

NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 216



CARCINOGENESIS BIOASSAY
OF
11-AMINOUNDECANOIC ACID
(CAS NO. 2432-99-7)
IN F344 RATS AND B6C3F₁ MICE
(FEED STUDY)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

NATIONAL TOXICOLOGY PROGRAM

The National Toxicology Program (NTP), established in 1978, develops and evaluates scientific information about potentially toxic and hazardous chemicals. This knowledge can be used for protecting the health of the American people and for the primary prevention of chemically induced disease. By bringing together the relevant programs, staff, and resources from the U.S. Public Health Service, DHHS, the National Toxicology Program has centralized and strengthened activities relating to toxicology research, testing and test development/validation efforts, and the dissemination of toxicological information to the public and scientific communities and to the research and regulatory agencies.

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**NTP Technical Report
on the
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**NATIONAL TOXICOLOGY PROGRAM
Research Triangle Park
Box 12233
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and
Bethesda, Maryland 20205**

May 1982

**NTP-80-34
NIH Publication No. 82-1772**

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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NOTE TO THE READER

This is one in a series of experiments designed to determine whether selected chemicals produce cancer in animals. Chemicals selected for testing in the NTP carcinogenesis bioassay program are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential. Negative results, in which the test animals do not have a greater incidence of cancer than control animals, do not necessarily mean that a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical is a potential hazard to humans. The determination of the risk to humans from chemicals found to be carcinogenic in animals requires a wider analysis which extends beyond the purview of this study.

This study was initiated by the National Cancer Institute's Carcinogenesis Testing Program, now part of the National Institute of Environmental Health Sciences, National Toxicology Program.

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Comments and questions about the National Toxicology Program Technical Reports on Carcinogenesis Bioassays should be directed to the National Toxicology Program, located at Room A-306, Landow Building, Bethesda, MD 20205 (301-496-1152) or at Research Triangle Park, North Carolina 27709 (919-541-3991).

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to communicate any mistakes to the Deputy Director, NTP (P.O. Box 12233, Research Triangle Park, NC 27709), so that corrective action may be taken. Further, anyone who is aware of related ongoing or published studies not mentioned in this report is encouraged to make this information known to the NTP.

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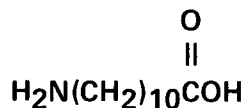
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**CARCINOGENESIS
BIOASSAY OF
11-AMINOUNDECANOIC ACID**



11-AMINOUNDECANOIC ACID

ABSTRACT

A carcinogenesis bioassay of 11-aminoundecanoic acid was carried out by administering diets containing 7,500 or 15,000 ppm of 11-aminoundecanoic acid to F344 rats and B6C3F1 mice. Groups of 50 rats and 50 mice of either sex were administered the test chemical for 104 weeks (rats) or 103 weeks (mice). Controls consisted of 50 untreated rats and 50 untreated mice of each sex.

Nonneoplastic effects included dose-related decreases in mean body weight gain and survival for male rats and for mice of each sex; a dose-related increased incidence of hyperplasia of the transitional epithelium of the kidney and urinary bladder in rats of each sex; and mineralization of the kidney in dosed mice of each sex.

Neoplastic nodules of the liver in dosed male rats (control 1/50, 2%; low dose 9/50, 18%; high dose 8/50, 16%; $P < 0.01$) and transitional-cell carcinomas of the urinary bladder in high-dose male rats (control 0/48, 0%; low dose 0/48, 0%; high dose 7/49, 14%; $P < 0.01$) were observed at significantly increased incidences compared with controls. Malignant lymphomas occurred at a significantly ($P < 0.05$) increased rate in low-dose male mice (control 2/50, 4%; low dose 9/50, 18%; high dose 4/50, 8%).

Under the conditions of this bioassay, 11-aminoundecanoic acid was carcinogenic for male F344 rats, inducing neoplastic nodules in the liver and transitional-cell carcinomas in the urinary bladder. The test chemical was not carcinogenic for female F344 rats. No clear evidence was found for the carcinogenicity of 11-aminoundecanoic acid in B6C3F1 mice of either sex, although the increase in malignant lymphoma in male mice may have been associated with administration of 11-aminoundecanoic acid.

CONTRIBUTORS

The bioassay of 11-aminoundecanoic acid was conducted at Litton Bionetics, Inc., under a sub-contract to Tracor Jitco, Inc., the prime contractor for the Carcinogenesis Testing Program. The prechronic study was started in May 1976 and finished in August 1976; the chronic study was begun in February 1977 and completed in March 1979.

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The pathology report and selected slides were evaluated by the NTP Pathology Working Group, which included Drs. G. Reznik, M. Stedham, and S. Stinson.

The chemicals used in this bioassay of 11-aminoundecanoic acid were analyzed by the Midwest Research Institute, 425 Volker Blvd., Kansas City, Missouri 64110; reanalysis of the bulk chemical and analysis of formulated diets were done by Litton Bionetics, Inc.

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SUMMARY OF PEER REVIEW COMMENTS ON THE BIOASSAY OF 11-AMINOUNDECANOIC ACID

On February 18, 1981, this carcinogenesis bioassay report on 11-aminoundecanoic acid underwent peer review and was approved by the National Toxicology Program Board of Scientific Counselors' Technical Report Review Subcommittee and associated Panel of Experts at an open meeting held in Building 31C, National Institutes of Health, Bethesda, Maryland.

Dr. Swenberg, a principal reviewer for the report on the bioassay of 11-aminoundecanoic acid, agreed with the conclusion that, under the conditions of the bioassay, 11-aminoundecanoic acid was carcinogenic for male F344 rats, inducing increased incidences of neoplastic nodules in the liver and transitional-cell carcinomas in the urinary bladder. The test chemical was not carcinogenic for female F344 rats. No clear evidence of carcinogenicity was demonstrated in B6C3F1 mice of either sex. Other effects included a dose-related decrease in mean body weight gain and survival for male rats and for mice of each sex, hyperplasia of the transitional epithelium of the kidney and urinary bladder in rats of each sex, and mineralization of the kidney in mice of each sex.

Dr. Swenberg stated that if early mortality in high-dose mice groups was due to toxicity then the high dose exceeded the maximum tolerated dose. If this were the case, the low dose group represented a maximum tolerated dose and the study is valid and not compromised. He said that more information on toxicity and cause of death would be preferable, particularly for the early deaths in the high dose male rats and mice.

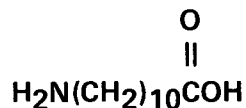
As another principal reviewer, Dr. Mirer, also agreed with the conclusions of the report. He noted that no transitional-cell carcinomas of the urinary bladder were observed in control male rats, and that this tumor is very rare in historical controls. He commented that compound-related toxicity in male mice (less than 50% survival) may have prevented the appearance of late developing tumors. Thus, this high mortality combined with a borderline statistically elevated incidence of lymphomas suggest that 11-aminoundecanoic acid was not adequately tested for carcinogenicity in male mice.

Dr. Shore questioned the word "clear" in the statement in the conclusions that "No clear evidence was found for the carcinogenicity of 11-aminoundecanoic acid in B6C3F1 mice of either sex." The qualifier derives from the finding of a statistically significant increase in malignant lymphoma in low-dose male mice but not in high-dose mice. After considerable discussion, Dr. Moore (NTP) proposed adding a clause to the statement such as, "although a significant incidence of malignant lymphoma in low-dose male mice may have been associated with chemical administration."

Dr. Swenberg moved that the report on the bioassay of 11-aminoundecanoic acid be accepted after minor changes and corrections described in the reviewers' comments and during the discussion are made. Dr. Mirer seconded the motion and the report was approved unanimously by the Peer Review Panel.

I. INTRODUCTION

I. INTRODUCTION



11-AMINOUNDECANOIC ACID

11-Aminoundecanoic acid (CAS No. 2432-99-7) is the monomer used in the manufacture of the polyamide, nylon-11. 11-Aminoundecanoic acid is synthesized through a series of reactions from ricinoleic acid isolated from castor bean oil (Hampel and Hawley, 1973; Hawley, 1977).

Nylon-11 is used in automobile parts, industrial fabrics (e.g., filter bags, work clothes, and netting), and brushes because of its resistance to vibration and shock and its stability when in contact with fuels (Kirk-Othmer, 1979). Nylon-11 resins are approved by the U.S. Food and Drug Administration for use in food contact films (U.S. CFR, 1977).

11-Aminoundecanoic acid is not produced in the United States, and specific production figures are not available for either 11-aminoundecanoic acid or nylon-11. The amount of nylon-11 used in the United States accounts for less than 1% of the nylon in use in this country. Nylon-11 is used more widely in France, Italy, and Brazil (Hampel and Hawley, 1973; Hawley, 1977).

11-Aminoundecanoic acid was one of a series of monomers assigned for testing by the Carcinogenesis Testing Program because of possible worker exposure and the absence of previous studies for carcinogenicity or other biological properties.

II. METHODS AND MATERIALS

CHEMICAL ANALYSIS

PRECHRONIC STUDIES

Single-Dose Study

Fourteen-Day Study

Thirteen-Week Study

CHRONIC STUDY

Study Design

Source and Specifications of Test Animals

Animal Maintenance

Preparation of Test Diets

Clinical Examinations and Pathology

Data Recording and Statistical Methods

II. METHODS AND MATERIALS: CHEMICAL ANALYSIS

CHEMICAL ANALYSIS

White crystalline 11-aminoundecanoic acid was obtained as a single batch (Lot No 503) from Rilsan Corporation (Glenrock, NJ) and was found to be 99.13% \pm 0.03 (δ)% pure by titration of the amine (Midwest Research Institute), the elemental analyses were in agreement

with the theoretical values (Appendix E) Results of thin-layer chromatography indicated one trace impurity or one trace and one slight impurity, depending on the solvent system used The infrared and nuclear magnetic resonance spectra were consistent with the structure

PRECHRONIC STUDIES

Single-Dose Study

Male and female F344 rats were obtained from Frederick Cancer Research Center (Frederick, MD), quarantined, and held for approximately 2 months before the test began Animals were approximately 11 weeks old when placed on study Mice were not used in the single-dose study

Groups of five male F344 rats were administered a single dose of 11-aminoundecanoic acid (14,700 or 21,500 mg/kg body weight) in corn oil by gavage and groups of five female rats received doses of 6,810, 10,000, 14,700, or 21,500 mg/kg by the same route All animals were observed for mortality for 14 days

Animals were housed two or three per cage and received water and feed *ad libitum* during the observation period Details of animal maintenance are presented in Table 1

Animals were observed for mortality every 30 minutes for the first 8 hours on the day of dosing and then daily for 14 days Weights were taken on the day of dosing and then on days 7 and 14 Gross necropsies were performed on all animals that died during the study and on those surviving to day 14

Fourteen-Day Study

Male and female F344 rats and B6C3F1 mice were obtained from Frederick Cancer Research Institute, quarantined, and held for approximately 3 months before the study began Animals were approximately 15 weeks old when placed on study

Groups of five males and five females of each species were fed diets containing 0, 5,000, 10,000, 15,000, 20,000, or 30,000 ppm 11-aminoundecanoic acid for 2 weeks Test diets were prepared several days before the start of the study by mixing the test chemical and ground

Purina® Lab Chow in a Patterson-Kelly® Twin Shell Blender Diets were refrigerated until use

Animals were housed two or three per cage and received water and feed *ad libitum* Details of animal maintenance are presented in Table 1 The rats and mice were observed daily for mortality and were weighed weekly Gross necropsies were performed on all animals at the end of the 14-day study

Thirteen-Week Study

Subchronic studies were conducted to determine the concentrations to be used in the chronic studies

Three-week-old male and female F344 rats and B6C3F1 mice were obtained from the NCI Frederick Cancer Research Center, observed for 2 weeks, and then randomized by weight and assigned to test groups so that average cage weights were approximately equal for all animals of the same sex and species

Rats and mice were housed four per cage in polycarbonate cages covered with nonwoven polyester filter sheets (Table 1) Racks and filters were replaced once every 2 weeks Cages and bedding were replaced twice per week, and water bottles were replaced three times per week

Test diets consisted of Purina® Lab Chow and the required amount of 11-aminoundecanoic acid (Lot No 503) The analytical procedures described in the chronic study were used Control diets consisted of Purina® Lab Chow Dosed feed, control diets, and bottled water (acidified with hydrochloric acid to pH 2.5 for bacterial control) were available *ad libitum*

Diets containing 0, 9,000, 12,000, 15,000, 18,000, 20,000 (mice), or 21,000 ppm (rats) 11-aminoundecanoic acid were fed for 13 weeks to groups of 12 male and 12 female rats and to groups of 10 male and 10 female mice

II. METHODS AND MATERIALS: PRECHRONIC STUDIES

Table 1. SOURCES AND DESCRIPTIONS OF MATERIALS USED FOR ANIMAL MAINTENANCE IN THE PRECHRONIC AND CHRONIC STUDIES

Item	Description	Source
Air Filter	AG-55 Ameriglass Roughing Filter	American Air Filter (Louisville, KY)
Air Filter	HEPA-100	American Air Filter (Louisville, KY)
Animal Feed	Purina® Lab Chow	Ralston Purina Co (Richmond, IN)
Bedding	Absorb-dri® hardwood chips	Lab Products, Inc (Garfield, NJ)
Cages	Polycarbonate	Lab Products, Inc (Garfield, NJ)
Filter Sheets	Nonwoven polyester	Snow Filtration (Cincinnati, OH)

Animals were checked for mortality and signs of morbidity twice daily. Those animals that were judged moribund were killed and necropsied. Each animal was given a clinical examination weekly, including palpation for tissue masses or swelling. Body weight and feed consumption data were collected weekly.

At the end of the 91-day study, survivors were killed with carbon dioxide and necropsies were performed on animals that survived to the end of the study and on all animals found dead, unless precluded in whole or in part by autolysis or cannibalization. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and does not necessarily represent the number of animals that were placed on study in each group. The following specimens were examined for control and high-dose groups: gross lesions, tissue masses, abnormal lymph nodes, skin, mandibular lymph

nodes, mammary gland, salivary gland, thigh muscle, sciatic nerve, bone marrow, costochondral junction (rib), thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenals, bladder, seminal vesicles/prostate/testes or ovaries/uterus, nasal cavity, brain, pituitary, and spinal cord. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin.

Histopathologic examination for all other dosed groups was limited to the kidneys and liver, except for male and female rats administered 12,000 ppm. The kidneys, liver, lungs, and heart of animals in the 12,000-ppm groups were examined histopathologically.

II. METHODS AND MATERIALS: CHRONIC STUDY

CHRONIC STUDY

Study Design

Diets containing 7,500 or 15,000 ppm 11-aminoundecanoic acid were fed to groups of 50 rats or mice of either sex for 104 weeks (rats) or 103 weeks (mice). Controls consisted of groups of 50 untreated rats and 50 untreated mice of either sex (Table 2). Rats and mice were approximately 5 weeks old when placed on study.

Source and Specifications of Test Animals

Three-week-old male and female F344 rats and B6C3F1 mice were obtained from the NCI Frederick Cancer Research Center (Frederick, MD), observed for 2 weeks, and randomly assigned to individual cages. The cages were then randomly assigned to control and dosed groups.

Animal Maintenance

Rats and mice were housed five per cage in polycarbonate cages covered with nonwoven polyester filter sheets (Table 1). Racks and filters were changed once every 2 weeks. Cages, bedding, and glass water bottles (equipped with stainless steel sipper tubes) were replaced twice per week. Dosed feed, control diets, and tap water (acidified with hydrochloric acid to pH 2.5 for bacterial control) were available *ad libitum*. Stainless steel feed containers were changed once per week.

The temperature in the animal rooms was 22°-26°C and the humidity was 30%-70%. Incoming air was first filtered through AG-55 Ameriglass roughing filters and then through HEPA-100 filters to remove particulate matter. Ten changes of room air per hour were provided. Fluorescent lighting provided illumination 12 hours per day.

Rats fed 11-aminoundecanoic acid were housed in a room with rats on feeding studies of 2,6-dichloro-p-phenylenediamine (CAS No. 609-20-1) (NTP TR 219, 1982). Mice fed 11-aminoundecanoic acid were housed in rooms with mice on feeding studies of caprolactam (CAS No. 105-60-2) (NTP TR 214, Rev 1982), bisphenol A (CAS No. 80-05-7) (NTP TR 215, 1982), and 2,6-dichloro-p-phenylenediamine (CAS No. 609-20-1) (NTP TR 219, 1982).

Preparation of Test Diets

Test diets were prepared by first mixing a small amount of Purina® Lab Chow (Table 1)

and the required amount of 11-aminoundecanoic acid (Lot No. 503) with a mortar and pestle and then adding this premix to the required amount of animal meal and mixing for 20 minutes in a Patterson-Kelly® twin shell blender equipped with an intensifier bar. Prepared diets containing 100,000 ppm 11-aminoundecanoic acid were analyzed at Midwest Research Institute and were found to be stable for 2 weeks at temperatures up to 45°C (Appendix F). Test diets were stored in the dark at 4°C for no longer than 2 weeks. Control animals were fed Purina® Lab Chow.

Dosed feed samples from the chronic studies were analyzed. The mean concentration of 11-aminoundecanoic acid (\pm standard deviation) in nine randomly selected dosed feed samples containing a target level of 7,500 ppm was 7,597 \pm 416 ppm (Appendix G). The mean concentration of 11-aminoundecanoic acid in eight samples containing a target level of 15,000 ppm was 14,701 \pm 618 ppm.

Clinical Examinations and Pathology

All animals were observed twice daily for signs of toxicity. Clinical signs were recorded monthly. Body weights and feed consumption by cage were recorded every 2 weeks for the first 13 weeks and monthly thereafter. The mean body weight of each group was calculated by dividing the total weight of all animals in the group by the number of surviving animals in the group. The average feed consumption per animal was calculated by dividing the total feed consumption measured for all cages by the number of surviving animals in the group. Moribund animals and animals that survived to the end of the bioassay were killed using carbon dioxide and necropsied.

Examinations for grossly visible lesions were performed on major tissues or organs. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following were examined microscopically: tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, sciatic nerve, bone marrow, costochondral junction (rib), thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes,

II. METHODS AND MATERIALS: CHRONIC STUDY

Table 2. EXPERIMENTAL DESIGN OF CHRONIC FEEDING STUDIES WITH 11-AMINO-UNDECANOIC ACID IN RATS AND MICE

Test Group	Initial No. of Animals	11-Aminoundecanoic Acid (ppm)	Weeks on Study	
			Dosed	Not Dosed
MALE RATS				
Control	50	0	0	109
Low-Dose	50	7,500	104	5
High-Dose	50	15,000	104	5
FEMALE RATS				
Control	50	0	0	109
Low-Dose	50	7,500	104	5
High-Dose	50	15,000	104	5
MALE MICE				
Control	50	0	0	109
Low-Dose	50	7,500	103	5-6
High-Dose	50	15,000	103	5-6
FEMALE MICE				
Control	50	0	0	109
Low-Dose	50	7,500	103	5-6
High-Dose	50	15,000	103	5-6

liver, gallbladder (mice), pancreas, spleen, kidneys, adrenals, bladder, seminal vesicles/prostate/testes or ovaries/uterus, nasal cavity, brain, pituitary, and spinal cord. Special staining techniques were used as necessary.

Necropsies were performed on all animals found dead and on those killed at the end of the study, unless precluded in whole or in part by autolysis or cannibalization. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study in each group.

The pathology report and selected slides were evaluated by the NTP Pathology Working Group as described by Ward et al. (1978). The classification of neoplastic nodules was done according to the recommendations of Squire and Levitt (1975), and the National Academy of Sciences (1980). The diagnoses represent a consensus of contracting pathologists and the NTP Pathology Working Group.

Data Recording and Statistical Methods

Data on this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969).

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) extensions of Cox's methods for testing for a dose-related trend.

II. METHODS AND MATERIALS: CHRONIC STUDY

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators included only those animals for which that site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) prior to histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

For the statistical analysis of tumor incidence data, two different methods of adjusting for intercurrent mortality were employed. Each used the classical methods for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise comparisons of high- and low-dosed groups with controls and tests for overall dose-response trends.

The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal", i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel methods to obtain an overall P-value. This method of adjusting for intercurrent mortality is the life

table method of Cox (1972) and of Tarone (1975).

The second method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "incidental", i.e., they were merely observed at autopsy in animals dying of an unrelated cause. According to this approach, the proportions of animals found to have tumors in dosed and control groups were compared in each of five time intervals: 0-52 weeks, 53-78 weeks, 79-92 weeks, 93-108 weeks, and 109 weeks (when all surviving animals were killed). The denominators of these proportions were the number of animals actually autopsied during the time interval. The individual time interval comparisons were then combined by the previously described methods to obtain a single overall result. (See Peto et al., 1980, for the computational details of both methods.)

In addition to these tests, one other set of statistical analyses was carried out and reported in the tables analyzing primary tumors: the Fisher's exact test for pairwise comparisons and the Cochran-Armitage linear trend test for dose-response trends (Armitage, 1971; Gart et al., 1979). These tests were based on the overall proportion of tumor-bearing animals. All reported P values are one-sided.

For studies in which there is little effect of compound administration on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death.

III. RESULTS

RATS

PRECHRONIC STUDIES

Single-Dose Study

Fourteen-Day Study

Thirteen-Week Study

CHRONIC STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

PRECHRONIC STUDIES

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CHRONIC STUDIES

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III. RESULTS: RATS—PRECHRONIC STUDIES

RATS

PRECHRONIC STUDIES

Single-Dose Study

Rats were observed for 14 days and, at the end of the 14-day observation period, survival was 100% in females administered 6,810 or 10,000 mg/kg and in males administered 14,700 or 21,500 mg/kg. Deaths occurred in 1/5 females administered 14,700 mg/kg and in 5/5 females administered 21,500 mg/kg; depressions in mean body weight were observed in males and females at these doses.

Fourteen-Day Study

All animals survived to the end of the dosing period. No compound associated effects were observed in rats fed 0-15,000 ppm, but groups of male and female rats fed 20,000 or 30,000 ppm had depressions in mean body weight gain compared with controls. Daily food consumption data were not collected.

Thirteen-Week Study

One of 12 female rats fed the 18,000-ppm diet died at day 9. Mean body weight gain in male rats fed diets containing 18,000 or 21,000 ppm 11-aminoundecanoic acid was depressed 13% and 14%, respectively (Table 3). Multifocal tubular mineralization of the kidneys was noted in 70%-100% of all groups of female rats administered 11-aminoundecanoic acid (Table 4). The severity of the mineralization was dose related. Transitional-cell hyperplasia was found in the kidneys of 1/10 male rats fed 21,000 ppm, in 6/10 females fed 21,000 ppm, and in 2/9 females fed 18,000 ppm 11-aminoundecanoic acid. Hyperplasias of the renal pelvis were seen in 2/9 females fed 18,000 ppm and in 1/10 males and 6/10 females fed 21,000 ppm.

Because of compound-related effects, including transitional cell hyperplasia in the kidneys and body weight depression, doses for rats in the chronic study were set at 7,500 and 15,000 ppm.

Table 3. DOSAGE, SURVIVAL, AND MEAN BODY WEIGHTS OF RATS FED DIETS CONTAINING 11-AMINOUNDECANOIC ACID FOR 13 WEEKS

Dose (ppm)	Survival (a)	Mean Body Weights (grams)			Weight Change Relative to Control (c) (Percent)
		Initial	Final (b)	Change	
MALE					
0	12/12	114	298	+184	
9,000	12/12	114	298	+184	0
12,000	12/12	113	298	+185	0
15,000	12/12	114	283	+169	- 8
18,000	12/12	114	275	+161	-13
21,000	12/12	114	273	+159	-14
FEMALE					
0	12/12	91	172	+ 81	
9,000	12/12	92	183	+ 91	+12
12,000	12/12	92	182	+ 90	+11
15,000	12/12	92	180	+ 88	+ 9
18,000	11/12	91	178	+ 87	+ 7
21,000	12/12	91	177	+ 86	+ 6

(a) Number surviving/number per group

(b) Weights taken at week 12 are used as final weights.

(c) Weight Change Relative to Controls =

$$\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$$

Table 4. NUMBER OF RATS WITH MINERALIZATION OR HYPERPLASIA OF THE KIDNEY OR RENAL PELVIS IN THE 13-WEEK STUDY

Dose (ppm)	Number of Animals with Mineralization of the Kidney	Number of Animals with Transitional-Cell Hyperplasia of the Kidney	Number of Animals with Hyperplasia of the Renal Pelvis
Male			
0	0/10	—	—
9,000	0/10	—	—
12,000	0/10	—	—
15,000	0/10	—	—
18,000	0/10	—	—
21,000	0/10	1/10	1/10
Female			
0	0/10	—	—
9,000	7/10	—	—
12,000	7/10	—	—
15,000	10/10	—	—
18,000	9/9	2/9	2/9
21,000	8/10	6/10	6/10

III. RESULTS RATS—CHRONIC STUDIES

CHRONIC STUDIES

Body Weights and Clinical Signs

Throughout the last year of the study, mean body weights of high-dose rats of either sex were lower than those of the controls (Figure 1 and

Table 5). The average daily feed consumption per rat by low- and high-dose rats was 98% and 88% that of the controls for males and 88% and 86% for females (Table 6). No compound-related clinical signs were observed.

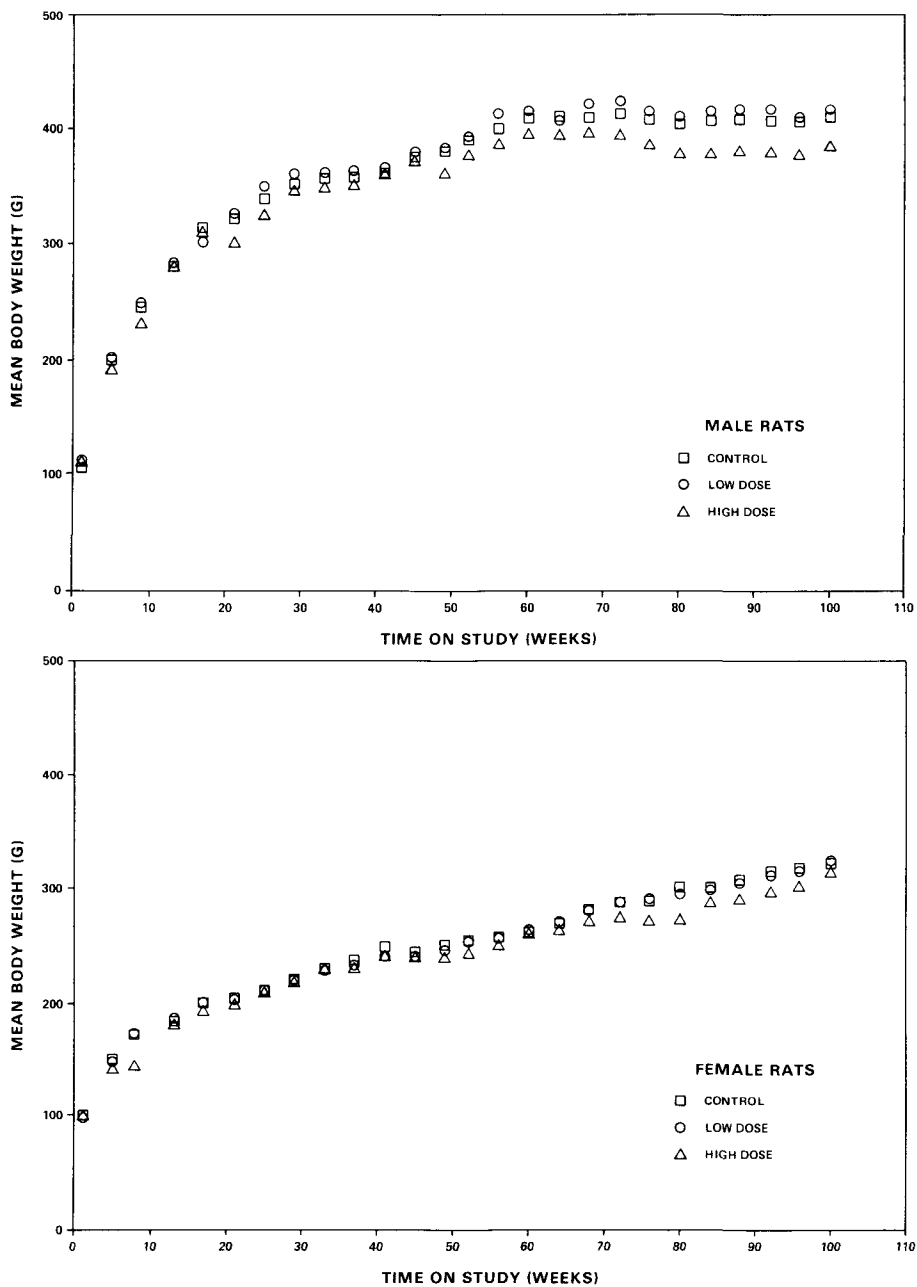


Figure 1. Growth Curves for Rats Fed Diets Containing 11-Aminoundecanoic Acid

Table 5. CUMULATIVE MEAN BODY WEIGHT CHANGE OF RATS FED DIETS CONTAINING 11-AMINOUNDECANOIC ACID

Week No.	Cumulative Mean Body Weight Change (grams)			Percent Weight Change Relative to Controls (a)	
	Control	Low Dose	High Dose	Low Dose	High Dose
MALE					
1	105 (b)	112 (b)	110 (b)		
5	+ 94	+ 90	+ 81	-4	-14
25	+233	+237	+215	+2	- 8
45	+270	+267	+260	-1	- 4
64	+307	+295	+285	-4	- 7
84	+302	+304	+267	+1	-12
100	+307	+306	+275	0	-10
FEMALE					
1	99 (b)	97 (b)	98 (b)		
5	+ 51	+ 51	+ 42	0	-18
25	+114	+116	+112	+2	- 2
45	+146	+144	+142	-1	- 3
64	+170	+173	+166	+2	- 2
84	+201	+201	+189	0	- 6
100	+222	+226	+216	+2	- 3

(a) Percent Weight Change Relative to Controls =

$$\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$$

(b) Initial weight

Table 6 AVERAGE DAILY FEED CONSUMPTION (IN GRAMS) PER RAT IN THE CHRONIC STUDY

Week	Control	Low Dose	Low Dose	High Dose	High Dose
			Control		Control
MALE					
8	30	27	0.9	21	0.7
24	23	25	1.1	22	1.0
36	24	24	1.0	24	1.0
48	23	23	1.0	21	0.9
60	26	25	1.0	24	0.9
72	30	30	1.0	25	0.8
84	32	30	0.9	27	0.8
96	27	27	1.0	25	0.9
FEMALE					
8	18	17	0.9	16	0.9
24	16	14	0.9	15	0.9
36	18	17	0.9	17	0.9
48	18	14	0.8	13	0.7
60	21	18	0.9	16	0.8
72	20	18	0.9	18	0.9
84	24	20	0.8	20	0.8
96	23	21	0.9	21	0.9

III. RESULTS RATS—CHRONIC STUDIES

Survival

Estimates of the probabilities of survival of male and female rats administered 11-aminoundecanoic acid in feed at the concentrations of this bioassay, together with those of the control group, are shown by the Kaplan and Meier curves in Figure 2. The Tarone test indicated a linear trend ($P=0.036$) in the mortality of male rats in positive relation to the dose levels. No significant trend was observed in the mortality of the female groups.

In male rats, 39/50 (78%) of the control group, 37/50 (74%) of the low-dose group, and 30/50 (60%) of the high-dose group lived to the end of the study at 109 weeks. In female rats, 38/50 (76%) of the control group, 32/50 (64%) of the low-dose group, and 42/50 (84%) of the high-dose group lived to the end of the study at 109 weeks. The cause of death of animals dying during the study was not determined.

Pathology and Statistical Analyses of Results

Histopathologic findings on neoplasms in rats are summarized in Appendix A, Tables A1 and A2, findings on nonneoplastic lesions are summarized in Appendix C, Tables C1 and C2. Appendix Tables A3 and A4 give the survival and tumor status for each individual animal in the male rat and female rat studies, respectively.

A variety of tumors was found in control and dosed groups, including leukemias, pituitary chromophobe adenomas, interstitial-cell tumors, pheochromocytomas, mammary fibroadenomas, and lesser incidences of other neoplasms.

Tables 7 and 8 contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups.

Urinary Bladder Transitional-cell carcinomas of the urinary bladder were observed in a significantly increased incidence ($P<0.01$) in the high-dose group of male rats (controls, 0/48, 0%, low-dose, 0/48, 0%, high-dose, 7/49, 14%). These tumors generally tended to grow toward the lumen of the bladder, often forming papillary processes. These tumors had a large number of anaplastic cells, mitotic activity, and areas of focal necrosis. Invasion of the basement membrane and underlying tissues was often seen in malignant tumors, however, no vascular invasion or metastases were observed. Transitional-cell carcinomas of the urinary bladder were not

observed in any of the three female rat groups.

Focal or diffuse hyperplasia of the transitional epithelium of the urinary bladder was observed with a significantly ($P<0.01$) increased incidence in high-dose male rats (controls, 0/48, 0%, low-dose, 2/48, 4%, high-dose, 20/49, 41%). These lesions were also observed with increased incidence in dosed female rats (controls, 4/49, 8%, low-dose, 12/47, 26%, high-dose, 9/48, 19%), but only in the low-dose group was this increase statistically significant ($P<0.05$) (Table 9).

An increased incidence of calculi of the urinary bladder was seen in males in the high-dose group (controls, 1/48, 2%, low-dose, 1/48, 2%, high-dose, 5/49, 10%). However, these calculi were not found in any of the animals for which transitional-cell carcinomas were seen.

Kidneys Focal or diffuse hyperplasia of the transitional epithelium of the kidney was observed with significantly ($P<0.01$) increased incidence in high-dose male rats (controls, 0/50, 0%, low-dose, 4/50, 8%, high-dose, 15/50, 30%) and female rats (controls, 0/49, 0%, low-dose, 5/50, 10%, high-dose, 34/50, 68%) administered 11-aminoundecanoic acid. The increased incidence in low-dose female rats was also statistically significant ($P<0.05$) (Table 9). None was seen in the controls. Foci of calcification in the renal cortex and medulla, especially at the cortico-medullary junction and tip of the medulla, were common lesions in dosed female rats. Nonneoplastic kidney lesions (e.g., chronic nephropathy), commonly seen in aging rats, were observed in all groups.

Liver Neoplastic nodules occurred with a significantly increased incidence ($P<0.01$) in dosed male rats (controls, 1/50, 2%, low-dose, 9/50, 18%, high-dose, 8/50, 16%). The neoplastic nodules were not life shortening. The slight increase in neoplastic nodules observed in female rats was not statistically significant. Hepatocellular carcinomas were also observed in two high-dose male rats and one low-dose male rat.

Mammary Gland Fibroadenomas showed an increased incidence ($P<0.05$) in the low-dose male rat group (controls, 0/50, 0%, low-dose, 5/50, 10%, high-dose, 2/50, 4%). The slight increase at the high dose was not statistically significant.

III. RESULTS RATS—CHRONIC STUDIES

Hematopoietic System: A significantly decreased incidence ($P < 0.05$) of leukemia was observed in male rats administered 11-aminoundecanoic acid (control, 14/50, 28%; low-dose, 4/50, 8%; high-dose, 5/50, 10%).

Subcutaneous Tissue: A decreasing trend ($P < 0.05$) was seen in neurofibromas of the subcutaneous tissue of male rats (control, 3/50, 6%; low-dose, 0/50, 0%; high-dose, 0/50, 0%).

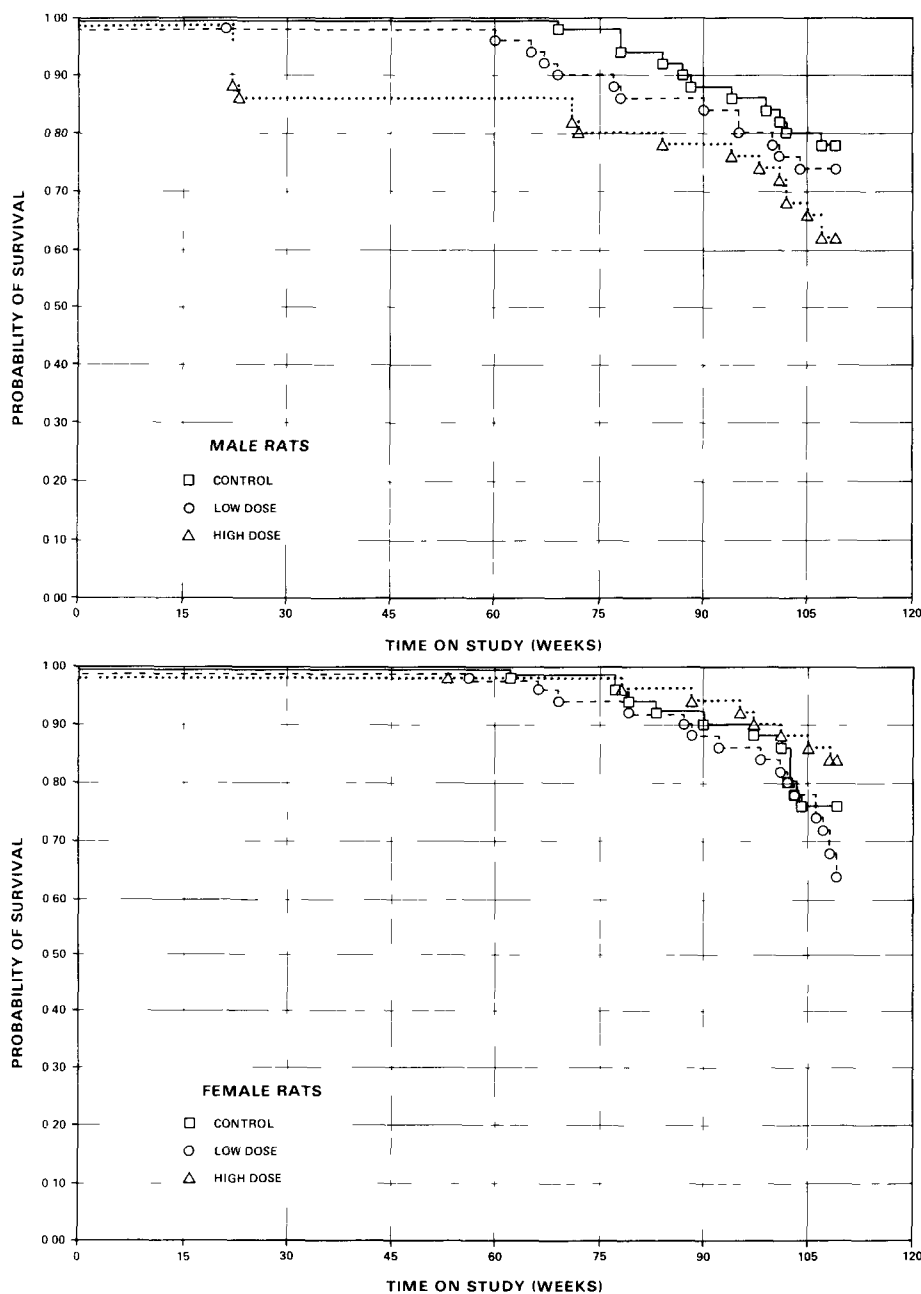


Figure 2. Survival Curves for Rats Fed Diets Containing 11-Aminoundecanoic Acid

Table 7. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (a)

Topography: Morphology:	Control	Low Dose	High Dose
Subcutaneous Tissue: Fibroma			
Tumor Rates			
Overall (b)	1/50(2)	1/50(2)	3/50(6)
Adjusted (c)	0.025	0.027	0.088
Terminal (d)	0/39(0)	1/37(3)	2/30(7)
Statistical Tests (e)			
Life Table	P=0.094	P=0.746	P=0.236
Incidental Tumor Test	P=0.122	P=0.754	P=0.310
Cochran-Armitage Trend, Fisher Exact Tests	P=0.202	P=0.753	P=0.309
Subcutaneous Tissue: Neurofibroma			
Tumor Rates			
Overall (b)	3/50(6)	0/50(0)	0/50(0)
Adjusted (c)	0.077	0.000	0.000
Terminal (d)	3/39(8)	0/37(0)	0/30(0)
Statistical Tests (e)			
Life Table	P=0.023N	P=0.131N	P=0.171N
Incidental Tumor Test	P=0.023N	P=0.131N	P=0.171N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.037N	P=0.121N	P=0.121N
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall (b)	0/50(0)	4/50(8)	1/50(2)
Adjusted (c)	0.000	0.103	0.028
Terminal (d)	0/39(0)	3/37(8)	0/30(0)
Statistical Tests (e)			
Life Table	P=0.228	P=0.059	P=0.474
Incidental Tumor Test	P=0.320	P=0.060	P=0.617
Cochran-Armitage Trend, Fisher Exact Tests	P=0.391	P=0.059	P=0.500
Hematopoietic System: Undifferentiated Leukemia			
Tumor Rates			
Overall (b)	12/50(24)	4/50(8)	4/50(8)
Adjusted (c)	0.284	0.099	0.114
Terminal (d)	9/39(23)	3/37(8)	1/30(3)
Statistical Tests (e)			
Life Table	P=0.028N	P=0.040N	P=0.084N
Incidental Tumor Test	P=0.003N	P=0.054N	P=0.016N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.014N	P=0.027N	P=0.027N

Table 7. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (a) (Continued)

Topography: Morphology:	Control	Low Dose	High Dose
Hematopoietic System: Leukemia			
Tumor Rates			
Overall (b)	14/50(28)	4/50(8)	5/50(10)
Adjusted (c)	0.322	0.099	0.136
Terminal (d)	10/39(26)	3/37(8)	1/30(3)
Statistical Tests (e)			
Life Table	P=0.023N	P=0.016N	P=0.075N
Incidental Tumor Test	P=0.003N	P=0.017N	P=0.020N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.009N	P=0.009N	P=0.020N
Liver: Neoplastic Nodule			
Tumor Rates			
Overall (b)	1/50(2)	9/50(18)	8/50(16)
Adjusted (c)	0.026	0.237	0.258
Terminal (d)	1/39(3)	8/37(22)	7/30(23)
Statistical Tests (e)			
Life Table	P=0.004	P=0.008	P=0.006
Incidental Tumor Test	P=0.006	P=0.008	P=0.008
Cochran-Armitage Trend, Fisher Exact Tests	P=0.023	P=0.008	P=0.015
Liver: Neoplastic Nodule or Carcinoma			
Tumor Rates			
Overall (b)	1/50(2)	10/50(20)	10/50(20)
Adjusted (c)	0.026	0.255	0.298
Terminal (d)	1/39(3)	8/37(22)	7/30(23)
Statistical Tests (e)			
Life Table	P=0.001	P=0.005	P=0.002
Incidental Tumor Test	P=0.002	P=0.003	P=0.004
Cochran-Armitage Trend, Fisher Exact Tests	P=0.007	P=0.004	P=0.004
Urinary Bladder: Transitional-Cell Carcinoma			
Tumor Rates			
Overall (b)	0/48(0)	0/48(0)	7/49(14)
Adjusted (c)	0.000	0.000	0.196
Terminal (d)	0/39(0)	0/37(0)	3/30(10)
Statistical Tests (e)			
Life Table	P<0.001	(f)	P=0.005
Incidental Tumor Test	P<0.001	(f)	P=0.017
Cochran-Armitage Trend, Fisher Exact Tests	P=0.001	(f)	P=0.007

Table 7. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (a) (Continued)

Topography: Morphology:	Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma			
Tumor Rates			
Overall (b)	3/48(6)	6/47(13)	5/47(11)
Adjusted (c)	0.079	0.159	0.156
Terminal (d)	3/38(8)	4/35(11)	4/30(13)
Statistical Tests (e)			
Life Table	P=0.153	P=0.209	P=0.242
Incidental Tumor Test	P=0.207	P=0.212	P=0.277
Cochran-Armitage Trend, Fisher Exact Tests	P=0.292	P=0.232	P=0.345
Adrenal: All Pheochromocytomas			
Tumor Rates			
Overall (b)	10/50(20)	12/50(24)	13/49(27)
Adjusted (c)	0.212	0.316	0.404
Terminal (d)	4/39(10)	11/37(30)	11/30(37)
Statistical Tests (e)			
Life Table	P=0.091	P=0.354	P=0.145
Incidental Tumor Test	P=0.081	P=0.290	P=0.120
Cochran-Armitage Trend, Fisher Exact Tests	P=0.259	P=0.405	P=0.298
Thyroid: C-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall (b)	6/42(14)	1/43(2)	3/42(7)
Adjusted (c)	0.194	0.029	0.111
Terminal (d)	6/31(19)	1/34(3)	3/27(11)
Statistical Tests (e)			
Life Table	P=0.141N	P=0.043N	P=0.309N
Incidental Tumor Test	P=0.141N	P=0.043N	P=0.309N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.157N	P=0.051N	P=0.241N
Testis: Interstitial-Cell Tumor			
Tumor Rates			
Overall (b)	45/50(90)	43/50(86)	40/50(80)
Adjusted (c)	0.978	1.000	1.000
Terminal (d)	38/39(97)	37/37(100)	30/30(100)
Statistical Tests (e)			
Life Table	P=0.101	P=0.568	P=0.159
Incidental Tumor Test	P=0.221	P=0.584	P=0.530
Cochran-Armitage Trend, Fisher Exact Tests	P=0.103N	P=0.380N	P=0.131N

Table 7. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (a) (Continued)

Topography: Morphology:	Control	Low Dose	High Dose
Mammary Gland: Fibroadenoma			
Tumor Rates			
Overall (b)	0/50(0)	5/50(10)	2/50(4)
Adjusted (c)	0.000	0.132	0.067
Terminal (d)	0/39(0)	4/37(11)	2/30(7)
Statistical Tests (e)			
Life Table	P=0.109	P=0.030	P=0.183
Incidental Tumor Test	P=0.136	P=0.031	P=0.183
Cochran-Armitage Trend, Fisher Exact Tests	P=0.239	P=0.028	P=0.247

(a) Dosed groups received doses of 7,500 or 15,000 ppm of 11-aminoundecanoic acid in the diet

(b) Number of tumor-bearing animals/number of animals examined at the site (percent)

(c) Kaplan-Meier estimated lifetime tumor incidence (proportion) after adjusting for intercurrent mortality

(d) Observed tumor incidence in surviving animals killed at the end of the study

(e) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying before the end of the study as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

(f) The configuration of tumor incidences precludes use of this statistic.

Table 8. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS (a)

Topography: Morphology:	Control	Low Dose	High Dose
Hematopoietic System: Undifferentiated Leukemia			
Tumor Rates			
Overall (b)	11/50(22)	12/50(24)	6/50(12)
Adjusted (c)	0/240	0/294	0/127
Terminal (d)	4/38(11)	7/34(21)	2/42(5)
Statistical Tests (e)			
Life Table	P=0.094N	P=0.437	P=0.132N
Incidental Tumor Test	P=0.145N	P=0.582N	P=0.260N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.128N	P=0.500	P=0.143N
Hematopoietic System: Leukemia			
Tumor Rates			
Overall (b)	11/50(22)	14/50(28)	6/50(12)
Adjusted (c)	0/240	0/330	0/127
Terminal (d)	4/38(11)	7/34(21)	2/42(5)
Statistical Tests (e)			
Life Table	P=0.100N	P=0.283	P=0.132N
Incidental Tumor Test	P=0.158N	P=0.442	P=0.260N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.134N	P=0.322	P=0.143N
Hematopoietic System: Leukemia or Lymphoma			
Tumor Rates			
Overall (b)	13/50(26)	15/50(30)	6/50(12)
Adjusted (c)	0/285	0/355	0/127
Terminal (d)	6/38(16)	8/34(24)	2/42(5)
Statistical Tests (e)			
Life Table	P=0.046N	P=0.350	P=0.060N
Incidental Tumor Test	P=0.068N	P=0.521N	P=0.118N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.061N	P=0.412	P=0.062N
Liver: Neoplastic Nodule			
Tumor Rates			
Overall (b)	4/50(8)	5/50(10)	6/50(12)
Adjusted (c)	0/105	0/147	0/143
Terminal (d)	4/38(11)	5/34(15)	6/42(14)
Statistical Tests (e)			
Life Table	P=0.313	P=0.430	P=0.433
Incidental Tumor Test	P=0.313	P=0.430	P=0.433
Cochran-Armitage Trend, Fisher Exact Tests	P=0.309	P=0.500	P=0.370

Table 8. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS (a) (Continued)

Topography: Morphology:	Control	Low Dose	High Dose
Liver: Neoplastic Nodule or Carcinoma			
Tumor Rates			
Overall (b)	5/50(10)	5/50(10)	6/50(12)
Adjusted (c)	0/132	0/147	0/143
Terminal (d)	5/38(13)	5/34(15)	6/42(14)
Statistical Tests (e)			
Life Table	P=0.444	P=0.560	P=0.570
Incidental Tumor Test	P=0.444	P=0.560	P=0.570
Cochran-Armitage Trend, Fisher Exact Tests	P=0.436	P=0.630	P=0.500
Pituitary: Chromophobe Adenoma			
Tumor Rates			
Overall (b)	21/50(42)	19/50(38)	18/49(37)
Adjusted (c)	0/509	0/445	0/408
Terminal (d)	18/38(47)	11/34(32)	16/42(38)
Statistical Tests (e)			
Life Table	P=0.182N	P=0.559N	P=0.222N
Incidental Tumor Test	P=0.305N	P=0.434N	P=0.311N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.332N	P=0.419N	P=0.371N
Adrenal: Pheochromocytoma			
Tumor Rates			
Overall (b)	3/48(6)	2/50(4)	2/49(4)
Adjusted (c)	0/073	0/059	0/049
Terminal (d)	1/38(3)	2/34(6)	2/41(5)
Statistical Tests (e)			
Life Table	P=0.296N	P=0.534N	P=0.471N
Incidental Tumor Test	P=0.327N	P=0.485N	P=0.540N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.397N	P=0.480N	P=0.490N
Thyroid: C-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall (b)	4/45(9)	2/45(4)	3/45(7)
Adjusted (c)	0/111	0/069	0/081
Terminal (d)	2/33(6)	2/29(7)	3/37(8)
Statistical Tests (e)			
Life Table	P=0.294N	P=0.383N	P=0.446N
Incidental Tumor Test	P=0.323N	P=0.338N	P=0.507N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.417N	P=0.338N	P=0.500N

Table 8. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS (a) (Continued)

Topography: Morphology:	Control	Low Dose	High Dose
Mammary Gland: Fibroadenoma			
Tumor Rates			
Overall (b)	11/50(22)	10/50(20)	11/50(22)
Adjusted (c)	0/289	0/282	0/255
Terminal (d)	11/38(29)	9/34(26)	10/42(24)
Statistical Tests (e)			
Life Table	P=0.398N	P=0.588	P=0.494N
Incidental Tumor Test	P=0.417N	P=0.599N	P=0.511N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.548	P=0.500N	P=0.595
Uterus: Endometrial Stromal Polyp			
Tumor Rates			
Overall (b)	15/50(30)	12/48(25)	10/50(20)
Adjusted (c)	0/382	0/328	0/238
Terminal (d)	14/38(37)	10/34(29)	10/42(24)
Statistical Tests (e)			
Life Table	P=0.076N	P=0.445N	P=0.110N
Incidental Tumor Test	P=0.095N	P=0.407N	P=0.132N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.150N	P=0.372N	P=0.178N

(a) Dosed groups received doses of 7,500 or 15,000 ppm of 11-aminoundecanoic acid in the diet

(b) Number of tumor bearing animals/number of animals examined at the site (percent)

(c) Kaplan-Meier estimated lifetime tumor incidence (proportion) after adjusting for intercurrent mortality

(d) Observed tumor incidence in surviving animals killed at the end of the study

(e) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying before the end of the study as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

Table 9. INCIDENCE OF TUMORS AND PROLIFERATIVE LESIONS OF TRANSITIONAL CELLS IN RATS FED DIETS CONTAINING 11-AMINOUNDECANOIC ACID

	Males			Females		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
Kidney						
Tissues Examined	50	50	50	49	50	50
Hyperplasia	0	4 (8%)	15 (30%) (a)	0	5 (10%) (b)	34 (68%) (a)
Papilloma	0	0	0	0	0	0
Carcinoma	0	0	1 (2%)	0	0	2 (4%)
Urinary Bladder						
Tissues Examined	48	48	49	49	47	48
Hyperplasia	0	2 (4%)	20 (41%) (a)	4 (8%)	12 (26%) (b)	9 (19%)
Papilloma	0	0	1 (2%)	0	0	1 (2%)
Carcinoma	0	0	7 (14%) (a)	0	0	0

(a) $P < 0.01$ (Fisher's exact tests) relative to controls

(b) $P < 0.05$ (Fisher's exact tests) relative to controls

III. RESULTS: MICE—PRECHRONIC STUDIES

MICE

PRECHRONIC STUDIES

Fourteen-Day Study

All animals survived to the end of the dosing period. No compound-associated effects were observed in mice at any dose level (5,000-30,000 ppm).

Thirteen-Week Study

Deaths occurred in 2/10 males and 2/10 females administered 15,000 ppm, 4/10 males and 2/10 females receiving 18,000 ppm, and 3/10 males receiving 20,000 ppm (Table 10). The cause of death of animals dying during the study

was not determined. Mean body weight gain was depressed 20% in male mice receiving 15,000 ppm, but only 10% in male mice receiving 18,000 or 20,000 ppm. Mean body weight gain was depressed by more than 10% in female mice fed diets containing 18,000-20,000 ppm 11-aminoundecanoic acid. Focal mineralization of the kidney was noted in males that received 15,000-20,000 ppm and in females that received 15,000-18,000 ppm, particularly in those mice that died (Table 11).

Doses for mice in the chronic study were set at 7,500 and 15,000 ppm.

Table 10. DOSAGE, SURVIVAL, AND MEAN BODY WEIGHTS OF MICE FED DIETS CONTAINING 11-AMINOUNDECANOIC ACID FOR 13 WEEKS

Dose (ppm)	Survival (a)	Mean Body Weights (grams)			Weight Change Relative to Control (c) (Percent)
		Initial	Final (b)	Change	
MALE					
0	10/10	20	30	+10	
9,000	10/10	20	31	+11	+10
12,000	10/10	20	30	+10	0
15,000	8/10	20	28	+8	-20
18,000	6/10	20	29	+9	-10
20,000	7/10	20	29	+9	-10
FEMALE					
0	10/10	17	25	+8	
9,000	10/10	17	25	+8	0
12,000	10/10	17	25	+8	0
15,000	8/10	17	25	+8	0
18,000	8/10	17	24	+7	-13
20,000	10/10	17	23	+6	-25

(a) Number surviving/number per group

(b) Weights taken at week 12 are used as final weights

(c) Weight Change Relative to Controls =

$$\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$$

Table 11. NUMBER OF MICE WITH MINERALIZATION OF THE KIDNEY IN THE 13-WEEK STUDY

Dose (ppm)	Number of Animals with Mineralization of the Kidney	Number of Animals with Mineralization that Died Before End of Study
Male		
0	0/10	0/0
9,000	0/10	0/0
15,000	2/10	1/2
18,000	4/10	3/4
20,000	2/10	2/3
Female		
0	0/10	0/0
9,000	0/10	0/0
15,000	1/10	1/2
18,000	2/10	2/2
20,000	0/10	0/0

III. RESULTS MICE—CHRONIC STUDIES

CHRONIC STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed mice of either sex were lower than those of the controls throughout the study, and the depressions in mean body weight gain were dose related (Figure 3 and

Table 12). The average daily feed consumption per mouse by low- and high-dose mice was 110% and 123% that of the controls for males and 110% and 97% for females. No other compound-related clinical signs were observed (Table 13).

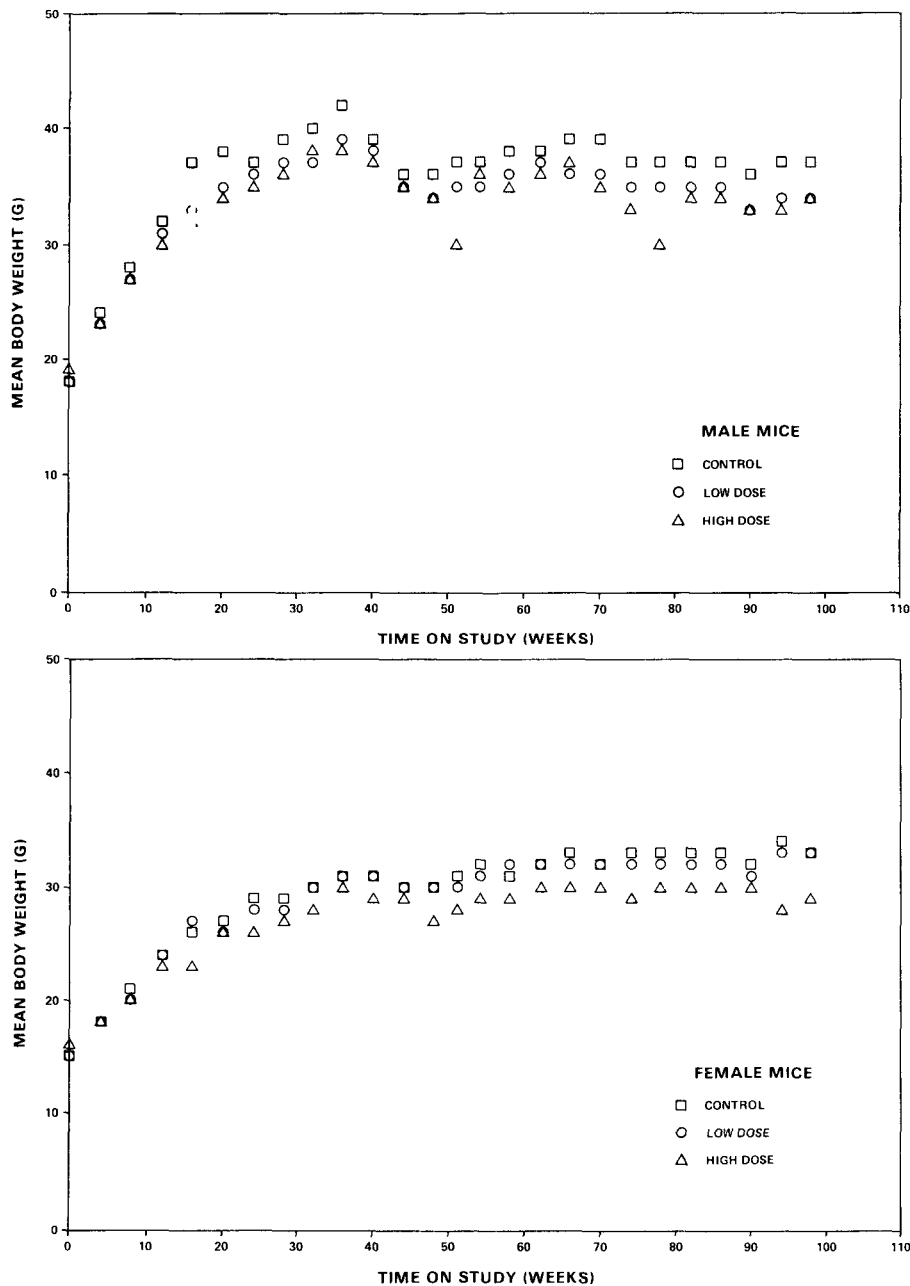


Figure 3. Growth Curves for Mice Fed Diets Containing 11-Aminoundecanoic Acid

Table 12. CUMULATIVE MEAN BODY WEIGHT CHANGE OF MICE FED DIETS CONTAINING 11-AMINOUNDECANOIC ACID

Week No.	Cumulative Mean Body Weight Change (grams)			Percent Weight Change Relative to Controls (a)	
	Control	Low Dose	High Dose	Low Dose	High Dose
MALE					
1	18 (b)	18 (b)	19 (b)		
4	+ 6	+ 5	+ 4	-17	-33
24	+19	+18	+16	- 5	-16
44	+18	+17	+16	- 6	-11
62	+20	+19	+17	- 5	-15
82	+19	+17	+15	-11	-21
98	+19	+16	+15	-16	-21
FEMALE					
1	15 (b)	15 (b)	16 (b)		
4	+ 3	+ 3	+ 2	0	-33
24	+14	+13	+10	- 7	-29
44	+15	+15	+13	0	-13
62	+17	+17	+14	0	-18
82	+18	+17	+14	- 6	-22
98	+18	+18	+13	0	-28

(a) Percent Weight Change Relative to Controls =

$$\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$$

(b) Initial weight

Table 13. AVERAGE DAILY FEED CONSUMPTION (IN GRAMS) PER MOUSE IN THE CHRONIC STUDY

Week	Control	Low Dose	Low Dose	High Dose	High Dose
			Control		Control
MALES					
8	6	6	10	7	12
24	6	5	08	6	10
36	6	8	13	6	10
48	5	6	12	6	12
60	4	5	13	7	18
72	4	4	10	5	13
85	5	6	12	6	12
97	4	4	10	6	15
FEMALES					
8	7	8	11	6	09
24	4	6	15	5	13
36	-	9	-	9	-
48	6	8	13	6	10
60	6	6	10	6	10
72	6	5	08	5	08
85	6	4	07	4	07
97	4	6	15	6	15

III. RESULTS MICE—CHRONIC STUDIES

Survival

Estimates of the probabilities of survival of male and female mice administered 11-aminoundecanoic acid in feed at the concentrations of this bioassay, together with those of the control group, are shown by the Kaplan and Meier curves in Figure 4. The Tarone test indicated a significant ($P < 0.001$), positive, dose-related linear trend in mortality in both male and female groups. Two female mice, one from the low-dose

and one from the high-dose groups, were missing.

In male mice, 37/50 (74%) of the control group, 34/50 (68%) of the low-dose group, and 18/50 (36%) of the high-dose group lived to the end of the study at 109 weeks. In female mice, 42/50 (84%) of the control group, 37/49 (76%) of the low-dose group, and 25/49 (51%) of the high-dose group lived to the end of the study at 109 weeks. The cause of death of animals dying during the study was not determined.

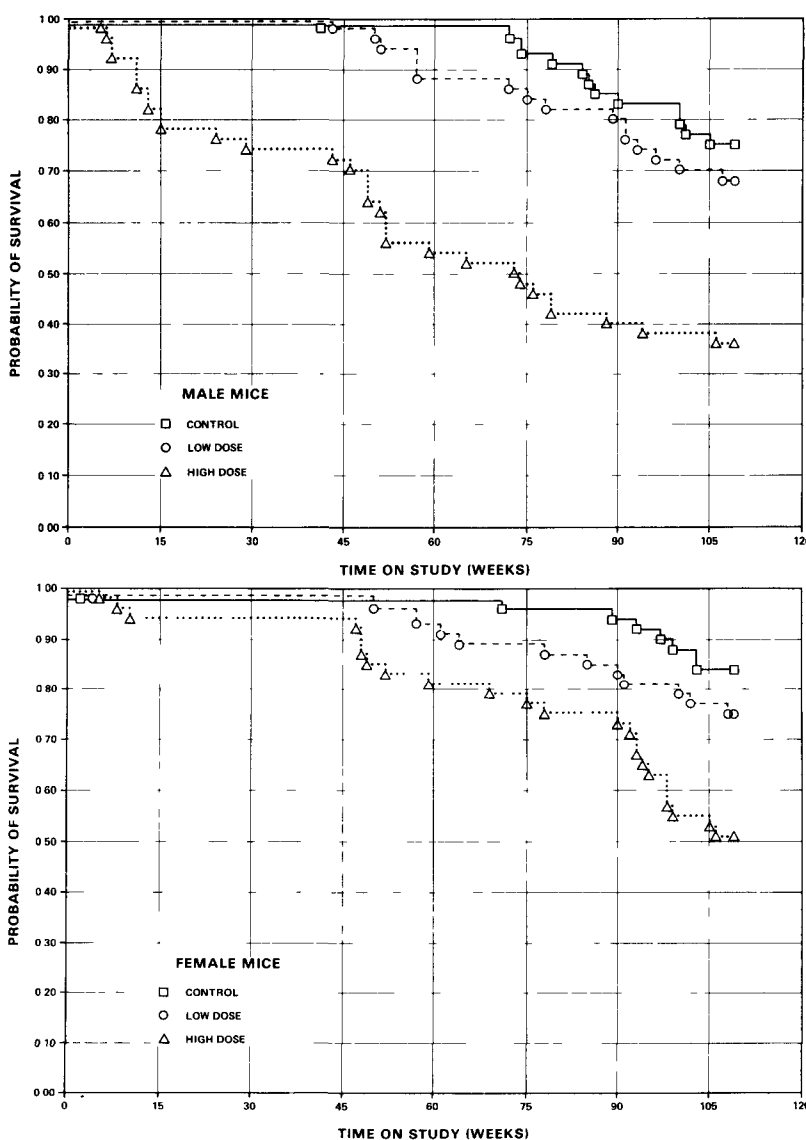


Figure 4. Survival Curves for Mice Fed Diets Containing 11-Aminoundecanoic Acid

III. RESULTS MICE—CHRONIC STUDIES

Pathology and Statistical Analyses of Results

Histopathologic findings on neoplasms occurring in mice are summarized in Table 14 and Appendix B, Tables B1 and B2; findings on non-neoplastic lesions are summarized in Appendix D, Tables D1 and D2. Tables B3 and B4 give the survival and tumor status for each individual animal in the male and female mouse studies, respectively.

Tables 15 and 16 contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups.

Hematopoietic System: Malignant lymphomas occurred with a significant ($P < 0.05$) increasing trend in male mice, as shown in Table 14 (control, 2/50, 4%; low-dose, 9/50, 18%, high-dose, 4/50, 8%). The increase was statistically significant ($P < 0.05$) at the low dose but not at the high dose. In most of the affected mice,

two or more organs were involved in the neoplastic process. For female mice, a slight increase in malignant lymphomas was not statistically significant. If the results of the two sexes are combined, then the increasing trend is significant ($P < 0.05$) by a life table analysis but not by an incidental tumor test.

Kidneys: The incidence of mineralization of the kidneys or kidney medulla was significantly ($P < 0.01$) increased in high-dose male mice (controls, 0/50, 0%; low-dose, 4/50, 8%; high-dose, 11/49, 22%), and in dosed female mice (controls, 0/50, 0%; low-dose, 8/49, 16%; high-dose, 9/49, 18%) fed 11-aminoundecanoic acid.

Liver: Hepatocellular vacuolization was observed with significantly ($P < 0.05$) increased incidence in high-dose male mice (controls, 2/50, 4%; low-dose, 2/50, 4%; high-dose 10/49, 20%) and in dosed female mice (controls, 0/50, 0%; low-dose, 5/49, 10%; high-dose, 6/49, 12%) fed 11-aminoundecanoic acid.

Table 14. INCIDENCE OF MALIGNANT LYMPHOMAS IN MALE MICE FED DIETS CONTAINING 11-AMINO-UNDECANOIC ACID IN THE CHRONIC STUDY

	Control	Low Dose	High Dose
Multiple Organs	2 (4%)	6 (12%)	4 (8%)
Localized			
Spleen	—	1 (2%)	—
Lymph Node	—	1 (2%)	—
Thymus	—	1 (2%)	—
Total	2 (4%)	9 (18%)	4 (8%)

Table 15. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (a)

Topography: Morphology:	Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall (b)	10/50(20)	3/50(6)	4/46(9)
Adjusted (c)	0.262	0.088	0.222
Terminal (d)	9/37(24)	3/34(9)	4/18(22)
Statistical Tests (e)			
Life Table	P=0.205N	P=0.051N	P=0.482N
Incidental Tumor Test	P=0.202N	P=0.049N	P=0.478N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.055N	P=0.036N	P=0.100N
Hematopoietic System: Malignant Lymphoma			
Tumor Rates			
Overall (b)	2/50(4)	9/50(18)	4/50(8)
Adjusted (c)	0.049	0.243	0.181
Terminal (d)	1/37(3)	6/34(18)	1/18(6)
Statistical Tests (e)			
Life Table	P=0.036	P=0.022	P=0.097
Incidental Tumor Test	P=0.044	P=0.017	P=0.175
Cochran-Armitage Trend, Fisher Exact Tests	P=0.309	P=0.026	P=0.339
Circulatory System: Hemangiosarcoma			
Tumor Rates			
Overall (b)	2/50(4)	3/50(6)	0/50(0)
Adjusted (c)	0.054	0.081	0.000
Terminal (d)	2/37(5)	2/34(6)	0/18(0)
Statistical Tests (e)			
Life Table	P=0.284N	P=0.463	P=0.407N
Incidental Tumor Test	P=0.201N	P=0.561	P=0.407N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.203N	P=0.500	P=0.247N
Liver: Adenoma			
Tumor Rates			
Overall (b)	1/50(2)	3/50(6)	3/49(6)
Adjusted (c)	0.024	0.088	0.140
Terminal (d)	0/37(0)	3/34(9)	2/18(11)
Statistical Tests (e)			
Life Table	P=0.041	P=0.273	P=0.114
Incidental Tumor Test	P=0.093	P=0.284	P=0.243
Cochran-Armitage Trend, Fisher Exact Tests	P=0.232	P=0.309	P=0.301

Table 15. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (a) (Continued)

Topography: Morphology:	Control	Low Dose	High Dose
Liver: Carcinoma			
Tumor Rates			
Overall (b)	16/50(32)	16/50(32)	9/49(18)
Adjusted (c)	0.379	0.415	0.377
Terminal (d)	11/37(30)	12/34(35)	4/18(22)
Statistical Tests (e)			
Life Table	P=0.347	P=0.473	P=0.449
Incidental Tumor Test	P=0.466	P=0.459	P=0.579N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.081N	P=0.585	P=0.091N
Liver: Adenoma or Carcinoma			
Tumor Rates			
Overall (b)	17/50(34)	18/50(36)	12/49(24)
Adjusted (c)	0.394	0.469	0.483
Terminal (d)	11/37(30)	14/34(41)	6/18(33)
Statistical Tests (e)			
Life Table	P=0.140	P=0.386	P=0.203
Incidental Tumor Test	P=0.258	P=0.368	P=0.405
Cochran-Armitage Trend, Fisher Exact Tests	P=0.184N	P=0.500	P=0.207N

(a) Dosed groups received doses of 7,500 or 15,000 ppm of 11-aminoundecanoic acid in the diet.

(b) Number of tumor bearing animals/ number of animals examined at the site (percent).

(c) Kaplan-Meier estimated lifetime tumor incidence (proportion) after adjusting for intercurrent mortality.

(d) Observed tumor incidence in surviving animals killed at the end of the study.

(e) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying before the end of the study as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

Table 16. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE (a)

Topography: Morphology:	Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall (b)	2/50(4)	3/49(6)	3/49(6)
Adjusted (c)	0 048	0 081	0 120
Terminal (d)	2/42(5)	3/37(8)	3/25(12)
Statistical Tests (e)			
Life Table	P=0 141	P=0 442	P=0 272
Incidental Tumor Test	P=0 141	P=0 442	P=0 272
Cochran-Armitage Trend, Fisher Exact Tests	P=0 403	P=0 490	P=0 490
Hematopoietic System: Malignant Lymphoma			
Tumor Rates			
Overall (b)	9/50(18)	10/49(20)	10/49(20)
Adjusted (c)	0 203	0 250	0 327
Terminal (d)	7/42(17)	7/37(19)	5 25(20)
Statistical Tests (e)			
Life Table	P=0 089	P=0 384	P=0 137
Incidental Tumor Test	P=0 339	P=0 434	P=0 424
Cochran-Armitage Trend, Fisher Exact Tests	P=0 430	P=0 480	P=0 480
Liver: Adenoma or Carcinoma			
Tumor Rates			
Overall (b)	7/50(14)	8/49(16)	5/49(10)
Adjusted (c)	0 162	0 202	0 176
Terminal (d)	6/42(14)	6/37(16)	3 25(12)
Statistical Tests (e)			
Life Table	P=0 374	P=0 399	P=0 515
Incidental Tumor Test	P=0 395N	P=0 415	P=0 502N
Cochran-Armitage Trend Fisher Exact Tests	P=0 344N	P=0 483	P=0 394N
Liver: Carcinoma			
Tumor Rates			
Overall (b)	5/50(10)	7 49(14)	4/49(8)
Adjusted (c)	0 116	0 176	0 139
Terminal (d)	4 42(10)	5 37(14)	2 25(8)
Statistical Tests (e)			
Life Table	P=0 320	P=0 299	P=0 484
Incidental Tumor Test	P=0 430N	P=0 313	P=0 537N
Cochran-Armitage Trend Fisher Exact Tests	P=0 450N	P=0 365	P=0 513N

Table 16. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE (a) (Continued)

Topography: Morphology:	Control	Low Dose	High Dose
Pituitary: Adenoma			
Tumor Rates			
Overall (b)	3/42(7)	5/39(13)	2/41(5)
Adjusted (c)	0.083	0.167	0.087
Terminal (d)	3/36(8)	5/30(17)	2/23(9)
Statistical Tests (e)			
Life Table	P=0.424	P=0.258	P=0.665
Incidental Tumor Test	P=0.424	P=0.258	P=0.665
Cochran-Armitage Trend, Fisher Exact Tests	P=0.434N	P=0.315	P=0.512N
Mammary Gland: Adenocarcinoma			
Tumor Rates			
Overall (b)	6/50(12)	1/49(2)	2/49(4)
Adjusted (c)	0.138	0.027	0.077
Terminal (d)	5/42(12)	1/37(3)	1/25(4)
Statistical Tests (e)			
Life Table	P=0.132N	P=0.083N	P=0.347N
Incidental Tumor Test	P=0.073N	P=0.094N	P=0.206N
Cochran-Armitage Trend, Fisher Exact Tests	P=0.075N	P=0.059N	P=0.141N

(a) Dosed groups received doses of 7,500 or 15,000 ppm of 11-aminoundecanoic acid in the diet.

(b) Number of tumor bearing animals/number of animals examined at the site (percent).

(c) Kaplan-Meier estimated lifetime tumor incidence (proportion) after adjusting for intercurrent mortality.

(d) Observed tumor incidence in surviving animals killed at the end of the study.

(e) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying before the end of the study as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher's exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

IV. DISCUSSION AND CONCLUSIONS

IV. DISCUSSION AND CONCLUSIONS

A carcinogenesis bioassay of 11-aminoundecanoic acid was conducted in F344 rats and B6C3F1 mice

The probable cause(s) of death in the high-dose male rats and in the high-dose mice of either sex was not determined, this poor survival rate, particularly for the mice (male, 36%, female, 51%) was due most likely to compound-related toxicity

11-Aminoundecanoic acid was carcinogenic for male F344 rats (Table 7), causing liver and urinary bladder tumors. Transitional-cell carcinomas of the urinary bladder were observed in a significantly increased incidence ($P < 0.01$) in the high-dose group of male rats (controls, 0/48, 0%, low-dose, 0/48, 0%, high-dose, 7/49, 14%). Urinary bladder tumors are rare in untreated male F344 rats in the Bioassay Program (Goodman et al., 1979, Sacksteder, 1976, Sass et al., 1975). In 3,512 untreated male F344 rats observed in the NCI/NTP Bioassay Program, there is a 0.02% incidence of undifferentiated carcinoma and a 0.11% incidence of transitional-cell papilloma of the urinary bladder. Transitional-cell carcinomas of the urinary bladder have not been seen in any untreated F344 male rats (0/780) examined at Litton Bionetics as part of the Bioassay Program.

Neoplastic nodules of the liver also occurred with a significant, dose-related ($P < 0.01$) increase in male rats (controls, 1/50, 2%, low-dose, 9/50, 18%, and high-dose, 8/50, 16%). The historical incidence of this tumor in untreated male F344 rats in the Bioassay Program is 1.62% (57/3,512), and at Litton Bionetics, 1.79% (14/780). The occurrence of neoplastic nodules is considered to be a manifestation of the carcinogenesis process (NAS, 1980). Female rats fed diets containing 11-aminoundecanoic acid did not show evidence of compound-related tumor development in the urinary bladder or liver or at any other site.

Additional evidence of urinary tract toxicity was seen in rats. An increased incidence of calculi of the urinary bladder was seen in males in the high-dose group (controls, 1/48, 2%, low-dose, 1/48, 2%, high-dose, 5/49, 10%). The rats with calculi were not the ones that had tumors of the urinary bladder. Hyperplasia of the transitional epithelium of the kidney and bladder was associated with the administration of 11-aminoundecanoic acid in male and female rats (Table 9). In particular, hyperplasia was associated with calculi of the urinary bladder in 2/5 high-dose

males. For the 20 high-dose male rats with hyperplasia of the urinary bladder, 7 of these had transitional-cell carcinomas and 1 other had a papilloma, the remaining 12 had hyperplasia in the apparent absence of urinary bladder tumors. Hyperplasia of the renal pelvis was also observed in the 13-week subchronic study in 2/9 females that received 18,000 ppm and in 1/10 males and 6/10 females that received 21,000 ppm.

Leukemia was observed in male rats at the following incidences: controls, 14/50, 28%, low-dose, 4/50, 8%, and high-dose, 5/50, 10%. Control F344 male rats at Litton Bionetics have a mean incidence of leukemia of 14% (111/780, range 0%-44%).

No clear evidence was found for the carcinogenicity of 11-aminoundecanoic acid in mice. Mean body weights for dosed mice of either sex were lower than those of the controls throughout the study. There was a significant ($P < 0.001$), positive, dose-related linear trend in mortality in both male and female groups. Early mortality in the high-dose male and female mice groups reduced the sensitivity of the bioassay for detecting increases in the incidence of late developing tumors.

Malignant lymphomas occurred with a statistically significant ($P < 0.05$), increase in low-dose male mice but not in the high-dose group (controls, 2/50, 4%, low-dose, 9/50, 18%, and high-dose, 4/50, 8%). The incidence of malignant lymphomas in untreated male B6C3F1 mice in this laboratory is 9% (44/507) (range 0%-20%). Malignant lymphomas in dosed male mice are not clearly associated with the administration of 11-aminoundecanoic acid because of the variable incidence of this tumor historically and the lack of a statistically significant effect at the high dose.

Evidence for renal toxicity was also seen in mice. Mineralization in the kidney was seen in dosed mice of either sex in both the subchronic and chronic studies.

11-Aminoundecanoic acid was tested in the same room with other chemicals undergoing carcinogenesis bioassay feeding studies—rats 2,6-dichloro-p-phenylenediamine, mice bisphenol A, caprolactam, and 2,6-dichloro-p-phenylenediamine. Abbreviated results from these three studies are given for comparative purposes. Bisphenol A (NTP TR 215, 1982) was not carcinogenic for F344 rats or B6C3F1 mice of either sex, yet, the increased incidences of leukemia in male rats (control 13/50, low dose

12/50, high dose 23/50*) and lymphoma in male mice (control 2/49, low dose 8/50*, high dose 3/50) may have been associated with the administration of bisphenol A. Caprolactam (NTP TR 214, Rev 1982) was not carcinogenic for F344 rats or B6C3F1 mice of either sex. 2,6-Dichloro-p-phenylenediamine (NTP TR 219, 1982) was not carcinogenic for F344 rats and was carcinogenic for B6C3F1 mice, causing an increased incidence of hepatocellular adenomas (male control 4/50, low dose 7/50, high dose 15/50*) and hepatocellular adenomas and carcinomas combined (female control 6/50, low dose 6/50, high dose 16/50*).

Although chemical cross-contamination among groups cannot be excluded completely, the responses in the separate testing experiments persuade that any adjacent chemical effect was absent or minimal. The results of these other studies support the conclusion that in male rats 11-aminoundecanoic acid caused transition-cell carcinomas of the urinary bladder and neoplastic nodules of the liver, additionally, in male mice an association may exist between the occur-

rence of malignant lymphoma (low dose) and administration of 11-aminoundecanoic acid. These data stand independently because the bisphenol A exposed animals and the caprolactam exposed groups did not show any definite compound-related tumor development and because 2,6-dichloro-p-phenylenediamine induced liver tumors distinctly in mice. The apparent correlative association between the 11-aminoundecanoic acid-induced and the bisphenol A-caused marginal increase in lymphomas in low dose male B6C3F1 mice may or may not be real and significant.

Conclusions Under the conditions of this bioassay, 11-aminoundecanoic acid was carcinogenic for male F344 rats, inducing neoplastic nodules in the liver and transitional-cell carcinomas in the urinary bladder. The test chemical was not carcinogenic for female F344 rats. No clear evidence was found for the carcinogenicity of 11-aminoundecanoic acid in B6C3F1 mice of either sex, although the increase in malignant lymphoma in male mice may have been associated with the administration of 11-aminoundecanoic acid.

*Increase is statistically significant ($P < 0.05$) relative to controls

V. REFERENCES

V. REFERENCES

- Armitage, P , Statistical methods in medical research New York John Wiley & Sons, Inc , 1971 362-365
- Berenblum, I , ed , Carcinogenicity testing a report of the panel on carcinogenicity of the cancer research commission of UICC Geneva International Union Against Cancer, Vol 2, 1969
- Cox, D R , Regression models and life tables J R Stat Soc B34, 187-220, 1972
- Gart, J , Chu, K , Tarone, R , Statistical issues in interpretation of chronic bioassay tests for carcinogenicity J Natl Cancer Inst 62(4) 957, 1979
- Goodman, D , Ward, J , Squire, R , Chu, K , Linhart, M , Neoplastic and nonneoplastic lesions in aging F344 rats Toxicol Appl Pharmacol 48 237-248, 1979
- Hampel, C , Hawley, G , ed , The encyclopedia of chemistry New York Van Nostrand Reinhold Co , 1973 874-875
- Hawley, G , ed , The condensed chemical dictionary New York Van Nostrand Reinhold Co , 1977 628-629
- Kaplan, E L , Meier, P , Nonparametric estimation of incomplete observations J Amer Stat Assoc 53 457-481, 1958
- Kirk-Othmer encyclopedia of chemical technology, 3rd ed New York John Wiley & Sons, Inc 5 6-7, 1979
- Linhart, M S , Cooper, J A , Martin, R L , Page, N P , Peters, J A , Carcinogenesis bioassay data system Comp Biomed Res 7 230-248, 1974
- Mantel, N , Haenszel, W , Statistical aspects of the analysis of data from retrospective studies of disease J Natl Cancer Inst 22 719-748, 1959
- NAS, National Academy of Sciences Histologic typing of liver tumors of the rat J Natl Cancer Inst 64 179, 1980
- NTP, National Toxicology Program Carcinogenesis bioassay of bisphenol A, U S Dept of Health and Human Services, Public Health Service, National Institutes of Health, 1982, TR 215
- NTP, National Toxicology Program Carcinogenesis bioassay of caprolactam, U S Dept of Health and Human Services, Public Health Service, National Institutes of Health, Rev 1982, TR 214
- NTP, National Toxicology Program Carcinogenesis bioassay of 2,6-dichloro-p-phenylenediamine, U S Dept of Health and Human Services, Public Health Service, National Institutes of Health, 1982, TR 219
- Peto, R , Pike, M , Day, N , Gray, R , Lee, P , Parish, S , Peto, J , Richard, S , Wahrendorf, J , Guidelines for simple, sensitive, significant tests for carcinogenic effects in long-term animal experiments International Agency for Research Against Cancer Monographs on the long-term and short-term screening assays for carcinogens A critical appraisal Geneva World Health Organization Supplement 2, 1980 311
- Rekhter, M A , Nesterova, I P , Uch Zap Kishinevsk Univ 68 82, 1963
- Sacksteder, M , Brief communication occurrence of spontaneous tumors in the germ free F344 rat J Natl Cancer Inst 57(6) 1371-1373, 1976
- Sadtler Research Laboratories Sadtler standard spectra Philadelphia Sadtler Research Laboratories, IR No 15268
- Sass, B , Rabstein, L , Madison, R , Nims, R , Peters, R , Kelloff, G , Incidence of spontaneous neoplasms in F344 rats throughout the natural lifespan J Natl Cancer Inst 54(6) 1449-1453, 1975
- Squire, R , Levitt, M , Report of a workshop on classification of specific hepatocellular lesions in rats Cancer Res 35 3214, 1975
- Tarone, R E , Tests for trend in life table analysis Biometrika 62 679-682, 1975
- U S Code of Federal Regulations 21 177 1500 and 179 45, 1977
- Ward, J M , Goodman, D G , Griesemer, R A , Hardisty, J F , Schueler, R L , Squire, R A , Strandberg, J D , Quality assurance for pathology in rodent carcinogenesis tests J Environ Path Toxicol 2 371-378, 1978

APPENDIX A
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS
FED DIETS CONTAINING 11-AMINOUNDECANOIC ACID

TABLE A1.
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN
MALE RATS FED DIETS CONTAINING 11-AMINOUNDECANOIC ACID

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
PAPILLOMA, NOS	2 (4%)	1 (2%)	
SQUAMOUS CELL CARCINOMA	1 (2%)	1 (2%)	
TRICHOEPITHELIOMA	1 (2%)	1 (2%)	
SEBACEOUS ADENOMA			1 (2%)
NEUROFIBROSARCOMA	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
SARCOMA, NOS		1 (2%)	
FIBROMA	1 (2%)	1 (2%)	3 (6%)
FIBROSARCOMA	1 (2%)	2 (4%)	
LIPOMA		1 (2%)	
NEUROFIBROMA	3 (6%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA		4 (8%)	1 (2%)
PHEOCHROMOCYTOMA, METASTATIC	1 (2%)		
FIBROSARCOMA, METASTATIC	1 (2%)		
OSTEOSARCOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
LEUKEMIA, NOS	2 (4%)		1 (2%)
UNDIFFERENTIATED LEUKEMIA	10 (20%)	3 (6%)	4 (8%)
#SPLEEN	(50)	(50)	(50)
UNDIFFERENTIATED LEUKEMIA	2 (4%)	1 (2%)	
CIRCULATORY SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#SALIVARY GLAND FIBROSARCOMA	(50)	(47) 1 (2%)	(49)
#LIVER NEOPLASTIC NODULE HEPATOCELLULAR CARCINOMA	(50) 1 (2%)	(50) 9 (18%) 1 (2%)	(50) 8 (16%) 2 (4%)
#STOMACH SQUAMOUS CELL CARCINOMA	(50)	(50) 1 (2%)	(50)
#DUODENUM ADENOCARCINOMA, NOS	(49)	(50)	(50) 1 (2%)
#COLON ADENOCARCINOMA, NOS ADENOMATOUS POLYP, NOS	(50)	(50)	(50) 1 (2%) 1 (2%)
URINARY SYSTEM			
#KIDNEY TRANSITIONAL-CELL CARCINOMA	(50)	(50)	(50) 1 (2%)
#URINARY BLADDER TRANSITIONAL-CELL PAPILOMA TRANSITIONAL-CELL CARCINOMA	(48)	(48)	(49) 1 (2%) 7 (14%)
ENDOCRINE SYSTEM			
#PITUITARY CHROMOPHOBE ADENOMA	(48) 3 (6%)	(47) 6 (13%)	(47) 5 (11%)
#ADRENAL CORTICAL ADENOMA PHEOCHROMOCYTOMA PHEOCHROMOCYTOMA, MALIGNANT	(50) 9 (18%) 1 (2%)	(50) 12 (24%)	(49) 1 (2%) 13 (27%)
#THYROID C-CELL ADENOMA C-CELL CARCINOMA	(42) 6 (14%)	(43) 1 (2%)	(42) 1 (2%) 2 (5%)
#PANCREATIC ISLETS ISLET-CELL ADENOMA	(50)	(46) 1 (2%)	(50) 1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS		1 (2%)	
FIBROADENOMA		5 (10%)	2 (4%)
*PREPUCE	(50)	(50)	(50)
SEBACEOUS ADENOCARCINOMA	1 (2%)		
*PREPUTIAL GLAND	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (2%)		
ADENOMA, NOS	1 (2%)	1 (2%)	
SEBACEOUS ADENOCARCINOMA	1 (2%)		
#TESTIS	(50)	(50)	(50)
INTERSTITIAL-CELL TUMOR	45 (90%)	43 (86%)	40 (80%)
NERVOUS SYSTEM			
#CEREBRUM	(50)	(49)	(49)
OLIGODENDROGLIOMA		1 (2%)	
SPECIAL SENSE ORGANS			
*ZYMBAL'S GLAND	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
LIPOMA		1 (2%)	
*ABDOMINAL CAVITY	(50)	(50)	(50)
MESOTHELIOMA, MALIGNANT		1 (2%)	
*PERITONEUM	(50)	(50)	(50)
MESOTHELIOMA, NOS		2 (4%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
 * NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
*TUNICA VAGINALIS MESOTHELIOMA, NOS	(50) 1 (2%)	(50)	(50) 1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS MESOTHELIOMA, METASTATIC	(50)	(50) 1 (2%)	(50)
LEG OSTEOSARCOMA		1	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH ^a	5	6	13
MORIBUND SACRIFICE	6	7	7
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	39	37	30
ANIMAL MISSING			
^a INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	49	48	42
TOTAL PRIMARY TUMORS	94	105	98
TOTAL ANIMALS WITH BENIGN TUMORS	48	43	41
TOTAL BENIGN TUMORS	71	78	70
TOTAL ANIMALS WITH MALIGNANT TUMORS	18	14	17
TOTAL MALIGNANT TUMORS	21	16	19
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	2	
TOTAL SECONDARY TUMORS	2	2	
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT	2	10	9
TOTAL UNCERTAIN TUMORS	2	11	9
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			
* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS			
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN			

TABLE A2.
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN
FEMALE RATS FED DIETS CONTAINING 11-AMINOUNDECANOIC ACID

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
PAPILLOMA, NOS	1 (2%)		2 (4%)
SQUAMOUS CELL CARCINOMA	1 (2%)		
BASAL-CELL TUMOR			1 (2%)
TRICHOEPITHELIOMA		1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)
NEUROFIBROMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(49)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
LEUKEMIA, NOS		2 (4%)	
UNDIFFERENTIATED LEUKEMIA	11 (22%)	11 (22%)	6 (12%)
#SPLEEN	(50)	(49)	(50)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
UNDIFFERENTIATED LEUKEMIA		1 (2%)	
#LYMPH NODE	(50)	(50)	(49)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
#MESENTERIC L. NODE	(50)	(50)	(49)
OSTEOSARCOMA, METASTATIC			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
#THYMUS THYMOMA	(43) 1 (2%)	(39)	(36)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#SALIVARY GLAND ADENOMA, NOS	(50)	(49) 1 (2%)	(49)
#PAROTID DUCT ADENOMA, NOS	(50) 1 (2%)	(49)	(49)
#LIVER NEOPLASTIC NODULE HEPATOCELLULAR CARCINOMA	(50) 4 (8%) 2 (4%)	(50) 5 (10%)	(50) 6 (12%)
#STOMACH SQUAMOUS CELL CARCINOMA	(50) 1 (2%)	(50)	(48)
URINARY SYSTEM			
#KIDNEY TRANSITIONAL-CELL CARCINOMA	(49)	(50)	(50) 2 (4%)
#URINARY BLADDER TRANSITIONAL-CELL PAPILLOMA	(49)	(47)	(48) 1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY ADENOMA, NOS CHROMOPHOBE ADENOMA CHROMOPHOBE CARCINOMA	(50) 1 (2%) 21 (42%)	(50) 1 (2%) 19 (38%) 1 (2%)	(49) 18 (37%)
#ADRENAL CORTICAL ADENOMA PHEOCHROMOCYTOMA	(48) 3 (6%)	(50) 1 (2%) 2 (4%)	(49) 2 (4%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
#THYROID	(45)	(45)	(45)
C-CELL ADENOMA	3 (7%)	2 (4%)	3 (7%)
C-CELL CARCINOMA	1 (2%)		
#PANCREATIC ISLETS	(50)	(50)	(50)
ISLET-CELL ADENOMA			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (2%)		
ADENOMA, NOS		1 (2%)	
PAPILLARY ADENOMA		1 (2%)	
FIBROADENOMA	11 (22%)	10 (20%)	11 (22%)
*PREPUTIAL GLAND	(50)	(50)	(50)
SEBACEOUS ADENOCARCINOMA		1 (2%)	
*VULVA	(50)	(50)	(50)
PAPILLOMA, NOS			1 (2%)
*CLITORAL GLAND	(50)	(50)	(50)
CARCINOMA, NOS	1 (2%)		
SQUAMOUS CELL CARCINOMA			1 (2%)
ADENOMA, NOS	1 (2%)		
SEBACEOUS ADENOCARCINOMA		1 (2%)	
#UTERUS	(50)	(48)	(50)
ADENOCARCINOMA, NOS	1 (2%)		
SARCOMA, NOS		1 (2%)	
LEIOMYOSARCOMA		1 (2%)	
ENDOMETRIAL STROMAL POLYP	15 (30%)	12 (25%)	10 (20%)
#OVARY	(50)	(50)	(50)
GRANULOSA-CELL TUMOR	1 (2%)		
OSTEOSARCOMA		1 (2%)	
NERVOUS SYSTEM			
#BRAIN/MENINGES	(50)	(49)	(50)
MENINGIOMA			1 (2%)
SPECIAL SENSE ORGANS			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
 * NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY LIPOMA	(50) 1 (2%)	(50)	(50)
ALL OTHER SYSTEMS			
LEG OSTEOSARCOMA			1
SOLE OF FOOT SQUAMOUS CELL CARCINOMA		1	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH ^a	4	5	3
MORIBUND SACRIFICE	8	13	5
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	38	32	42
ANIMAL MISSING			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	46	47	37
TOTAL PRIMARY TUMORS	86	80	67
TOTAL ANIMALS WITH BENIGN TUMORS	38	38	31
TOTAL BENIGN TUMORS	60	53	51
TOTAL ANIMALS WITH MALIGNANT TUMORS	17	20	9
TOTAL MALIGNANT TUMORS	21	22	10
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		1
TOTAL SECONDARY TUMORS	1		1
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT	4	5	6
TOTAL UNCERTAIN TUMORS	5	5	6
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			
^a INCLUDES AUTOLYZED ANIMALS			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) CONTROL

ANIMAL NUMBER																					TOTAL TISSUES TUMORS
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	2	2	2	2	3	3	3	3	3	3	4	4	4	4	4	4	4	4	4	4	
	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	
WEEKS ON STUDY	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	0	0	0	9	0	8	0	0	0	0	0	0	0	0	9	0	0	0	0	0	
	9	9	1	4	9	7	9	9	9	9	9	9	9	9	9	9	9	9	9	9	
INTEGUMENTARY SYSTEM																					
SKIN																					
PAPILLOMA, NOS																					
SQUAMOUS CELL CARCINOMA																					
TRICHOEPITHELIOMA																					
NEUROFIBROSARCOMA																					
SUBCUTANEOUS TISSUE FIBROMA																					
FIBROSARCOMA																					
NEUROFIBROMA																					
RESPIRATORY SYSTEM																					
LUNGS AND BRONCHI																					
PNEUOMOCTOMA, METASTATIC																					
FIBROSARCOMA, METASTATIC																					
TRACHEA																					
HEMATOPOIETIC SYSTEM																					
BONE MARROW																					
SPLEEN																					
UNDIFFERENTIATED LEUKEMIA																					
LYMPH NODES																					
THYMUS																					
CIRCULATORY SYSTEM																					
HEART																					
DIGESTIVE SYSTEM																					
SALIVARY GLAND																					
LIVER																					
NEOPLASTIC NODULE																					
BILE DUCT																					
GALLBLADDER & COMMON BILE DUCT																					
PANCREAS																					
ESOPHAGUS																					
STOMACH																					
SMALL INTESTINE																					
LARGE INTESTINE																					
URINARY SYSTEM																					
KIDNEY																					
URINARY BLADDER																					
ENDOCRINE SYSTEM																					
PITUITARY CHROMOPHOBE ADENOMA																					
ADRENAL PNEUOMOCTOMA																					
PNEUOMOCTOMA, MALIGNANT																					
THYROID C-CELL ADENOMA																					
PARATHYROID																					
REPRODUCTIVE SYSTEM																					
MAMMARY GLAND																					
TESTIS																					
INTERSTITIAL-CELL TUMOR																					
PROSTATE																					
PENIS																					
SEBACEOUS ADENOCARCINOMA																					
PREPUITAL/CLITORAL GLAND																					
SQUAMOUS CELL CARCINOMA																					
ADENOMA, NOS																					
SEBACEOUS ADENOCARCINOMA																					
BODY CAVITIES																					
TUNICA VAGINALIS																					
MESOTHELIOMA, NOS																					
ALL OTHER SYSTEMS																					
MULTIPLE ORGANS NOS																					
LEUKEMIA, NOS																					
UNDIFFERENTIATED LEUKEMIA																					

+ TISSUE EXAMINED MICROSCOPICALLY
 - REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
 X TUMOR INCIDENCE
 N NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
 C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
 A: AUTOLYSIS
 M: ANIMAL MISSING
 B: NO NECROPSY PERFORMED

* ANIMALS NECROPSIED

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED)

LOW DOSE

ANIMAL NUMBER	WEEKS ON STUDY																				TOTAL TISSUES TUMORS	
	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9		
INTEGUMENTARY SYSTEM																						
SKIN PAPILLOMA, NOS SQUAMOUS CELL CARCINOMA TRICHOEPITHELIOMA																					X	50 1 1 1
SUBCUTANEOUS TISSUE SARCOMA, NOS FIBROMA FIBROSARCOMA LIPOMA																					X	50 1 1 2 1
RESPIRATORY SYSTEM																						
LUNGS AND BRONCHI ALVEOLAR/BRONCHOLAR ADENOMA OSTEOSARCOMA, METASTATIC																					X	50 4 1
TRACHEA																						50
HEMATOPOIETIC SYSTEM																						
BONE MARROW																					-	47
SPLEEN UNDIFFERENTIATED LEUKEMIA																						50 1
LYMPH NODES																					-	48
THYMUS																					-	38
CIRCULATORY SYSTEM																						
HEART																						50
DIGESTIVE SYSTEM																						
SALIVARY GLAND FIBROSARCOMA																					-	47 1
LIVER NEOPLASTIC NODULE HEPATOCELLULAR CARCINOMA																					X	50 9 1
BILE DUCT																						50
GALLBLADDER & COMMON BILE DUCT																					N	50*
PANCREAS																					-	46
ESOPHAGUS																						50
STOMACH SQUAMOUS CELL CARCINOMA																						50 1
SMALL INTESTINE																						50
LARGE INTESTINE																						50
URINARY SYSTEM																						
KIDNEY																						50
URINARY BLADDER																					-	48
ENDOCRINE SYSTEM																						
PITUITARY CHROMOPHOBE ADENOMA																					X	47 6
ADRENAL PHEOCHROMOCYTOMA																					X	50 12
THYROID C-CELL ADENOMA																						43 1
PARATHYROID																					-	36
PANCREATIC ISLETS ISLET-CELL ADENOMA																					X	45 1
REPRODUCTIVE SYSTEM																						
MAMMARY GLAND ADENOCARCINOMA, NOS FIBROADENOMA																					X	50 1 5
TESTIS INTERSTITIAL-CELL TUMOR																					X	50 43
PROSTATE																					-	39
PREPUTIAL/CLITORAL GLAND ADENOMA, NOS																					N	50 1
NERVOUS SYSTEM																						
BRAIN OLIGODENDROGLIOMA																					X	49 1
SPECIAL SENSE ORGANS																						
ZYMBAL'S GLAND SQUAMOUS CELL CARCINOMA																					X	50 1
BODY CAVITIES																						
MEDIASTINUM LIPOMA																					X	50 1
PERITONEUM MESOTHELIOMA, NOS MESOTHELIOMA, MALIGNANT																					X	50 2 1
ALL OTHER SYSTEMS																						
MULTIPLE ORGANS NOS MESOTHELIOMA, METASTATIC UNDIFFERENTIATED LEUKEMIA																					X	50 1 3
LEG NOS OSTEOSARCOMA																						1

+ TISSUE EXAMINED MICROSCOPICALLY
 - REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
 X TUMOR INCIDENCE
 N NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
 * ANIMALS NECROPSIED
 C NO TISSUE INFORMATION SUBMITTED
 A NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
 AUTOLYSIS
 M ANIMAL MISSING
 B NO NECROPSY PERFORMED

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF 11-AMINOUNDECANOIC ACID

HIGH DOSE

ANIMAL NUMBER	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
WEEKS ON STUDY	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	
INTEGUMENTARY SYSTEM																																								
SKIN																																								
SEBACEOUS ADENOMA																																								
SUBCUTANEOUS TISSUE FIBROMA																																								
RESPIRATORY SYSTEM																																								
LUNGS AND BRONCHI ALVEOLAR/BRONCHIOLAR ADENOMA																																								
TRACHEA																																								
HEMATOPOIETIC SYSTEM																																								
BONE MARROW																																								
SPLEEN																																								
LYMPH NODES																																								
THYMUS																																								
CIRCULATORY SYSTEM																																								
HEART																																								
DIGESTIVE SYSTEM																																								
SALIVARY GLAND																																								
LIVER																																								
NEOPLASTIC NODULE																																								
HEPATOCELLULAR CARCINOMA																																								
BILE DUCT																																								
GALLBLADDER & COMMON BILE DUCT																																								
PANCREAS																																								
ESOPHAGUS																																								
STOMACH																																								
SMALL INTESTINE ADENOCARCINOMA, NOS																																								
LARGE INTESTINE ADENOCARCINOMA, NOS																																								
ADENOMATOUS POLYP, NOS																																								
URINARY SYSTEM																																								
KIDNEY TRANSITIONAL-CELL CARCINOMA																																								
URINARY BLADDER TRANSITIONAL-CELL PAPILLOMA																																								
TRANSITIONAL-CELL CARCINOMA																																								
ENDOCRINE SYSTEM																																								
PITUITARY CHROMOPHOBE ADENOMA																																								
ADRENAL CORTICAL ADENOMA																																								
PHEOCHROMOCYTOMA																																								
THYROID C-CELL ADENOMA																																								
C-CELL CARCINOMA																																								
PARATHYROID																																								
PANCREATIC ISLETS ISLET-CELL ADENOMA																																								
REPRODUCTIVE SYSTEM																																								
MAMMARY GLAND FIBROADENOMA																																								
TESTIS INTERSTITIAL-CELL TUMOR																																								
PROSTATE																																								
BODY CAVITIES																																								
TUNICA VAGINALIS MESOTHELIOMA, NOS																																								
ALL OTHER SYSTEMS																																								
MULTIPLE ORGANS NOS																																								
LEUKEMIA, NOS																																								
UNDIFFERENTIATED LEUKEMIA																																								

+ TISSUE EXAMINED MICROSCOPICALLY
 - REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
 X TUMOR INCIDENCE
 N NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
 C NO TISSUE INFORMATION SUBMITTED
 A NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
 M AUTOLYSIS
 B ANIMAL MISSING
 D NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF 11-AMINOUNDECANOIC ACID

HIGH DOSE

ANIMAL NUMBER	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0								
WEEKS ON STUDY	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
INTEGUMENTARY SYSTEM																													
SKIN PAPILLOMA, NOS																													
BASAL-CELL TUMOR	X																												
RESPIRATORY SYSTEM																													
LUNGS AND BRONCHI																													
TRACHEA																													
HEMATOPOIETIC SYSTEM																													
BONE MARROW																													
SPLEEN																													
LYMPH NODES																													
OSTEOSARCOMA, METASTATIC	X																												
THYMUS																													
CIRCULATORY SYSTEM																													
HEART																													
DIGESTIVE SYSTEM																													
SALIVARY GLAND																													
LIVER																													
NEOPLASTIC NODULE	X																												
BILE DUCT																													
GALLBLADDER & COMMON BILE DUCT	N																												
PANCREAS																													
ESOPHAGUS																													
STOMACH																													
SMALL INTESTINE																													
LARGE INTESTINE																													
URINARY SYSTEM																													
KIDNEY TRANSITIONAL-CELL CARCINOMA																													
URINARY BLADDER TRANSITIONAL-CELL PAPILLOMA	X																												
ENDOCRINE SYSTEM																													
PITUITARY CHROMOPHOBE ADENOMA	X																												
ADRENAL PHEOCHROMOCYTOMA	X																												
THYROID C-CELL ADENOMA	X																												
PARATHYROID																													
PANCREATIC ISLETS ISLET-CELL ADENOMA	X																												
REPRODUCTIVE SYSTEM																													
MAMMARY GLAND FIBROADENOMA	X																												
PREPUTIAL/CLITORAL GLAND SQUAMOUS CELL CARCINOMA	N																												
FEMALE EXTERNAL GENITALIA PAPILLOMA, NOS	N																												
UTERUS ENDDOMETRIAL STRDMAL POLYP	X																												
OVARY																													
NERVOUS SYSTEM																													
BRAIN MENINGIOMA	X																												
ALL OTHER SYSTEMS																													
MULTIPLE ORGANS NOS UNDIFFERENTIATED LEUKEMIA	N																												
LEG NOS OSTEOSARCOMA	X																												

+: TISSUE EXAMINED MICROSCOPICALLY
 -: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
 X: TUMOR INCIDENCE
 N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
 -: NO TISSUE INFORMATION SUBMITTED
 C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
 A: AUTOLYSIS
 M: ANIMAL MISSING
 D: NO NECROPSY PERFORMED

APPENDIX B
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE
FED DIETS CONTAINING 11-AMINOUNDECANOIC ACID

TABLE B1.
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN
MALE MICE FED DIETS CONTAINING 11-AMINOUNDECANOIC ACID

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(46)
HEPATOCELLULAR CARCINOMA, METAST	3 (6%)	2 (4%)	1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	10 (20%)	3 (6%)	4 (9%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	2 (4%)	6 (12%)	4 (8%)
#SPLEEN	(50)	(47)	(47)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
#LYMPH NODE	(33)	(43)	(32)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
#THYMUS	(24)	(25)	(17)
MALIGNANT LYMPHOMA, NOS		1 (4%)	
CIRCULATORY SYSTEM			
*SKIN	(50)	(50)	(50)
HEMANGIOMA		1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)
HEMANGIOMA	1 (2%)		
#SPLEEN	(50)	(47)	(47)
HEMANGIOSARCOMA		3 (6%)	
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
#HEART HEMANGIOSARCOMA	(50) 1 (2%)	(50)	(49)
#LIVER HEMANGIOSARCOMA	(50) 1 (2%)	(50) 1 (2%)	(49)
DIGESTIVE SYSTEM			
#LIVER HEPATOCELLULAR ADENOMA HEPATOCELLULAR CARCINOMA	(50) 1 (2%) 16 (32%)	(50) 3 (6%) 16 (32%)	(49) 3 (6%) 9 (18%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#ADRENAL CORTICAL ADENOMA PHEOCHROMOCYTOMA	(44) 1 (2%) 1 (2%)	(48)	(42)
#THYROID FOLLICULAR-CELL ADENOMA	(47) 1 (2%)	(42) 1 (2%)	(36) 1 (3%)
REPRODUCTIVE SYSTEM			
#TESTIS INTERSTITIAL-CELL TUMOR	(49)	(50) 1 (2%)	(47) 1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND ADENOMA, NOS	(50) 1 (2%)	(50) 1 (2%)	(50)
MUSCULOSKELETAL SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
 * NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH ^a	7	12	28
MORIBUND SACRIFICE	5	4	4
SCHEDULED SACRIFICE	1		
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	37	34	18
ANIMAL MISSING			
^a INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	30	29	18
TOTAL PRIMARY TUMORS	36	39	22
TOTAL ANIMALS WITH BENIGN TUMORS	15	8	9
TOTAL BENIGN TUMORS	16	10	9
TOTAL ANIMALS WITH MALIGNANT TUMORS	19	25	12
TOTAL MALIGNANT TUMORS	20	29	13
TOTAL ANIMALS WITH SECONDARY TUMORS#	3	2	1
TOTAL SECONDARY TUMORS	3	2	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			
* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS			
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN			

TABLE B2.
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN
FEMALE MICE FED DIETS CONTAINING 11-AMINOUNDECANOIC ACID

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	1
ANIMALS NECROPSIED	50	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	49
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(49)
PAPILLOMA, NOS	1 (2%)		
NEUROFIBROSARCOMA	1 (2%)		
*SUBCUT TISSUE	(50)	(49)	(49)
OSTEOSARCOMA		1 (2%)	
NEUROFIBROSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(49)	(49)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)	3 (6%)	3 (6%)
OSTEOSARCOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(49)	(49)
MALIGNANT LYMPHOMA, NOS	7 (14%)	10 (20%)	9 (18%)
#SPLEEN	(50)	(49)	(47)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
#SMALL INTESTINE	(49)	(49)	(47)
MALIGNANT LYMPHOMA, NOS			1 (2%)
#KIDNEY	(50)	(49)	(49)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
CIRCULATORY SYSTEM			
*SUBCUT TISSUE	(50)	(49)	(49)
HEMANGIOMA			1 (2%)
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
#SPLEEN HEMANGIOSARCOMA	(50) 2 (4%)	(49)	(47)
#OVARY HEMANGIOMA	(46)	(46) 1 (2%)	(45)
DIGESTIVE SYSTEM			
#LIVER HEPATOCELLULAR ADENOMA	(50) 2 (4%)	(49) 1 (2%)	(49) 1 (2%)
HEPATOCELLULAR CARCINOMA	5 (10%)	7 (14%)	4 (8%)
OSTEOSARCOMA, METASTATIC		1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY ADENOMA, NOS	(42) 3 (7%)	(39) 5 (13%)	(41) 2 (5%)
#ADRENAL CORTICAL ADENOMA	(47)	(46) 1 (2%)	(48)
PHEOCHROMOCYTOMA		1 (2%)	1 (2%)
#THYROID FOLLICULAR-CELL ADENOMA	(37) 1 (3%)	(41)	(40)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND ADENOCARCINOMA, NOS	(50) 6 (12%)	(49) 1 (2%)	(49) 2 (4%)
*VULVA PAPILLOMA, NOS	(50) 1 (2%)	(49)	(49)
#UTERUS ADENOCARCINOMA, NOS	(48) 1 (2%)	(49)	(49)
#OVARY/OVIDUCT PAPILLARY ADENOMA	(48)	(49)	(49) 1 (2%)
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
#OVARY TERATOMA, BENIGN	(46)	(46)	(45) 1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND ADENOMA, NOS	(50)	(49) 2 (4%)	(49)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH ^a	4	8	19
MORIBUND SACRIFICE	4	4	5
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	42	37	25
ANIMAL MISSING		1	1
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	28	27	19
TOTAL PRIMARY TUMORS	34	34	26
TOTAL ANIMALS WITH BENIGN TUMORS	10	13	9
TOTAL BENIGN TUMORS	10	14	10
TOTAL ANIMALS WITH MALIGNANT TUMORS	21	20	13
TOTAL MALIGNANT TUMORS	24	20	16
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	
TOTAL SECONDARY TUMORS		2	
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			
^a INCLUDES AUTOLYZED ANIMALS			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF 11-AMINOUNDECANOIC ACID

CONTROL

ANIMAL NUMBER	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
WEEKS ON STUDY	1	2	3	4	5	6	7	8	9	0	1	1	1	1	1	1	1	2	2	2	2	2	2
INTEGUMENTARY SYSTEM	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
SUBCUTANEOUS TISSUE HEMANGIOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	
RESPIRATORY SYSTEM																							
LUNGS AND BRONCHI HEPATOCELLULAR CARCINOMA, METASTA ALVEOLAR/BRONCHIOLAR ADENOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
TRACHEA	X	X			X									X						X			
HEMATOPOIETIC SYSTEM																							
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
LYMPH NODES	+	-	-	-	-	-	-	-	-	+	+	+	+	-	+	+	+	+	+	+	+	+	
THYMUS	+	-	-	-	-	+	+	-	-	+	+	-	-	+	+	+	+	+	-	-	+	+	
CIRCULATORY SYSTEM																							
HEART HEMANGIOSARCOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
DIGESTIVE SYSTEM																							
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	
LIVER HEPATOCELLULAR ADENOMA HEPATOCELLULAR CARCINOMA HEMANGIOSARCOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
BILE DUCT	X	X												X	X	X				X	X		
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
ESOPHAGUS	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
URINARY SYSTEM																							
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
URINARY BLADDER	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
ENDOCRINE SYSTEM																							
PITUITARY	+	-	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	-	-	+	+	+	
ADRENAL CORTICAL ADENOMA PHEOCHROMOCYTOMA	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	
THYROID FOLLICULAR-CELL ADENOMA	X							X															
PARATHYROID	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	
REPRODUCTIVE SYSTEM																							
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	
SPECIAL SENSE ORGANS																							
HARDERIAN GLAND ADENOMA, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
ALL OTHER SYSTEMS																							
MULTIPLE ORGANS NOS MALIGNANT LYMPHOMA, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	

+ TISSUE EXAMINED MICROSCOPICALLY
 - REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
 X TUMOR INCIDENCE
 N NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
 C NO TISSUE INFORMATION SUBMITTED
 NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
 A AUTOLYSIS
 M ANIMAL MISSING
 B NO NECROPSY PERFORMED

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF 11-AMINOUNDECANOIC ACID

LOW DOSE

Table with columns for Animal Number (0-22) and Weeks on Study (0-9). Rows include Integumentary System (SKIN HEMANGIOMA), Respiratory System (LUNGS AND BRONCHI, HEPATOCELLULAR CARCINOMA, METASTA ALVEOLAR/BRONCHIOLAR ADENOMA, TRACHEA), Hematopoietic System (BONE MARROW, SPLEEN HEMANGIOSARCOMA, MALIGNANT LYMPHOMA, NOS, LYMPH NODES MALIGNANT LYMPHOMA, NOS, THYMUS MALIGNANT LYMPHOMA, NOS), Circulatory System (HEART), Digestive System (SALIVARY GLAND, LIVER HEPATOCELLULAR ADENOMA, HEPATOCELLULAR CARCINOMA, HEMANGIOSARCOMA, BILE DUCT, GALLBLADDER & COMMON BILE DUCT, PANCREAS, ESOPHAGUS, STOMACH, SMALL INTESTINE, LARGE INTESTINE), Urinary System (KIDNEY, URINARY BLADDER), Endocrine System (PITUITARY, ADRENAL, THYROID FOLLICULAR-CELL ADENOMA, PARATHYROID), Reproductive System (MAMMARY GLAND, TESTIS INTERSTITIAL-CELL TUMOR, PROSTATE), and Special Sense Organs (HARDERIAN GLAND ADENOMA, NOS). Legend at bottom defines symbols: + (tissue examined), - (required tissue not examined), X (tumor incidence), N (necropsy), C (no tissue info), A (autolysis), M (animal missing), B (no necropsy).

TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	TOTAL TISSUES																		
WEEKS ON STUDY	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	TUMORS																		
INTEGUMENTARY SYSTEM																																								
SKIN HEMANGIOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	50* 1																		
RESPIRATORY SYSTEM																																								
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50																		
HEPATOCELLULAR CARCINOMA, METASTA																				X	X	X																	2 3	
ALVEOLAR/BRONCHIOLAR ADENOMA																																								
TRACHEA	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	43																		
HEMATOPOIETIC SYSTEM																																								
BONE MARROW	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	-	+	+	43																		
SPLEEN HEMANGIOSARCOMA	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47 3 1																		
MALIGNANT LYMPHOMA, NOS																																								
LYMPH NODES	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	43 1																		
MALIGNANT LYMPHOMA, NOS																																								
THYMUS	-	-	-	-	+	-	+	-	-	-	-	-	-	-	+	-	+	-	-	-	-	25 1																		
MALIGNANT LYMPHOMA, NOS																																								
CIRCULATORY SYSTEM																																								
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50																		
DIGESTIVE SYSTEM																																								
SALIVARY GLAND	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	47																		
LIVER																																								
HEPATOCELLULAR ADENOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 3 16 1																		
HEPATOCELLULAR CARCINOMA																				X	X	X	X	X	X	X	X	X												
HEMANGIOSARCOMA																																								
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50																		
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	N	+	+	+	+	50*																		
PANCREAS	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48																		
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46																		
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48																		
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50																		
LARGE INTESTINE	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	46																		
URINARY SYSTEM																																								
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50																		
URINARY BLADDER	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44																		
ENDOCRINE SYSTEM																																								
PITUITARY	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	-	+	40																		
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48																		
THYROID	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42 1																		
FOLLICULAR-CELL ADENOMA																																								
PARATHYROID	-	-	-	-	+	-	+	-	-	-	+	-	-	-	+	-	-	-	-	-	-	18																		
REPRODUCTIVE SYSTEM																																								
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*																		
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 1																		
INTERSTITIAL-CELL TUMOR																																								
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50																		
SPECIAL SENSE ORGANS																																								
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50* 1																		
ADENOMA, NOS																																								
ALL OTHER SYSTEMS																																								
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50* 6																		
MALIGNANT LYMPHOMA, NOS																				X	X																			

+ : TISSUE EXAMINED MICROSCOPICALLY
 - : TISSUE INFORMATION SUBMITTED
 - : REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
 C : NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
 X : TUMOR INCIDENCE
 A : AUTOLYSIS
 N : NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
 M : ANIMAL MISSING
 B : NO NECROPSY PERFORMED
 * ANIMALS NECROPSIED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF 11-AMINOUNDECANOIC ACID

CONTROL

	ANIMAL NUMBER	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	WEEKS ON STUDY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
INTEGUMENTARY SYSTEM																					
SKIN PAPILLOMA, NOS NEUROFIBROSARCOMA		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																					
LUNGS AND BRONCHI ALVEOLAR/BRONCHIOALAR ADENOMA		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA		-	+	+	+	+	+	-	+	+	-	+	+	-	+	+	+	+	+	+	-
HEMATOPOIETIC SYSTEM																					
BONE MARROW		+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
SPLEEN HEMANGIOSARCOMA MALIGNANT LYMPHOMA, NOS		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES		+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS		-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+
CIRCULATORY SYSTEM																					
HEART		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																					
SALIVARY GLAND		+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER HEPATOCELLULAR ADENOMA HEPATOCELLULAR CARCINOMA		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT		+	+	N	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+
PANCREAS		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS		-	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	+
STOMACH		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE		+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																					
KIDNEY MALIGNANT LYMPHOMA, NOS		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																					
PITUITARY ADENOMA, NOS		+	+	+	-	+	-	+	-	+	+	+	-	+	+	+	+	+	+	-	+
ADRENAL		+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID FOLLICULAR-CELL ADENOMA		-	+	+	+	-	+	-	+	-	+	+	+	+	+	+	+	+	+	+	-
PARATHYROID		-	+	-	-	+	+	-	-	+	-	-	+	-	-	+	-	-	+	-	-
REPRODUCTIVE SYSTEM																					
MAMMARY GLAND ADENOCARCINOMA, NOS		+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	N	+
FEMALE EXTERNAL GENITALIA PAPILLOMA, NOS		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
UTERUS ADENOCARCINOMA, NOS		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
OVARY		-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																					
MULTIPLE ORGANS NOS MALIGNANT LYMPHOMA, NOS		N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N

+ TISSUE EXAMINED MICROSCOPICALLY
 - REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
 X TUMOR INCIDENCE
 N NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
 C NO TISSUE INFORMATION SUBMITTED
 A NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
 A AUTOLYSIS
 N ANIMAL MISSING
 B NO NECROPSY PERFORMED

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) CONTROL

ANIMAL NUMBER	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	TOTAL TISSUES TUMORS	
WEEKS ON STUDY	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50x	
PAPILLOMA, NOS																					X			1	
NEUROFIBROSARCOMA	X																							1	
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
ALVEOLAR/BRONCHIOLAR ADENOMA												X												2	
TRACHEA	+	+	+	+	-	-	-	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	39	
HEMATOPOIETIC SYSTEM																									
BONE MARROW	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46	
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
HEMANGIOSARCOMA																X								2	
MALIGNANT LYMPHOMA, NOS																								1	
LYMPH NODES	+	-	-	-	+	+	+	+	+	-	+	+	+	+	+	-	-	+	-	+	+	+	+	35	
THYMUS	+	+	+	+	+	-	-	-	+	+	-	-	+	-	+	+	+	+	+	+	-	+	-	30	
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
HEPATOCELLULAR ADENOMA																						X		2	
HEPATOCELLULAR CARCINOMA																	X						X	5	
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50x	
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
ESOPHAGUS	+	+	+	-	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	-	35	
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
MALIGNANT LYMPHOMA, NOS						X																		1	
URINARY BLADDER	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
ENDOCRINE SYSTEM																									
PITUITARY ADENOMA, NOS	+	-	+	+	+	+	+	+	X	+	+	+	+	+	-	+	+	+	+	+	+	+	+	42	
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	3	
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
THYROID FOLLICULAR-CELL ADENOMA	+	-	+	-	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	37	
PARATHYROID	-	-	+	-	-	-	-	-	-	-	+	-	+	-	+	-	-	+	-	-	-	-	-	16	
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND ADENOCARCINOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	50x	
FEMALE EXTERNAL GENITALIA PAPILLOMA, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	6	
UTERUS ADENOCARCINOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	50x	
OVARY	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	1	
+																								46	
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50x	
MALIGNANT LYMPHOMA, NOS	X					X																		7	

+ TISSUE EXAMINED MICROSCOPICALLY
- REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X TUMOR INCIDENCE
N NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
* ANIMALS NECROPSIED
· NO TISSUE INFORMATION SUBMITTED
C NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A AUTOLYSIS
M ANIMAL MISSING
B NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF 11-AMINOUNDECANOIC ACID

LOW DOSE

ANIMAL NUMBER	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
WEEKS ON STUDY	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE OSTEOSARCOMA NEUROFIBROSARCOMA	+ + + + + + + + + + + + + + + + + + + N + + + + + + +																								
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI ALVEOLAR/BRONCHIOLAR ADENOMA OSTEOSARCOMA, METASTATIC	+ + + + + + + + + + + + + + + + + + + X + + + + + + +																								
TRACHEA	+ + + + - + - + - + - + + + + + + - + + + + + + +																								
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+ + + - + + + + + + + + + + + + + + + + + + + - - +																								
SPLEEN	+ +																								
LYMPH NODES	+ + + + + + - + - + - + + + + + + + + + + + + - + + + +																								
THYMUS	+ + + + - + + - + + + + + - + + - + - - + + + - +																								
CIRCULATORY SYSTEM																									
HEART	+ +																								
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+ +																								
LIVER HEPATOCELLULAR ADENOMA HEPATOCELLULAR CARCINOMA OSTEOSARCOMA, METASTATIC	+ X X X X X																								
BILE DUCT	+ +																								
GALLBLADDER & COMMON BILE DUCT	+ + + + + + N N + + + N + + + + + + + + + + + + + + + + +																								
PANCREAS	+ +																								
ESOPHAGUS	+ + + + + + + + + + - + - + + + + + + + + + + - + - +																								
STOMACH	+ +																								
SMALL INTESTINE	+ +																								
LARGE INTESTINE	+ + + + + + + + + + - + + + + + + + + + + + + + + + + + +																								
URINARY SYSTEM																									
KIDNEY	+ +																								
URINARY BLADDER	+ + + + + - +																								
ENDOCRINE SYSTEM																									
PITUITARY ADENOMA, NOS	+ + + + + + + + + - + - + - + + + + + - - + + + + X X X X																								
ADRENAL CORTICAL ADENOMA PHEOCHROMOCYTOMA	+ + + + + + + + + + + + - + + + + + + + + - + + - +																								
THYROID	+ + + + - + - + + - + + - + + + - + + + + - + + +																								
PARATHYROID	- - + + - + - - - - - + - - - - - - - - + + - - +																								
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND ADENOCARCINOMA, NOS	+ + + + + N + + + + + + + + + + + + N N + + + N + + +																								
UTERUS	+ +																								
OVARY HEMANGIOMA	+ + + + + + + + + + + + - + + + + + + + + + + + + + + + + X																								
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND ADENOMA, NOS	N X X X X																								
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS MALIGNANT LYMPHOMA, NOS	N X X X X																								

+ TISSUE EXAMINED MICROSCOPICALLY
 - REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
 X TUMOR INCIDENCE
 N NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
 C NO TISSUE INFORMATION SUBMITTED
 A NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
 M AUTOLYSIS
 B ANIMAL MISSING
 B NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF 11-AMINOUNDECANOIC ACID

HIGH DOSE

ANIMAL NUMBER	WEEKS ON STUDY																			
	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9
INTEGUMENTARY SYSTEM																				
SUBCUTANEOUS TISSUE HEMANGIOMA	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																				
LUNGS AND BRONCHI ALVEOLAR/BRONCHIOGLAR ADENOMA	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	M	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-
HEMATOPOIETIC SYSTEM																				
BONE MARROW	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
SPLEEN	+	+	M	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	M	+	-	+	-	+	+	+	-	+	+	+	+	-	-	+	-	+
THYMUS	-	-	M	-	-	-	-	+	-	+	-	+	+	+	+	-	+	+	+	-
CIRCULATORY SYSTEM																				
HEART	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																				
SALIVARY GLAND	+	+	M	+	+	-	+	+	+	+	+	+	+	+	+	-	-	+	-	+
LIVER HEPATOCELLULAR ADENOMA HEPATOCELLULAR CARCINOMA	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	M	+	N	+	N	+	+	+	+	+	+	+	+	+	+	N	+	N
PANCREAS	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE MALIGNANT LYMPHOMA, NOS	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
LARGE INTESTINE	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
URINARY SYSTEM																				
KIDNEY	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																				
PITUITARY ADENOMA, NOS	+	+	M	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	-
ADRENAL PHEOCHROMOCYTOMA	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	+	M	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
PARATHYROID	+	+	M	-	+	-	-	+	+	+	-	-	-	-	-	+	+	-	+	-
REPRODUCTIVE SYSTEM																				
MAMMARY GLAND ADENOCARCINOMA, NOS	+	+	M	+	N	N	N	+	+	+	N	+	+	+	+	N	+	+	N	+
UTERUS PAPILLARY ADENOMA	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
OVARY TERATOMA, BENIGN	+	+	M	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+
ALL OTHER SYSTEMS																				
MULTIPLE ORGANS NOS	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIGNANT LYMPHOMA, NOS	X			X				X							X	X		X		

+ TISSUE EXAMINED MICROSCOPICALLY
 - REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
 X TUMOR INCIDENCE
 N NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
 C NO TISSUE INFORMATION SUBMITTED
 A NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
 M AUTOLYSIS
 M ANIMAL MISSING
 B NO NECROPSY PERFORMED

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	TOTAL
WEEKS ON STUDY	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	TISSUES TUMORS
INTEGUMENTARY SYSTEM																						
SUBCUTANEOUS TISSUE HEMANGIOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49*
																						1
RESPIRATORY SYSTEM																						
LUNGS AND BRONCHI ALVEOLAR/BRONCHIOLAR ADENOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
																						3
TRACHEA	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
HEMATOPOIETIC SYSTEM																						
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SPLEEN	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
LYMPH NODES	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
THYMUS	-	-	+	-	-	-	-	+	+	-	+	-	+	-	+	-	+	-	+	-	-	22
CIRCULATORY SYSTEM																						
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																						
SALIVARY GLAND	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
LIVER HEPATOCELLULAR ADENOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR CARCINOMA																						4
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49*
PANCREAS	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ESOPHAGUS	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE MALIGNANT LYMPHOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
																						1
LARGE INTESTINE	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																						
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY BLADDER	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																						
PITUITARY ADENOMA NOS	-	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
																						2
ADRENAL PHEOCHROMOCYTOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
THYROID	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
PARATHYROID	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
REPRODUCTIVE SYSTEM																						
MAMMARY GLAND ADENOCARCINOMA, NOS	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49*
																						2
UTERUS PAPILLARY ADENOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
																						1
OVARY TERATOMA, BENIGN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
ALL OTHER SYSTEMS																						
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
MALIGNANT LYMPHOMA, NOS																						5

+ TISSUE EXAMINED MICROSCOPICALLY
 -+ REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
 X TUMOR INCIDENCE
 N NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
 C NO TISSUE INFORMATION SUBMITTED
 A NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
 M AUTOLYSIS
 B ANIMAL MISSING
 NO NECROPSY PERFORMED

* ANIMALS NECROPSIED

APPENDIX C
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS
IN RATS FED DIETS CONTAINING 11-AMINOUNDECANOIC ACID

TABLE C1.

**SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN
MALE RATS FED DIETS CONTAINING 11-AMINOUNDECANOIC ACID**

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST	1 (2%)	1 (2%)	2 (4%)
ABSCESS, NOS			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
CUTANEOUS HORN	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
DEFORMITY, NOS			1 (2%)
EDEMA, NOS	1 (2%)		
RESPIRATORY SYSTEM			
*NASAL CAVITY	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE		1 (2%)	
#LUNG	(50)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
PNEUMONIA, ASPIRATION		2 (4%)	
ALVEOLAR MACROPHAGES		1 (2%)	
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)		
HEMATOPOIETIC SYSTEM			
#MANDIBULAR L. NODE	(50)	(48)	(49)
HYPERPLASIA, RETICULUM CELL		1 (2%)	
#COLON	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)	2 (4%)	
#THYMUS	(42)	(38)	(33)
HYPERPLASIA, RETICULUM CELL			1 (3%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
#LUNG PERIARTERITIS	(50) 1 (2%)	(50)	(50)
#HEART/ATRIUM THROMBOSIS, NOS	(50) 2 (4%)	(50) 3 (6%)	(50)
#AURICULAR APPENDAGE THROMBOSIS, NOS	(50) 1 (2%)	(50)	(50)
#MYOCARDIUM INFLAMMATION, NOS INFLAMMATION, CHRONIC FIBROSIS	(50) 2 (4%)	(50) 1 (2%)	(50) 1 (2%)
*AORTA MEDIAL CALCIFICATION	(50)	(50)	(50) 1 (2%)
*PULMONARY ARTERY MEDIAL CALCIFICATION	(50) 14 (28%)	(50) 11 (22%)	(50) 13 (26%)
*MESENTERY PERIARTERITIS	(50)	(50) 2 (4%)	(50)
DIGESTIVE SYSTEM			
#LIVER HERNIA, NOS	(50)	(50) 1 (2%)	(50)
GRANULOMA, NOS	9 (18%)	15 (30%)	4 (8%)
NECROSIS, FOCAL	1 (2%)	1 (2%)	1 (2%)
METAMORPHOSIS FATTY	2 (4%)	1 (2%)	2 (4%)
CYTOPLASMIC VACUOLIZATION	1 (2%)	14 (28%)	5 (10%)
BASOPHILIC CYTO CHANGE		2 (4%)	4 (8%)
FOCAL CELLULAR CHANGE		2 (4%)	3 (6%)
EOSINOPHILIC CYTO CHANGE		4 (8%)	
CLEAR-CELL CHANGE	1 (2%)	4 (8%)	5 (10%)
#LIVER/CENTRIOBULAR NECROSIS, NOS	(50)	(50) 1 (2%)	(50)
#LIVER/HEPATOCTYES NECROSIS, NOS	(50)	(50)	(50) 1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
#BILE DUCT	(50)	(50)	(50)
INFLAMMATION, FOCAL	1 (2%)		
HYPERPLASIA, NOS	4 (8%)		1 (2%)
HYPERPLASIA, FOCAL	1 (2%)		
#PANCREAS	(50)	(46)	(50)
INFLAMMATION, NOS		1 (2%)	
ATROPHY, NOS	2 (4%)	2 (4%)	3 (6%)
ATROPHY, FOCAL	1 (2%)		
#STOMACH	(50)	(50)	(50)
INFLAMMATION, ACUTE			3 (6%)
HYPERPLASIA, EPITHELIAL			1 (2%)
HYPERKERATOSIS	1 (2%)		
#DUODENUM	(49)	(50)	(50)
POLYP		1 (2%)	
#COLON	(50)	(50)	(50)
NEMATODIASIS			2 (4%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
HYDRONEPHROSIS		1 (2%)	
NEPHROPATHY, TOXIC	1 (2%)		
GLOMERULOSCLEROSIS, NOS	32 (64%)	35 (70%)	27 (54%)
CALCIFICATION, FOCAL		1 (2%)	2 (4%)
#KIDNEY/PELVIS	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL		4 (8%)	15 (30%)
#URINARY BLADDER	(48)	(48)	(49)
CALCULUS, NOS	1 (2%)	1 (2%)	5 (10%)
HYPERPLASIA, EPITHELIAL		2 (4%)	20 (41%)
*URETHRA	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(48)	(47)	(47)
CYST, NOS		3 (6%)	1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
GRANULOMA, FOREIGN BODY	1 (2%)		
HYPERPLASIA, CHROMOPHOBE-CELL	1 (2%)	1 (2%)	3 (6%)
#ADRENAL	(50)	(50)	(49)
EDEMA, NOS		1 (2%)	
METAMORPHOSIS FATTY	1 (2%)	1 (2%)	1 (2%)
#ADRENAL MEDULLA	(50)	(50)	(49)
HYPERPLASIA, NOS		3 (6%)	3 (6%)
#THYROID	(42)	(43)	(42)
CYST, NOS			1 (2%)
HYPERPLASIA, C-CELL	4 (10%)	2 (5%)	3 (7%)
#PARATHYROID	(36)	(36)	(30)
HYPERPLASIA, NOS	1 (3%)	1 (3%)	1 (3%)
#PANCREATIC ISLETS	(50)	(46)	(50)
HYPERPLASIA, NOS	1 (2%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
CYST, NOS			1 (2%)
LACTATION	1 (2%)		1 (2%)
*PREPUCE	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
*PREPUTIAL GLAND	(50)	(50)	(50)
DISTENTION	1 (2%)		
CYSTIC DUCTS		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	
HYPERPLASIA, NOS		1 (2%)	
#PROSTATE	(45)	(39)	(44)
INFLAMMATION, SUPPURATIVE		2 (5%)	
*SEMINAL VESICLE	(50)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, SUPPURATIVE			1 (2%)
GRANULOMA, NOS			1 (2%)
GRANULOMA, SPERMATIC		1 (2%)	
#TESTIS	(50)	(50)	(50)
ATROPHY, NOS	1 (2%)	1 (2%)	3 (6%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, INTERSTITIAL CELL	1 (2%)		1 (2%)
*EPIDIDYMIS DEGENERATION, NOS	(50)	(50)	(50) 1 (2%)
*SCROTUM NECROSIS, FAT	(50) 1 (2%)	(50)	(50)
NERVOUS SYSTEM			
#CEREBELLUM HEMORRHAGE	(50)	(49) 1 (2%)	(49)
SPECIAL SENSE ORGANS			
*EYE CATARACT	(50) 8 (16%)	(50) 9 (18%)	(50) 5 (10%)
*EYE ANTERIOR CHAMBER FIBROSIS	(50)	(50) 1 (2%)	(50)
*EYE/CORNEA INFLAMMATION, NOS ULCER, NOS INFLAMMATION, SUPPURATIVE SCAR DEGENERATION, HYALINE	(50) 1 (2%) 1 (2%) 1 (2%) 1 (2%)	(50)	(50) 2 (4%) 1 (2%)
*EYE/RETINA ATROPHY, NOS	(50) 8 (16%)	(50) 9 (18%)	(50) 5 (10%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY ACCESSORY SPLEEN NECROSIS, FAT	(50)	(50) 1 (2%) 1 (2%)	(50)
*PERITONEUM INFLAMMATION, FOCAL	(50)	(50)	(50) 1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
*MESENTERY NECROSIS, FAT	(50) 1 (2%)	(50)	(50) 3 (6%)
ALL OTHER SYSTEMS			
TAIL HEMORRHAGIC CYST			1
ADIPOSE TISSUE NECROSIS, NOS		1	
OMENTUM NECROSIS, FAT			1
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED			5
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN
FEMALE RATS FED DIETS CONTAINING 11-AMINOUNDECANOIC ACID

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
ULCER, NOS	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(49)
PNEUMONIA, ASPIRATION	2 (4%)		
PNEUMONIA, CHRONIC MURINE		1 (2%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(50)	(49)	(48)
HYPOPLASIA, NOS	2 (4%)		5 (10%)
#SPLEEN	(50)	(49)	(50)
HYPERPLASIA, NODULAR		2 (4%)	1 (2%)
#LIVER	(50)	(50)	(50)
HYPERPLASIA, RETICULUM CELL	1 (2%)		
CIRCULATORY SYSTEM			
#HEART	(50)	(50)	(50)
DILATATION, NOS		1 (2%)	
FIBROELASTOSIS ENDOCARDIAL			1 (2%)
#MYOCARDIUM	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)		
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
FIBROSIS		1 (2%)	1 (2%)
*CORONARY ARTERY THROMBUS, CANALIZED	(50)	(50)	(50) 1 (2%)
*PULMONARY ARTERY MINERALIZATION MEDIAL CALCIFICATION	(50) 10 (20%)	(50) 1 (2%) 11 (22%)	(50) 1 (2%) 8 (16%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
HERNIA, NOS		1 (2%)	
GRANULOMA, NOS	21 (42%)	26 (52%)	27 (54%)
NECROSIS, FOCAL		1 (2%)	
METAMORPHOSIS FATTY	8 (16%)	10 (20%)	
CYTOPLASMIC VACUOLIZATION			3 (6%)
BASOPHILIC CYTO CHANGE	3 (6%)	1 (2%)	5 (10%)
FOCAL CELLULAR CHANGE			1 (2%)
EOSINOPHILIC CYTO CHANGE		2 (4%)	
CLEAR-CELL CHANGE	1 (2%)	3 (6%)	
#LIVER/CENTRIOLOBULAR NECROSIS, NOS METAMORPHOSIS FATTY	(50)	(50) 1 (2%)	(50) 1 (2%)
#BILE DUCT HYPERPLASIA, NOS	(50)	(50) 1 (2%)	(50)
#PANCREAS	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
FIBROSIS, FOCAL		1 (2%)	1 (2%)
ATROPHY, NOS	3 (6%)		
ATROPHY, FOCAL	1 (2%)		
#STOMACH	(50)	(50)	(48)
ULCER, NOS	1 (2%)		
INFLAMMATION, ACUTE			1 (2%)
HYPERKERATOSIS	1 (2%)	1 (2%)	
#GASTRIC MUCOSA CYST, NOS	(50) 1 (2%)	(50)	(48)
URINARY SYSTEM			
#KIDNEY MINERALIZATION	(49)	(50) 1 (2%)	(50)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
CYST, NOS			3 (6%)
NEPHROSIS, TOXIC		1 (2%)	
GLOMERULOSCLEROSIS, NOS	4 (8%)	1 (2%)	12 (24%)
METAMORPHOSIS FATTY	1 (2%)		
CALCIFICATION, NOS			3 (6%)
CALCIFICATION, FOCAL	3 (6%)	18 (36%)	26 (52%)
#KIDNEY/MEDULLA	(49)	(50)	(50)
CYST, NOS			1 (2%)
#KIDNEY/PELVIS	(49)	(50)	(50)
DEGENERATION, MUCOID			1 (2%)
HYPERPLASIA, EPITHELIAL		5 (10%)	34 (68%)
#URINARY BLADDER	(49)	(47)	(48)
ULCER, NOS			1 (2%)
HYPERPLASIA, EPITHELIAL	4 (8%)	12 (26%)	9 (19%)
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(50)	(49)
CYST, NOS	1 (2%)		1 (2%)
HEMATOMA, NOS			1 (2%)
HEMORRHAGIC CYST	1 (2%)		
HYPERPLASIA, CHROMOPHOBE-CELL	1 (2%)	2 (4%)	4 (8%)
ANGIECTASIS		1 (2%)	
#ADRENAL	(48)	(50)	(49)
NECROSIS, CORTICAL		2 (4%)	
METAMORPHOSIS FATTY	5 (10%)	2 (4%)	1 (2%)
LIPOIDOSIS		1 (2%)	
#ADRENAL CORTEX	(48)	(50)	(49)
HYPERPLASIA, NODULAR	1 (2%)		
#ADRENAL MEDULLA	(48)	(50)	(49)
HYPERPLASIA, NOS	1 (2%)		1 (2%)
#THYROID	(45)	(45)	(45)
HYPERPLASIA, C-CELL	5 (11%)	5 (11%)	4 (9%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
CYST, NOS			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
LACTATION	13 (26%)	10 (20%)	11 (22%)
*CLITORAL GLAND HYPERPLASIA, NOS	(50)	(50)	(50) 1 (2%)
*VAGINA POLYP	(50)	(50) 1 (2%)	(50)
#UTERUS CYST, NOS	(50)	(48) 1 (2%)	(50)
HEMORRHAGIC CYST HYPERPLASIA, EPITHELIAL	1 (2%)		1 (2%)
#UTERUS/ENDOMETRIUM CYST, NOS	(50)	(48)	(50) 4 (8%)
HYPERPLASIA, CYSTIC HYPERPLASIA, STROMAL	1 (2%) 1 (2%)	2 (4%)	1 (2%)
#OVARY/OVIDUCT ABSCESS, NOS	(50)	(48) 1 (2%)	(50)
#OVARY CYST, NOS	(50) 1 (2%)	(50)	(50) 3 (6%)
ATROPHY, NOS	1 (2%)		
NERVOUS SYSTEM			
#BRAIN HYDROCEPHALUS, NOS	(50) 1 (2%)	(49)	(50)
SCAR ATROPHY, PRESSURE	3 (6%)	1 (2%) 6 (12%)	3 (6%)
SPECIAL SENSE ORGANS			
*EYE SYNECHIA, ANTERIOR	(50)	(50) 1 (2%)	(50)
SYNECHIA, POSTERIOR CATARACT	1 (2%) 12 (24%)	8 (16%)	8 (16%)
*SCLERA CALCIFICATION, NOS	(50)	(50)	(50) 1 (2%)
CALCIFICATION, FOCAL		1 (2%)	
*EYE/CORNEA INFLAMMATION, NOS	(50)	(50) 1 (2%)	(50) 2 (4%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
DEGENERATION, HYALINE KERATOCONUS	4 (8%)	1 (2%)	
*EYE/RETINA DEGENERATION, NOS	(50) 2 (4%)	(50)	(50)
ATROPHY, NOS	10 (20%)	7 (14%)	7 (14%)
*EYE/CRYSTALLINE LENS CATARACT	(50)	(50)	(50) 1 (2%)
*EYE/CONJUNCTIVA INFLAMMATION, NOS	(50) 1 (2%)	(50)	(50)
MUSCULOSKELETAL SYSTEM			
*BONE HYPEROSTOSIS	(50)	(50) 1 (2%)	(50)
*SKELETAL MUSCLE CALCIFICATION, NOS	(50) 1 (2%)	(50)	(50)
BODY CAVITIES			
*ABDOMINAL CAVITY STEATITIS NECROSIS, FAT	(50) 1 (2%)	(50) 1 (2%)	(50) 2 (4%)
*PLEURA INFLAMMATION, CHRONIC FOCAL	(50)	(50)	(50) 1 (2%)
*MESENTERY NECROSIS, FAT	(50) 1 (2%)	(50) 4 (8%)	(50) 1 (2%)
ALL OTHER SYSTEMS			
DIAPHRAGM HERNIA, NOS		1	
SPECIAL MORPHOLOGY SUMMARY			
NONE			
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

APPENDIX D
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS
IN MICE FED DIETS CONTAINING 11-AMINOUNDECANOIC ACID

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN
MALE MICE FED DIETS CONTAINING 11-AMINOUNDECANOIC ACID

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)	1 (2%)	
HYPERKERATOSIS	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
ABSCESS, NOS		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	
INFLAMMATION, GRANULOMATOUS		1 (2%)	
RESPIRATORY SYSTEM			
*LARYNX	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
#TRACHEA	(45)	(43)	(44)
INFLAMMATION, SUPPURATIVE			1 (2%)
#LUNG	(50)	(50)	(46)
MINERALIZATION		2 (4%)	
CONGESTION, NOS	2 (4%)	4 (8%)	9 (20%)
EDEMA, NOS	1 (2%)		
HEMORRHAGE			1 (2%)
SEQUESTRATION	1 (2%)		
HISTIOCYTOSIS	3 (6%)		
HEMATOPOIETIC SYSTEM			
#SPLEEN	(50)	(47)	(47)
CONGESTION, NOS	1 (2%)	1 (2%)	
PLASMOCYTOSIS	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, LYMPHOID HEMATOPOIESIS	5 (10%) 7 (14%)	3 (6%) 5 (11%)	4 (9%) 3 (6%)
#MESENTERIC L. NODE CONGESTION, NOS	(33)	(43)	(32)
EDEMA, NOS	1 (3%)	1 (2%)	
HEMORRHAGE	14 (42%)	10 (23%)	4 (13%)
HEMOSIDEROSIS			1 (3%)
PLASMACYTOSIS	1 (3%)	1 (2%)	
HYPERPLASIA, LYMPHOID	9 (27%)	3 (7%)	
#INGUINAL LYMPH NODE PLASMACYTOSIS	(33)	(43)	(32)
HYPERPLASIA, LYMPHOID	3 (9%) 3 (9%)		
#LUNG PLASMACYTOSIS	(50)	(50)	(46)
	1 (2%)		
#LIVER HEMATOPOIESIS	(50)	(50)	(49)
	1 (2%)		
#PEYER'S PATCH HYPERPLASIA, LYMPHOID	(46)	(50)	(45)
			1 (2%)
#THYMUS EDEMA, NOS	(24)	(25)	(17)
		1 (4%)	
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS PERIARTERITIS	(50)	(50)	(50)
		1 (2%)	
#MESENTERIC L. NODE THROMBOSIS, NOS	(33)	(43)	(32)
	1 (3%)		
#HEART MINERALIZATION	(50)	(50)	(49)
FIBROSIS		1 (2%)	
DEGENERATION, NOS	1 (2%) 3 (6%)	1 (2%)	
*AORTA MINERALIZATION	(50)	(50)	(50)
		2 (4%)	2 (4%)
#LIVER THROMBUS, FIBRIN	(50)	(50)	(49)
			1 (2%)

* NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
*MESENTERY THROMBUS, FIBRIN	(50) 1 (2%)	(50)	(50)
DIGESTIVE SYSTEM			
#SALIVARY GLAND LYMPHOCYTIC INFLAMMATORY INFILTR NECROSIS, NOS	(49)	(47) 1 (2%) 1 (2%)	(48)
#LIVER	(50)	(50)	(49)
MINERALIZATION	1 (2%)		
INFLAMMATION, SUPPURATIVE	1 (2%)		
INFLAMMATION, NECROTIZING		1 (2%)	
ABSCESS, NOS	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC SUPPURATIV		1 (2%)	
GRANULOMA, NOS			1 (2%)
INFLAMMATION, PYOGRANULOMATOUS		3 (6%)	
DEGENERATION, NOS			1 (2%)
NECROSIS, NOS	2 (4%)		
NECROSIS, COAGULATIVE	1 (2%)		
CYTOPLASMIC VACUOLIZATION	2 (4%)	2 (4%)	10 (20%)
FOCAL CELLULAR CHANGE			1 (2%)
ATROPHY, NOS			1 (2%)
ANGIECTASIS			1 (2%)
#LIVER/CENTRIOLOBULAR	(50)	(50)	(49)
NECROSIS, NOS	1 (2%)		
CYTOPLASMIC VACUOLIZATION	1 (2%)		
ATROPHY, NOS			1 (2%)
*GALLBLADDER	(50)	(50)	(50)
INFLAMMATION, NECROTIZING		1 (2%)	
#PANCREAS	(50)	(48)	(47)
CYST, NOS	1 (2%)		
ATROPHY, NOS		1 (2%)	
#STOMACH	(48)	(48)	(47)
MINERALIZATION			6 (13%)
INFLAMMATION ACUTE AND CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC SUPPURATIV	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
 * NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, EPITHELIAL	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(49)
MINERALIZATION		4 (8%)	11 (22%)
HYDRONEPHROSIS		1 (2%)	
POLYCYSTIC KIDNEY			1 (2%)
PYELONEPHRITIS SUPPURATIVE	1 (2%)		
INFLAMMATION, CHRONIC	38 (76%)	35 (70%)	21 (43%)
NECROSIS, MEDULLARY			3 (6%)
CYTOPLASMIC VACUOLIZATION			1 (2%)
ATROPHY, NOS	1 (2%)	4 (8%)	3 (6%)
#KIDNEY/TUBULE	(50)	(50)	(49)
NECROSIS, NOS	1 (2%)		
#KIDNEY/PELVIS	(50)	(50)	(49)
INFLAMMATION, SUPPURATIVE			1 (2%)
#URINARY BLADDER	(48)	(44)	(39)
INFLAMMATION, SUPPURATIVE			1 (3%)
INFLAMMATION, CHRONIC	17 (35%)	17 (39%)	4 (10%)
INFLAMMATION, CHRONIC SUPPURATIV	1 (2%)		
HYPERPLASIA, EPITHELIAL	1 (2%)		
ENDOCRINE SYSTEM			
#ADRENAL	(44)	(48)	(42)
FOCAL CELLULAR CHANGE		1 (2%)	1 (2%)
#THYROID	(47)	(42)	(36)
LYMPHOCYTTIC INFLAMMATORY INFILTR			2 (6%)
HYPERPLASIA, FOLLICULAR-CELL		1 (2%)	1 (3%)
REPRODUCTIVE SYSTEM			
*PREPUCE	(50)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)
*PREPUTIAL GLAND	(50)	(50)	(50)
DILATATION/DUCTS	4 (8%)	1 (2%)	5 (10%)
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, CHRONIC	1 (2%)	1 (2%)	2 (4%)
INFLAMMATION, CHRONIC SUPPURATIV	2 (4%)		
INFLAMMATION, GRANULOMATOUS	2 (4%)		1 (2%)
INFLAMMATION, PYOGRANULOMATOUS			2 (4%)
#PROSTATE	(49)	(50)	(48)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)	3 (6%)	
INFLAMMATION, SUPPURATIVE	1 (2%)		
INFLAMMATION, ACUTE		1 (2%)	
#TESTIS	(49)	(50)	(47)
MINERALIZATION	2 (4%)	2 (4%)	
CYST, NOS		1 (2%)	
ATROPHY, NOS	2 (4%)		1 (2%)
#TESTIS/TUBULE	(49)	(50)	(47)
MINERALIZATION		1 (2%)	
*EPIDIDYMISS	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	3 (6%)	1 (2%)	1 (2%)
GRANULOMA, SPERMATIC			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
CATARACT		1 (2%)	
*EYE/RETINA	(50)	(50)	(50)
DETACHMENT		1 (2%)	
ATROPHY, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*STERNUM	(50)	(50)	(50)
INFLAMMATION ACUTE AND CHRONIC		1 (2%)	
NECROSIS, NOS		1 (2%)	
BODY CAVITIES			
*PERITONEUM	(50)	(50)	(50)
INFLAMMATION ACUTE AND CHRONIC			1 (2%)
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
*PLEURA INFLAMMATION ACUTE AND CHRONIC	(50)	(50) 1 (2%)	(50)
*PERICARDIUM INFLAMMATION, SUPPURATIVE	(50)	(50) 1 (2%)	(50)
*MESENTERY INFLAMMATION, CHRONIC	(50)	(50) 1 (2%)	(50)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS MINERALIZATION	(50)	(50) 2 (4%)	(50) 5 (10%)
INFLAMMATION, ACUTE	1 (2%)		
ABSCESS, NOS	1 (2%)		
INFLAMMATION ACUTE AND CHRONIC	1 (2%)		
SITE UNKNOWN MINERALIZATION			1
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		1	
AUTO/NECROPSY/HISTO PERF			2
AUTO/NECROPSY/NO HISTO			1
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

TABLE D2.

**SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN
FEMALE MICE FED DIETS CONTAINING 11-AMINOUNDECANOIC ACID**

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	1
ANIMALS NECROPSIED	50	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	49
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(49)
INFLAMMATION, CHRONIC	1 (2%)	2 (4%)	
HYPERKERATOSIS	1 (2%)	1 (2%)	
ACANTHOSIS	2 (4%)		
RESPIRATORY SYSTEM			
#TRACHEA	(39)	(42)	(43)
INFLAMMATION, FIBRINOUS	1 (3%)		
#LUNG	(50)	(49)	(49)
MINERALIZATION		1 (2%)	4 (8%)
CONGESTION, NOS		2 (4%)	5 (10%)
EDEMA, NOS			1 (2%)
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)		
HYPERPLASIA, NOS	1 (2%)		
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(46)	(44)	(47)
HEMOSIDEROSIS		1 (2%)	
GRANULOPOIESIS		1 (2%)	1 (2%)
#SPLEEN	(50)	(49)	(47)
HEMOSIDEROSIS			1 (2%)
HYPERPLASIA, LYMPHOID	5 (10%)	4 (8%)	3 (6%)
HEMATOPOIESIS	5 (10%)	3 (6%)	3 (6%)
#LYMPH NODE	(35)	(38)	(38)
CONGESTION, NOS	1 (3%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
HEMORRHAGE PLASMACYTOSIS	1 (3%)	1 (3%)	
#MANDIBULAR L. NODE HEMOSIDEROSIS HYPERPLASIA, LYMPHOID	(35)	(38)	(38) 1 (3%)
#ABDOMINAL LYMPH NODE HYPERPLASIA, LYMPHOID	(35) 1 (3%)	(38)	(38)
#LUMBAR LYMPH NODE EDEMA, NOS HEMOSIDEROSIS	(35) 1 (3%) 1 (3%)	(38)	(38)
#MESENTERIC L. NODE HEMORRHAGE HYPERPLASIA, LYMPHOID	(35) 1 (3%) 1 (3%)	(38) 1 (3%)	(38) 2 (5%)
#THYMUS INFLAMMATION, SUPPURATIVE NECROSIS, CORTICAL	(30)	(32) 1 (3%)	(22) 1 (5%)
CIRCULATORY SYSTEM			
#HEART MINERALIZATION INFLAMMATION ACUTE AND CHRONIC DEGENERATION, NOS NECROSIS, NOS	(50) 3 (6%)	(49)	(49) 2 (4%) 1 (2%) 1 (2%)
*AORTA MINERALIZATION	(50)	(49) 1 (2%)	(49) 2 (4%)
#UTERUS THROMBUS, FIBRIN	(48)	(49) 1 (2%)	(49)
DIGESTIVE SYSTEM			
*TONGUE INFLAMMATION, GRANULOMATOUS	(50)	(49)	(49) 1 (2%)
#LIVER CONGESTION, NOS	(50)	(49) 1 (2%)	(49)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, NOS	1 (2%)		
INFLAMMATION ACUTE AND CHRONIC	1 (2%)		
INFLAMMATION, GRANULOMATOUS		1 (2%)	1 (2%)
INFLAMMATION, PYOGRANULOMATOUS	1 (2%)		
NECROSIS, NOS	1 (2%)		
INFARCT, NOS			1 (2%)
CYTOPLASMIC VACUOLIZATION		5 (10%)	6 (12%)
FOCAL CELLULAR CHANGE	1 (2%)		1 (2%)
#PANCREAS	(50)	(49)	(47)
DILATATION/DUCTS			2 (4%)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	1 (2%)
ATROPHY, NOS	1 (2%)		3 (6%)
#STOMACH	(50)	(48)	(49)
MINERALIZATION			4 (8%)
INFLAMMATION, SUPPURATIVE			1 (2%)
HYPERPLASIA, ADENOMATOUS	1 (2%)		
HYPERKERATOSIS	1 (2%)	2 (4%)	
#FORESTOMACH	(50)	(48)	(49)
HYPERPLASIA, NOS	1 (2%)		
#COLON	(50)	(45)	(47)
EDEMA, NOS	1 (2%)		1 (2%)
INFLAMMATION, SEROUS	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(50)	(49)	(49)
MINERALIZATION		6 (12%)	9 (18%)
INFLAMMATION, CHRONIC	36 (72%)	36 (73%)	32 (65%)
SCLEROSIS			1 (2%)
NECROSIS, MEDULLARY		4 (8%)	1 (2%)
CYTOPLASMIC VACUOLIZATION		1 (2%)	
ATROPHY, NOS		4 (8%)	4 (8%)
#KIDNEY/MEDULLA	(50)	(49)	(49)
MINERALIZATION		2 (4%)	
SCLEROSIS			1 (2%)
DEGENERATION, NOS		1 (2%)	
#URINARY BLADDER	(49)	(48)	(46)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, CHRONIC INFLAMMATION, PYOGRANULOMATOUS	40 (82%)	32 (67%)	28 (61%) 1 (2%)
ENDOCRINE SYSTEM			
#ADRENAL CYST, NOS DEGENERATION, LIPOID AMYLOIDOSIS	(47) 1 (2%)	(46) 1 (2%) 1 (2%)	(48)
#THYROID LYMPHOCYTIC INFLAMMATORY INFILTR HYPERPLASIA, FOLLICULAR-CELL	(37) 2 (5%) 1 (3%)	(41) 1 (2%) 1 (2%)	(40)
#PARATHYROID LYMPHOCYTIC INFLAMMATORY INFILTR	(16)	(15) 1 (7%)	(21)
REPRODUCTIVE SYSTEM			
#UTERUS HYDROMETRA ABSCESS, NOS	(48)	(49)	(49) 1 (2%) 1 (2%)
#UTERUS/ENDOMETRIUM CYST, NOS HYPERPLASIA, CYSTIC	(48) 40 (83%)	(49) 34 (69%)	(49) 1 (2%) 23 (47%)
#OVARY CYST, NOS HEMORRHAGE HEMATOMA, NOS HEMORRHAGIC CYST	(46) 16 (35%)	(46) 19 (41%) 1 (2%)	(45) 7 (16%) 1 (2%) 1 (2%) 1 (2%)
NERVOUS SYSTEM			
#BRAIN/MENINGES LYMPHOCYTIC INFLAMMATORY INFILTR	(49) 3 (6%)	(49) 1 (2%)	(49) 3 (6%)
#BRAIN LYMPHOCYTIC INFLAMMATORY INFILTR	(49) 2 (4%)	(49) 2 (4%)	(49) 1 (2%)
SPECIAL SENSE ORGANS			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM INFLAMMATION, SUPPURATIVE NECROSIS, FAT	(50)	(49) 1 (2%) 1 (2%)	(49)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS MINERALIZATION	(50)	(49)	(49) 3 (6%)
SPECIAL MORPHOLOGY SUMMARY			
ANIMAL MISSING/NO NECROPSY		1	1
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

APPENDIX E
ANALYSIS OF 11-AMINOUNDECANOIC ACID
MIDWEST RESEARCH INSTITUTE

APPENDIX E

A. ELEMENTAL ANALYSIS

Element	C	H	N
Theory	65.63	11.52	6.96
Determined	65.54 65.71	11.46 11.60	6.95 6.97

B. WATER ANALYSIS

(Karl Fisher) 0.5% \pm 0.1 (δ)%

C. TITRATION OF AMINO GROUP WITH PERCHLORIC ACID IN GLACIAL ACETIC ACID

99.13% \pm 0.03 (δ)%

D. MELTING POINT

Determined	Literature Values
190°-191°C, dec (Dupont 900DTA)	184°-185°C
188°-189°C, dec (visual, capillary)	(Rekhter and Nesterova, 1963)

E. THIN-LAYER CHROMATOGRAPHY

Plates Silica gel 60	Ref Standard
Amount spotted 100 and 300 μ g	L-phenylalanine
System 1 Phenol water formic acid (72:28:1)	Visualization Ninhydrin
R _f 0.83 (trace), 0.66	
R _{st} 1.4, 1.1	
System 2 Chloroform methanol water ammonium hydroxide (45:45:4:6)	
R _f 0.94 (slight trace), 0.88 (trace), 0.48 (major)	
R _{st} 1.8, 1.7, 0.91	

F. HIGH-PRESSURE LIQUID CHROMATOGRAPHY

Derivation procedure The amino acid was suspended in 0.5M aqueous sodium bicarbonate buffer and an equivalent amount of 10 mM 5-(dimethylamino)naphthalene sulphonyl chloride (dansyl chloride) solution in acetonitrile was added. The resulting solution was incubated at 37°C for 1 hour and then diluted with 50% aqueous acetonitrile. This resulting solution was analyzed by high-pressure liquid chromatography, using the following system:

Instrument Waters ALC202, with Model 660 Solvent Programmer

Column μ Bondapak C₁₈, 30 cm x 4 mm I.D.

Detector UV-254 nm

Solvent 37% acetonitrile in 0.01M aqueous sodium bicarbonate

Flow 1 ml/min

Results A single peak with retention time of 7.5 minutes was detected in the samples.

APPENDIX E

G. SPECTRAL DATA

- | | |
|---|---|
| (1) Infrared | Literature Values |
| Instrument Beckman IR-12 | Consistent with literature spectrum (Sadtler Research Laboratories) |
| Cell 1% KBr pellet | |
| Results (See Figure 5) | |
| (2) Ultraviolet/Visible | No literature values found |
| Instrument Cary 118 | |
| Results No absorbance detected between 350 and 800 nm (visible range) No maximum between 200 and 350 nm (ultraviolet range), however, the absorbance increases from 250 nm to the instrument cutoff at 220 nm | |
| Concentration 1.2 mg/ml | |
| Solvent 0.1N HCl | |
| (3) Nuclear Magnetic Resonance | No literature spectrum found |
| Instrument Varian HA-100 | |
| Solvent Deuterated trifluoroacetic acid with internal tetramethylsilane | |
| Assignments (See Figure 6) | |
| (a) s, δ 1.35 ppm, (b) m, δ 1.54 to 1.94 ppm, (c) t, δ 2.46 ppm, $J_{bc} = 7\text{ Hz}$, (d) m, δ 3.01 to 3.35 ppm, (e) s, δ 6.29 to 6.84 ppm | |
| Integration ratios
(a) 13.2, (b) 3.7, (c) 1.8, (d) 1.4, (e) 0.5 | |

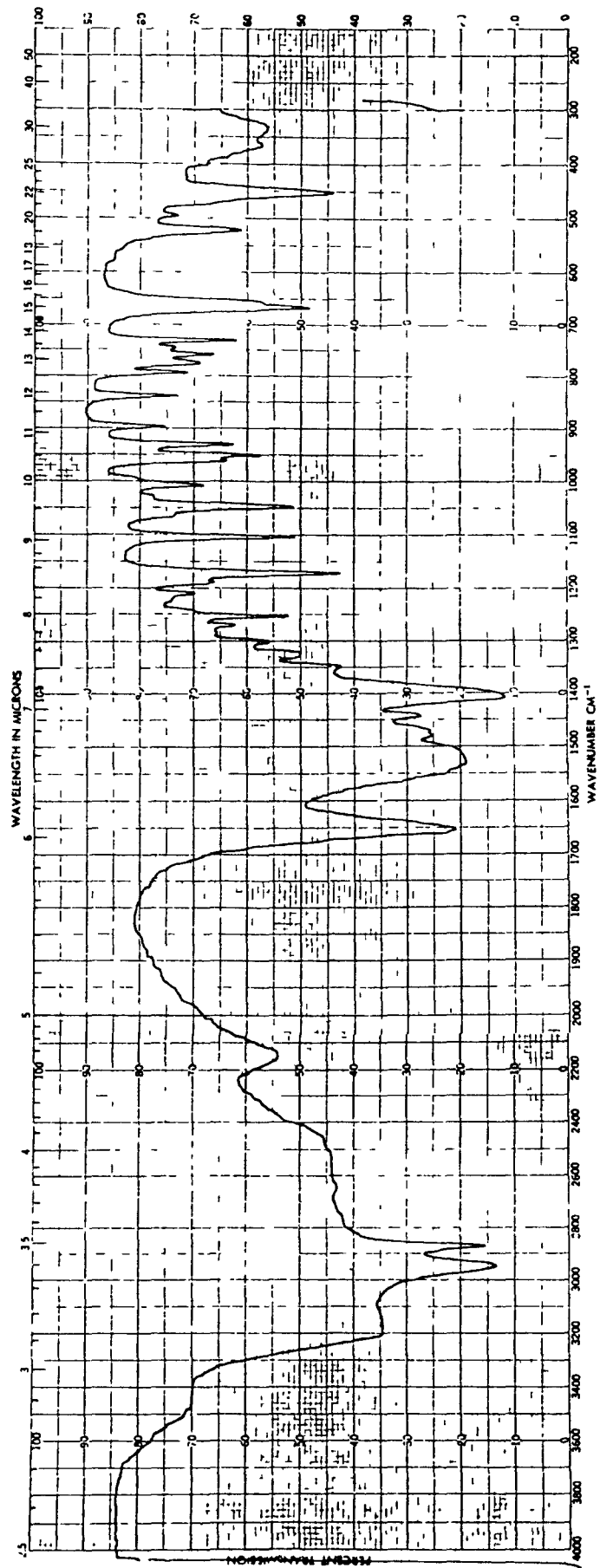


Figure 5. Infrared Absorption Spectrum 11-Aminoundecanoic Acid

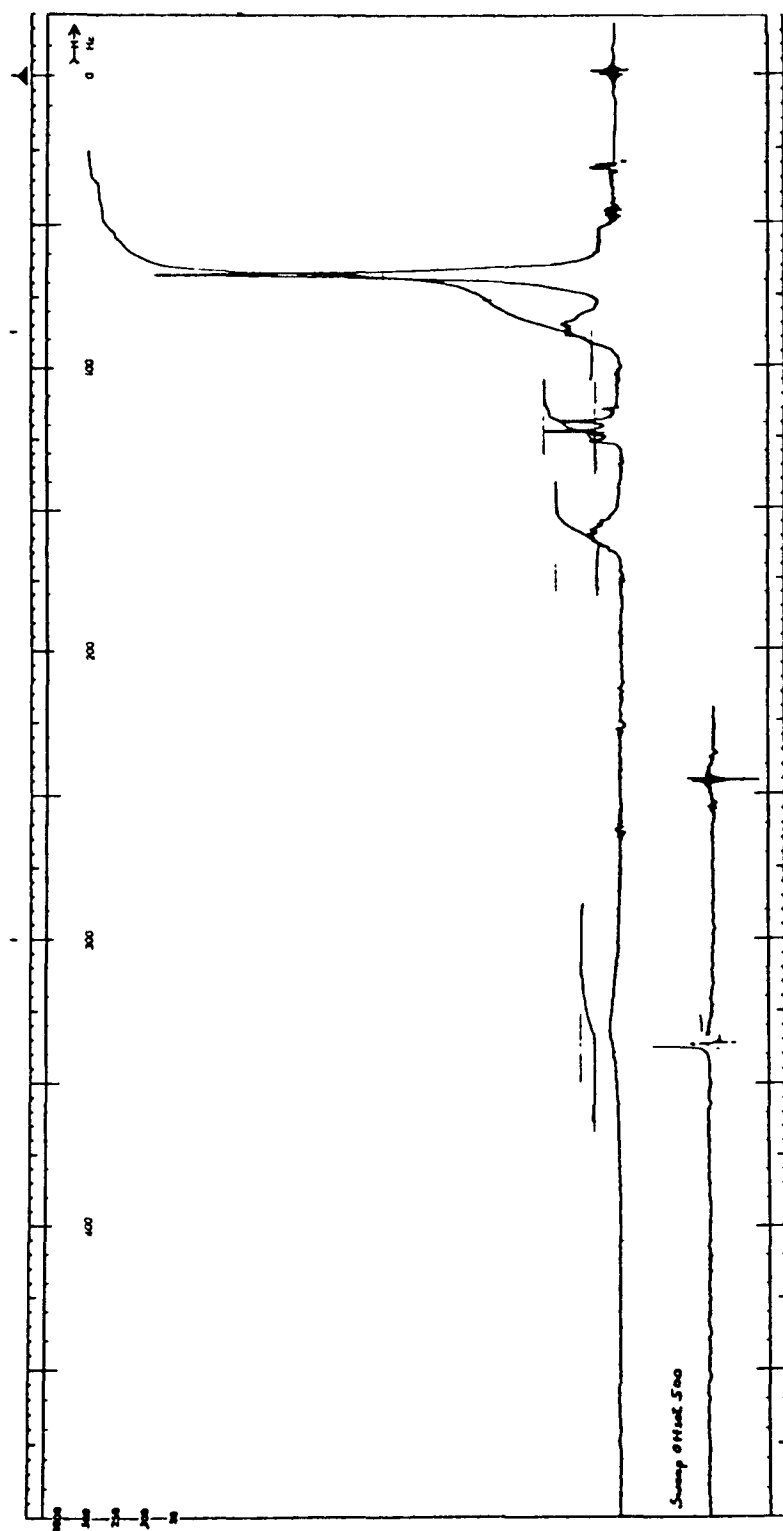


Figure 6. Nuclear Magnetic Resonance Spectrum 11-Aminoundecanoic Acid

APPENDIX F
ANALYSIS OF FORMULATED DIETS FOR STABILITY OF
11-AMINOUNDECANOIC ACID
MIDWEST RESEARCH INSTITUTE

APPENDIX F

1. MIXING AND STORAGE: 11-Aminoundecanoic acid (20 g) and Wayne Lab Blox® Rodent feed (180 g) were mixed in a mortar. Samples of the mixture were then removed and stored for 2 weeks at -20°, 5°, 25°, and 45°C. These samples were extracted and analyzed by the high-pressure liquid chromatographic method described below.

2. PROCEDURES FOR EXTRACTION AND ANALYSIS: Samples of the chemical/feed mixtures were triturated three times with 0.1N nitric acid using a Polytron® mixer, and the combined mixtures were centrifuged. The supernatant solutions were separated and neutralized to approximately pH7 with 0.35N sodium hydroxide solution and then buffered by adding solid sodium bicarbonate (to make the solution 0.5M in NaHCO₃). This solution was then treated with an equivalent amount of 10 mM 5-(dimethylamino)naphthalene sulphonyl chloride (dansyl chloride) solution in acetonitrile. The resulting solution was incubated at 37°C for 1 hour and then diluted with 50% aqueous acetonitrile. This resulting solution was analyzed by high-pressure liquid chromatography, using the following system:

Instrument: Waters ALC202, with Model 660 Solvent Programmer

Column: μ Bondapak C₁₈, 30 cm x 4 mm I.D.

Detector: UV-254 nm

Solvent: 37% acetonitrile in 0.01M aqueous sodium bicarbonate

Flow: 1 ml/min

3. RESULTS:

<u>Temperature (°C)</u>	<u>Average % Compound Recovered</u>
-20	9.8 \pm 0.4
5	9.8 \pm 0.4
25	10.1 \pm 0.4
45	10.6 \pm 0.4

There is no significant difference between the samples stored at the various temperatures.

4. CONCLUSION: 11-Aminoundecanoic acid mixed with feed is stable for two weeks at temperatures up to 45°C.

APPENDIX G
ANALYSIS OF FORMULATED DIETS FOR CONCENTRATIONS
OF 11-AMINOUNDECANOIC ACID
LITTON BIONETICS, INC.

APPENDIX G

A 5-g portion of feed was extracted with three 40-ml portions of 0.1N nitric acid. After the mixture was shaken for 10 minutes on an automatic shaker and centrifuged for 10 minutes at 1,500 rpm, the supernatant was filtered through glass wool into a 200-ml volumetric flask. The total extract was diluted to volume with additional dilute nitric acid. A 1.0- to 2.0-ml aliquot of the extract was transferred to a test tube; 0.1N nitric acid was added, if necessary, to make the final volume 2.0 ml in all cases. A reference standard was prepared by pipetting 2.0 ml of the 0.1N nitric acid containing 375 μ g aminoundecanoic acid into a test tube. To both the sample and the standard were added 5.0 ml of 0.5M NaHCO₃ and 5.0 ml of 10 mM dansyl chloride in acetonitrile. The tubes were incubated for 1 hour at 37°C and allowed to cool. Two milliliters of acetonitrile were added and the volume adjusted to 15 ml with 50% acetonitrile/water.

Analysis was performed with a Waters Model No. 204 high-pressure liquid chromatograph with a UV detector at 254 nm. The column was stainless steel, 25 cm x 4.6 mm I.D., packed with μ Bondapak/C₁₈. The solvent system was 37% acetonitrile in 0.01 M aqueous sodium bicarbonate at a flow rate of 2.0 ml/min. The amount of test compound in the feed was calculated by reference to a calibration curve obtained by analysis of the reference standard in the same manner. Control feed and control feed treated with a known amount of aminoundecanoic acid were analyzed concurrently to correct for possible feed background and method recovery.

Table G-1. ANALYSIS OF FORMULATED DIETS

Date Mixed (a)	Date Used (week of)	Concentration (b) of 11-Aminoundecanoic Acid in Feed for Target Concentration	
		7,500 ppm	15,000 ppm
11/12/77	11/15 - 11/22	7,951	15,135
		7,805	13,833
		7,146	
12/12/77	12/14 - 12/21		14,411
2/23/78	2/25 - 3/1	6,892	
4/06/78	4/8 - 4/15		14,561
5/19/78	5/22 - 5/29		14,879
7/28/78	8/1 - 8/8	8,028	14,628
		7,930	
8/31/78	9/1 - 9/8	7,517	
9/14/78	9/16 - 9/23		15,884
10/26/78	10/28 - 11/4		14,278
11/09/78	11/11 - 11/18	7,232	
12/21/78	12/23 - 12/30	7,874	
Mean (ppm)		7,597	14,701
Standard deviation		416	618
Coefficient of variation (%)		5.5	4.2
Range (ppm)		6,892-	13,833-
		8,028	15,884
Number of samples		9	8

(a) 2/2/77 was the start date for rats and 2/1/77 was the start date for mice.

(b) The data presented are the average of the results of duplicate analyses.

NIH Publication No. 82-1772
May 1982