponds to 97.7±7.2% of the theoretical value. For the 300 ppm level, the average value obtained was 303±15 ppm, which corresponds to 101±0.5% of the theoretical value. For the 1000 ppm level, the average value obtained was 991±55 ppm, which is equivalent to 99.1±5.5% of the theoretical value.

Submitted by:

Harold Tanner Jr 03/04/80

J.D. Mitchell Date
Analytical Chemist

Reviewed by:

Jerry M Fitzgerald 3/4/80

Jerry M. Fitzgerald, Ph.D. Date
Head, Analytical
Chemistry Section

Approved by:

James L. Liverman 3/4/80

James Liverman, Ph.D. Date
Acting Director
Department of Chemistry

TABLE II-F-52

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE 1

WEEKLY DCPD FEED ANALYSIS

| MIX DATE | ANALYSIS DATE | SAMPLE NUMBER | DOSAGE (PPM) | ANALYSIS VALUE (PPM)[a] |
|---|---|---|---|---|
| 05/10/78 | 05/12/78 | R0034K78 | 0 | 0 |
| | | R0035K78 | 100 | 90.1 |
| | | R0036K78 | 300 | 303 |
| | | R0037K78 | 1000 | 946 |
| 05/18/78 | 05/19/78 | R0049K78 | 0 | 0 |
| | | R0050K78 | 100 | 96.1 |
| | | R0051K78 | 300 | 304 |
| | | R0052K78 | 1000 | 996 |
| 05/25/78 | 05/26/78 | R0062K78 | 0 | 0 |
| | | R0063K78 | 100 | 94.7 |
| | | R0064K78 | 300 | 303 |
| | | R0065K78 | 1000 | 919 |
| 06/01/78 | 06/02/78 | R0072K78 | 0 | 0 |
| | | R0073K78 | 100 | 106 |
| | | R0074K78 | 300 | 280 |
| | | R0075K78 | 1000 | 931 |
| 06/08/78 | 06/11/78 | R0089K78 | 0 | 0 |
| | | R0090K78 | 100 | 107 |
| | | R0091K78 | 300 | 325 |
| | | R0092K78 | 1000 | 1011 |
| 06/14/78 | 06/19/78 | R0097K78 | 0 | 0 |
| | | R0098K78 | 100 | 98.4 |
| | | R0099K78 | 300 | 321 |
| | | R0100K78 | 1000 | 992 |
| 06/21/78 | 06/28/78 | R0117K78 | 0 | 0 |
| | | R0118K78 | 100 | 93.4 |
| | | R0119K78 | 300 | 281 |
| | | R0120K78 | 1000 | 1037 |
| 06/28/78 | 07/05/78 | R0136K78 | 0 | 0 |
| | | R0137K78 | 100 | 103 |
| | | R0138K78 | 300 | 296 |
| | | R0139K78 | 1000 | 996 |
| 07/05/78 | 07/08/78 | R0150K78 | 0 | 0 |
| | | R0151K78 | 100 | 105.2 |
| | | R0152K78 | 300 | 285 |
| | | R0153K78 | 1000 | 1019 |

[a]All values have been corrected for respective method recovery, run simultaneously with analysis.

TABLE II-F-52 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE 1 (CONTINUED)

WEEKLY DCPD FEED ANALYSIS

| MIX DATE | ANALYSIS DATE | SAMPLE NUMBER | DOSAGE (PPM) | ANALYSIS VALUE (PPM)[a] |
|---|---|---|---|---|
| 07/12/78 | 07/16/78 | R0180K78 | 0 | 0 |
| | | R0181K78 | 100 | 101 |
| | | R0182K78 | 300 | 314 |
| | | R0183K78 | 1000 | 915 |
| 07/19/78 | 07/24/78 | R0189K78 | 0 | 0 |
| | | R0190K78 | 100 | 92.6 |
| | | R0191K78 | 300 | 279 |
| | | R0192K78 | 1000 | 952 |
| 07/26/78 | 07/28/78 | R0223K78 | 0 | 0 |
| | | R0224K78 | 100 | 100 |
| | | R0225K78 | 300 | 309 |
| | | R0226K78 | 1000 | 1061 |
| 08/02/78 | 08/04/78 | R0263K78 | 0 | 0 |
| | | R0264K78 | 100 | 107 |
| | | R0265K78 | 300 | 320 |
| | | R0266K78 | 1000 | 1095 |
| 08/09/78 | 08/13/78 | R0323K78 | 0 | 0 |
| | | R0324K78 | 100 | 82.2 |
| | | R0325K78 | 300 | 300 |
| | | R0326K78 | 1000 | 945 |

[a]All values have been corrected for respective method recovery, run simultaneously with analysis.

DIPLOMATE: AMERICAN COLLEGE
OF VETERINARY OPHTHALMOLOGISTS

JAMES M. CLINTON, V. M. D.
300 BROOKMEAD DRIVE
CHERRY HILL, NEW JERSEY 08034

AREA CODE 609
TELEPHONE 429-7798

Litton Bionetic Inc.
Project 10734-09
Robert P. Beliles, Ph.D.
Elliot Gordon, Ph.D.

9 January 1978

OPHTHALMOSCOPIC SUMMARY

Both eyes of 34 Beagle dogs were examined by focal illumination, indirect ophthalmoscopy and, when indicated, slit-lamp microscopy. Mydriasis was produced with 1% tropicamide (Mydriacyl 1%, Alcon, expir. date July, 1979). The examination was conducted in a darkened room 229, and darkness maintained until the following day. The dogs examined were eartag numbered as follows:

| Male dog | Female dog |
|---|---|
| GB77 | LL77 |
| NW77 | OU77 |
| LS77 | EZ77 |
| LT77 | JL77 |
| KK77 | LO77 |
| LI77 | HO77 |
| OL77 | PF77 |
| MK77 | FJ77 |
| PI77 | AS77 |
| MM77 | EI77 |
| FF77 | AR77 |
| DI77 | IT77 |
| OJ77 | OH77 |
| QS77 | IR77 |
| NY77 | GL77 |
| PK77 | FO77 |
| MB77 | LB77 |

Female dog JL77 has a bilateral epiphora, mainly in the left eye, and female dog HO77 has a slight mucinous exudate in each ventral conjunctival sac. Such findings occasionally precede abnormalities in the precorneal tear film. Both eyes of these two dogs are normal now, however. The findings are not likely to be of major significance in a 90 day study, but because of the known association between the ocular discharge and subsequent changes in the precorneal tear film, I would recommend that if dogs JL77 and HO77 are used, they not be used in the high dose group. The remaining 32 dogs are ophthalmoscopically normal and clinically visual.

James M. Clinton

DIPLOMATE: AMERICAN COLLEGE
OF VETERINARY OPHTHALMOLOGISTS

JAMES M. CLINTON, V. M. D.
300 BROOKMEAD DRIVE
CHERRY HILL, NEW JERSEY 08034

AREA CODE 609
TELEPHONE 429-7788

Litton Bionetics Inc. 11 August 1978
Project 10734-09
Robert P. Belilos, Ph. D.
D. Djurickovic, D.V.M.

FINAL
OPHTHALMOSCOPIC SUMMARY

Both eyes of 16 male and 16 female adult Beagle dogs were examined by focal illumination, indirect ophthalmoscopy and, when indicated, slit-lamp microscopy. Mydriasis was produced with 1% tropicamide (1% Mydriacyl, Alcon, lot ZJC, Oct. 1979) and the eyes examined in a darkened room. Dr. Djurickovic participated fully in the examinations.

The following dogs were ophthalmoscopically normal:

434. 417, 418, 408, 425, 426, 429, 431,407, 419, 420, 412, 414, 436, 424, 427, 406. 415, 433, 409, 437, 423, 416,404, 421, 411 and 435.

Ocular abnormalities were found in the following dogs:

| Dog | Sex | Observations |
|---|---|---|
| 422 | F | Left eye: ghost vessels emanating from the limbus, 9 to 2 o'clock |
| 432 | F | Right eye: cluster of punctate superficial corneal opacities |
| 405 | F | Left eye: cluster of superficial punctate opacities forming a band in the central cornea |
| 430 | F | Left eye: Occasional ghost vessels in temporal quadrant of cornea |
| 413 | M | Right eye: cluster of superficial punctate paracentral corneal opacities |

COMMENTS

Both eyes of all 32 dogs are visual. The ghost vessels in 422 and 430 indicate a prior but now inactive keratitis. The ghost vessels are permanent and should be detectable histologically. The superficial corneal opacities may be sequelae to corneal trauma and should gradually disappear. The lesions observed in the five dogs described above are minor.

At this juncture, I do not believe that the compound being evaluated according to this protocol produces ocular changes in dogs.

James M. Clinton

James M. Clinton, V.M.D.

SUBJECT: FINAL PATHOLOGY REPORT
Mammalian Toxicological Evaluation of DIMP and DCPD
LBI Project No. 10734-09

This report summarizes histopathologic findings in a total of sixteen dogs. Four each males and females, were given 1000 ppm of DCPD in the diet for 3 months. Eight similar dogs served as controls. Tissues collected at necropsy were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned at 5-6 microns and stained with hematoxylin and eosin by standard methods. The following tissues were examined histopathologically: unusual lesions, brain, spinal cord, pituitary gland, sciatic nerve, kidneys, adrenal glands, liver, spleen, pancreas, lung, heart, stomach, small intestine, colon, cecum, mesenteric lymph node, gallbladder, urinary bladder, skin and mammary gland, skeletal muscle, thyroid, testes with epididymis or ovary, prostate or uterus, eye, rib junction and sternum. At least one of the latter two specimens contained bone marrow.

There were few lesions in this group of dogs and none were considered to be related to administration of the compound. Several dogs in both the high dose and control groups had small inflammatory foci in the lungs. Some of these lesions were associated with aspirated foreign material (probably dry food). One dog had an intact, apparently viable nematode in the lung, and there was a minimal inflammatory reaction associated with the parasite. In the majority of the dogs it was not possible to determine the precise cause of the inflammatory lesions in the lungs.

A few dogs in both groups had small cysts in the pituitary glands. These cysts, considered to be cystic Rathke's pouch remnants, are quite common in dogs and are of no clinical significance.

One female in the high dose group had chronic active inflammation of the kidney, renal pelvis and urinary bladder. Such pyelonephritis and cystitis are relatively common spontaneous lesions in dogs and usually are produced by various bacterial pathogens in the lower urinary tract.

Mild hydrocephalus was noted when the brain of one high dose female was trimmed for embedding. This relatively common spontaneous condition often is of unknown etiology, as in the present case. It appears most commonly in young dogs such as those used in this study.

All other lesions were insignificant incidental findings or part of spontaneous disease complexes of dogs. This study indicates that DCPD administered at 1000 ppm in the diet for 3 months produces no discernible histopathologic lesions in dogs.

SUBMITTED BY:

G. A. Parker

27 Dec 1978
Date

George A. Parker, D.V.M.
Veterinary Pathologist

REVIEWED BY:

Richard H. Cardy

2 JAN 79
Date

Richard H. Cardy, D.V.M.
Director
Department of Pathology

# TABLE II-F-53

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE 1

INCIDENCE OF HISTOLOGIC FINDINGS

| GROUP NUMBER<br>SEX<br>NUMBER OF ANIMALS EXAMINED | GROUP 1<br>MALES<br>4 | GROUP 4<br>MALES<br>4 | GROUP 1<br>FEMALES<br>4 | GROUP 4<br>FEMALES<br>4 |
|---|---|---|---|---|
| BRAIN | 4* | 4* | 4* | 4* |
| Hydrocephalus | - | - | - | 1 |
| Mineralization, periarteriolar, focal | - | - | - | 1 |
| PITUITARY GLAND | 4* | 4* | 4* | 4* |
| Cyst(s) | - | 2 | 3 | 1 |
| KIDNEYS | 4* | 4* | 4* | 4* |
| Fibrosis, interstitial | - | - | - | 1 |
| Inflammation, nonsuppurative | - | - | - | 1 |
| LIVER | 4* | 4* | 4* | 4* |
| Eosinophilic leukocyte infiltrate | 1 | - | - | - |
| LUNGS | 4* | 4* | 4* | 4* |
| Inflammation, interstitial | 2 | 1 | 3 | 4 |
| Granuloma, mineralized | - | 1 | - | - |
| Parasitism, nematodiasis | - | - | - | 1 |
| HEART | 4* | 4* | 4* | 4* |
| Lymphocytic inflammatory infiltrate | 1 | - | - | - |
| SMALL INTESTINE | 4* | 4* | 4* | 4* |
| Eosinophilic leukocyte infiltrate | - | 1 | - | - |
| MESENTERIC LYMPH NODE | 4* | 4* | 4* | 4* |
| Eosinophilic leukocyte infiltrate | 1 | 1 | - | - |
| URINARY BLADDER | 4* | 4* | 4* | 4* |
| Hemorrhage, acute | - | - | - | 1 |
| Inflammation, nonsuppurative | - | - | - | 1 |
| Hyperplasia, mucosal | - | - | - | 1 |

* Number of tissues examined.

## TABLE II-F-53 (Continued)

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE 1 (continued)

| GROUP NUMBER<br>SEX<br>NUMBER OF ANIMALS EXAMINED | GROUP 1<br>MALES<br>4 | GROUP 4<br>MALES<br>4 | GROUP 1<br>FEMALES<br>4 | GROUP 4<br>FEMALES<br>4 |
|---|---|---|---|---|
| THYROIDS | 3* | 4* | 4* | 4* |
| Cystic remnant, ultimobranchial duct | - | - | - | 1 |
| PARATHYROIDS (NOT TAKEN ROUTINELY) | | | | 1* |
| Cystic remnant, ultimobranchial duct | | | | 1 |

* Number of tissues examined.

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

LEGEND TO SUMMARY OF HISTOLOGIC FINDINGS

| | | |
|---|---|---|
| - | = | negative finding in a designated tissue or organ; tissue examined. |
| + | = | positive finding (ungraded lesion) encountered in a designated tissue or organ. |
| NP | = | glandular tissue not present in plane of section. |
| NR | = | tissue not received for trimming. |
| 1 | = | positive finding graded "minimal". |
| 2 | = | positive finding graded "mild". |
| 3 | = | positive finding graded "moderate". |

# TABLE II-F-54

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE 2

SUMMARY OF HISTOLOGIC FINDINGS

| GROUP NUMBER | GROUP 1 MALES | | | | GROUP 4 MALES | | | | GROUP 1 FEMALES | | | | GROUP 4 FEMALES | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SEX / ANIMAL NUMBER | 408 | 411 | 417 | 418 | 413 | 416 | 419 | 420 | 425 | 426 | 434 | 435 | 423 | 432 | 436 | 436 |
| BRAIN | | | | | | | | | | | | | 2 | | | |
| Hydrocephalus | | | | | | | | | | | | | 1 | | | |
| Mineralization, periarteriolar, focal | | | | | | | | | | | | | | | | |
| SPINAL CORD | | | | | | | | | | | | | | | | |
| PITUITARY GLAND | | | | | | | + | + | + | + | + | | | | + | |
| Cyst(s) | | | | | | | | | | | | | | | | |
| SCIATIC NERVE | | | | | | | | | | | | | | | | |
| KIDNEYS | | | | | | | | | | | | | 3 | | | |
| Fibrosis, interstitial, radial | | | | | | | | | | | | | 3 | | | |
| Inflammation, nonsuppurative | | | | | | | | | | | | | | | | |
| ADRENAL GLANDS | | | | | | | | | | | | | | | | |
| LIVER | | | 1 | | | | | | | | | | | | | |
| Eosinophilic leukocyte infiltrate, focal | | | | | | | | | | | | | | | | |
| SPLEEN | | | | | | | | | | | | | | | | |
| PANCREAS | | | | | | | | | | | | | | | | |
| LUNGS | | | | | | | | | 2 | 1 | 2 | | 2 | 2 | 1 | 2 |
| Inflammation, interstitial, multifocal | 1 | | | | | 2 | | | | | | | | | | |
| Inflammation, interstitial, focal | | 1 | | | | | 1 | | | | | | | | 2 | |
| Granuloma, mineralized | | | | | | | | | | | | | | | | |
| Parasitism, nematodiasis | | | | | | | | | | | | | | | | |

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE 2 (continued)

| GROUP NUMBER | GROUP 1 MALES | | | | GROUP 4 MALES | | | | GROUP 1 FEMALES | | | | GROUP 4 FEMALES | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SEX | | | | | | | | | | | | | | | | |
| ANIMAL NUMBER | 408 | 411 | 417 | 418 | 413 | 416 | 419 | 420 | 425 | 426 | 434 | 435 | 423 | 432 | 436 | 436 |
| HEART | | | | | | | | | | | | | | | | |
| Lymphocytic inflammatory infiltrate, focal, branch of coronary artery | | | 2 | | | | | | | | | | | | | |
| STOMACH | | | | | | | | | | | | | | | | |
| SMALL INTESTINE | | | | | | | | | | | | | | | | |
| Eosinophilic leukocyte infiltrate, focal | | | | | | | | 1 | | | | | | | | |
| COLON | | | | | | | | | | | | | | | | |
| CECUM | | | | | | | | | | | | | | | | |
| MESENTERIC LYMPH NODE | | | | | | | | | | | | | | | | |
| Eosinophilic leukocyte infiltrate, focal | | 1 | | | | | 1 | | | | | | | | | |
| GALLBLADDER | | | | | | | | | | | | | | | | |
| URINARY BLADDER | | | | | | | | | | | | | | | | |
| Hemorrhage, acute, multifocal | | | | | | | | | | | | | 2 | | | |
| Inflammation, nonsuppurative, multifocal | | | | | | | | | | | | | 2 | | | |
| Mucosal hyperplasia | | | | | | | | | | | | | 2 | | | |
| MAMMARY AND SKIN | NP | | | | NP | | | NP | | | | | | | | |
| MUSCLE | | | | | | | | | | | | | | | | |
| THYROIDS | NR | | | | | | | | | | | | | + | | |
| Cystic remnant, ultimobranchial duct | | | | | | | | | | | | | | | | |

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

TABLE 2 (continued)

| GROUP NUMBER | GROUP 1 MALES | | | | GROUP 4 MALES | | | | GROUP 1 FEMALES | | | | GROUP 4 FEMALES | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SEX | | | | | | | | | | | | | | | | |
| ANIMAL NUMBER | 408 | 411 | 417 | 418 | 413 | 416 | 419 | 420 | 425 | 426 | 434 | 435 | 423 | 432 | 436 | 437 |
| PROSTATE | | | | | | | | | | | | | | | | |
| TESTES | | | | | | | | | | | | | | | | |
| EPIDIDYMIDES | | | | | | | | | | | | | | | | |
| UTERUS | | | | | | | | | | | | | | | | |
| OVARIES | | | | | | | | | | | | | | | | |
| EYE | | | | | | | | | | | | | | | | |
| RIB JUNCTION | | | | | | | | | | | | | | | | |
| STERNUM | | | | | | | | | | | | | | | | |
| PARATHYROID (NOT TAKEN ROUTINELY) Cystic remnant, ultimobranchial duct | | | | | | | | | | | | | | | | + |

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 408 | PM NUMBER: | 78/6108 |
| DOSAGE: | 0 ppm | GROUP NUMBER: | 1 |
| DATE OF DEATH: | 8/15/78 | SPECIES: | Dog |
| DEATH: | Terminal sacrifice | SEX: | Male |
| METHOD OF KILL: | Somlethol | | |

GROSS FINDINGS:
Lungs - pleural adhesions, left side.
Thyroids - left thyroid not located; was not in typical location.

MICROSCOPIC FINDINGS:
Lungs - inflammation, interstitial, multifocal, minimal.

MISSING TISSUES:
Thyroids - not received for trimming.
Mammary and skin - glandular tissue not present in plane of section.

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 411 | PM NUMBER: | 78/6109 |
| DOSAGE: | 0 ppm | GROUP NUMBER: | 1 |
| DATE OF DEATH: | 8/15/78 | SPECIES: | Dog |
| DEATH: | Terminal sacrifice | SEX: | Male |
| METHOD OF KILL: | Somlethol | | |

GROSS FINDINGS:
All tissues appear normal.

MICROSCOPIC FINDINGS:
Lungs - inflammation, interstitial, focal, minimal.
Mesenteric lymph node - eosinophilic leukocyte infiltrate, focal, minimal.

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 417
DOSAGE: 0 ppm
DATE OF DEATH: 8/16/78
DEATH: Terminal sacrifice
METHOD OF KILL: Somlethol

PM NUMBER: 78/6110
GROUP NUMBER: 1
SPECIES: Dog
SEX: Male

GROSS FINDINGS:
All tissues appear normal.

MICROSCOPIC FINDINGS:
Liver - eosinophilic leukocyte infiltrate, focal, minimal.
Heart - lymphocytic inflammatory infiltrate, focal, mild, branch of coronary artery.

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 418 | PM NUMBER: | 78/6111 |
| DOSAGE: | 0 ppm | GROUP NUMBER: | 1 |
| DATE OF DEATH: | 8/16/78 | SPECIES: | Dog |
| DEATH: | Terminal sacrifice | SEX: | Male |
| METHOD OF KILL: | Somlethol | | |

GROSS FINDINGS:
All tissues appear normal.

MICROSCOPIC FINDINGS:
All tissues essentially normal.

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 413 | PM NUMBER: | 78/6116 |
| DOSAGE: | 1000 ppm | GROUP NUMBER: | 4 |
| DATE OF DEATH: | 8/15/78 | SPECIES: | Dog |
| DEATH: | Terminal sacrifice | SEX: | Male |
| METHOD OF KILL: | Somlethol | | |

GROSS FINDINGS:
Mesenteric lymph node - minute white nodules along nodes; also reddened.

MICROSCOPIC FINDINGS:
Mesenteric lymph node - essentially normal; white nodules noted in mesenteric lymph nodes at necropsy probably were germinal centers.

MISSING TISSUES:
Mammary and skin - glandular tissue not present in plane of section.

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 416 | PM NUMBER: | 78/6117 |
| DOSAGE: | 1000 ppm | GROUP NUMBER: | 4 |
| DATE OF DEATH: | 8/16/78 | SPECIES: | Dog |
| DEATH: | Terminal sacrifice | SEX: | Male |
| METHOD OF KILL: | Somlethol | | |

GROSS FINDINGS:
All tissues appear normal.

MICROSCOPIC FINDINGS:
Lungs - inflammation, interstitial, focal, mild.

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 419 | PM NUMBER: | 78/6118 |
| DOSAGE: | 1000 ppm | GROUP NUMBER: | 4 |
| DATE OF DEATH: | 8/17/78 | SPECIES: | Dog |
| DEATH: | Terminal sacrifice | SEX: | Male |
| METHOD OF KILL: | Somlethol | | |

GROSS FINDINGS:
All tissues appear normal.

MICROSCOPIC FINDINGS:
Pituitary gland - cyst.
Mesenteric lymph node - eosinophilic leukocyte infiltrate, focal, minimal.

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 420 | PM NUMBER: | 78/6119 |
| DOSAGE: | 1000 ppm | GROUP NUMBER: | 4 |
| DATE OF DEATH: | 8/17/78 | SPECIES: | Dog |
| DEATH: | Terminal sacrifice | SEX: | Male |
| METHOD OF KILL: | Somlethol | | |

GROSS FINDINGS:
All tissues appear normal.

MICROSCOPIC FINDINGS:
Pituitary gland - cysts.
Lungs - granuloma, mineralized, minimal.
Small intestine - eosinophilic leukocyte infiltrate, focal, minimal.

MISSING TISSUES:
Mammary and skin - glandular tissue not present in plane of section.

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

ANIMAL NUMBER: 425
DOSAGE: 0 ppm
DATE OF DEATH: 8/15/78
DEATH: Terminal sacrifice
METHOD OF KILL: Somlethol

PM NUMBER: 78/6112
GROUP NUMBER: 1
SPECIES: Dog
SEX: Female

GROSS FINDINGS:
Mesenteric lymph node - reddened.

MICROSCOPIC FINDINGS:
Pituitary gland - cyst.
Mesenteric lymph node - essentially normal.

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 426 | PM NUMBER: | 78/6113 |
| DOSAGE: | 0 ppm | GROUP NUMBER: | 1 |
| DATE OF DEATH: | 8/16/78 | SPECIES: | Dog |
| DEATH: | Terminal sacrifice | SEX: | Female |
| METHOD OF KILL: | Somlethol | | |

GROSS FINDINGS:
Mesenteric lymph node - reddened.

MICROSCOPIC FINDINGS:
Pituitary gland - cyst.
Lungs - inflammation, interstitial, multifocal, mild, associated with foreign material.

Comment - the mesenteric lymph node was histologically normal.

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 434 | PM NUMBER: | 78/6114 |
| DOSAGE: | 0 ppm | GROUP NUMBER: | 1 |
| DATE OF DEATH: | 8/17/78 | SPECIES: | Dog |
| DEATH: | Terminal sacrifice | SEX: | Female |
| METHOD OF KILL: | Somlethol | | |

GROSS FINDINGS:
All tissues appear normal.

MICROSCOPIC FINDINGS:
Pituitary gland - cyst.
Lungs - inflammation, interstitial, multifocal, minimal.

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 435 | PM NUMBER: | 78/6115 |
| DOSAGE: | 0 ppm | GROUP NUMBER: | 1 |
| DATE OF DEATH: | 8/17/78 | SPECIES: | Dog |
| DEATH: | Terminal sacrifice | SEX: | Female |
| METHOD OF KILL: | Somlethol | | |

GROSS FINDINGS:
All tissues appear normal.

MICROSCOPIC FINDINGS:
Lungs - inflammation, interstitial, multifocal, mild.

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 423 | PM NUMBER: | 78/6120 |
| DOSAGE: | 1000 ppm | GROUP NUMBER: | 4 |
| DATE OF DEATH: | 8/15/78 | SPECIES: | Dog |
| DEATH: | Terminal sacrifice | SEX: | Female |
| METHOD OF KILL: | Somlethol | | |

GROSS FINDINGS:
Kidneys - both appear scarry.
Urinary bladder - numerous small red spots about 1mm in measurement.

MICROSCOPIC FINDINGS:
Brain - hydrocephalus, mild; mineralization, periarteriolar, focal, minimal.
Kidneys - fibrosis, interstitial, radial, moderate, bilateral, cortex and medulla; inflammation, nonsuppurative, moderate, bilateral, papilla and pelvis.
Lungs - inflammation, interstitial, multifocal, mild, associated with foreign material.
Urinary bladder - hemorrhage, acute, multifocal, mild; inflammation, nonsuppurative, multifocal, mild; with mild mucosal hyperplasia.

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 432 | PM NUMBER: | 78/6121 |
| DOSAGE: | 1000 ppm | GROUP NUMBER: | 4 |
| DATE OF DEATH: | 8/15/78 | SPECIES: | Dog |
| DEATH: | Terminal sacrifice | SEX: | Female |
| METHOD OF KILL: | Somlethol | | |

GROSS FINDINGS:
All tissues appear normal.

MICROSCOPIC FINDINGS:
Lungs - inflammation, interstitial, multifocal, mild.
Thyroids - cystic ultimobranchial duct remnant.

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 436 | PM NUMBER: | 78/6122 |
| DOSAGE: | 1000 ppm | GROUP NUMBER: | 4 |
| DATE OF DEATH: | 8/16/78 | SPECIES: | Dog |
| DEATH: | Terminal sacrifice | SEX: | Female |
| METHOD OF KILL: | Somlethol | | |

GROSS FINDINGS:
Pituitary gland - small cyst.
Uterus - mild mucometra.

MICROSCOPIC FINDINGS:
Pituitary gland - cyst.
Lungs - parasitism, nematodiasis, mild; inflammation, interstitial, focal, minimal.
Uterus - no lesion recognized; the slight increase in uterine fluid noted at necropsy was due to normal cyclic secretory activity.

LITTON BIONETICS, INC.
PROJECT NO. 10734-09

INDIVIDUAL ANIMAL PATHOLOGY EVALUATION

| | | | |
|---|---|---|---|
| ANIMAL NUMBER: | 437 | PM NUMBER: | 78/6123 |
| DOSAGE: | 1000 ppm | GROUP NUMBER: | 4 |
| DATE OF DEATH: | 8/16/78 | SPECIES: | Dog |
| DEATH: | Terminal sacrifice | SEX: | Female |
| METHOD OF KILL: | Somlethol | | |

GROSS FINDINGS:
All tissues appear normal.

MICROSCOPIC FINDINGS:
Lungs - inflammation, interstitial, multifocal, mild.
Parathyroids - cystic ultimobranchial duct remnant.

# APPENDIX

## Distribution List

| | |
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