NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 214

CARCINOGENESIS BIOASSAY OF CAPROLACTAM

(CAS NO. 105-60-2)

F344 RATS AND B6C3F$_1$ 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

CARCINOGENESIS BIOASSAY

OF

CAPROLACTAM

(CAS NO. 105-60-2)

IN F344 RATS AND $B6C3F_1$ MICE

(FEED STUDY)

NATIONAL CANCER INSTITUTE
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Comments and questions about the National Toxicology Program Technical Reports on Carcinogenesis Bioassays should be directed to Ms. Joan Chase, Technical Information Section, Room A-306, Landow Building, Bethesda, MD 20014 (301-496-1152).

CARCINOGENESIS BIOASSAY
OF
CAPROLACTAM
(CAS No. 105-60-2)

FOREWORD

This is one of a series of experiments designed to determine whether selected chemicals have the capacity to produce cancer in animals. A negative result, in which the test animals do not have a greater incidence of cancer than control animals, does not necessarily mean that a test chemical is not a carcinogen inasmuch as the experiments are conducted under a limited set of circumstances. A positive result demonstrates that a test chemical is carcinogenic for animals under the conditions of the test and indicates that exposure to the chemical may pose a potential risk to man. The actual determination of the risk to man from chemicals found to be carcinogenic in animals requires a wider analysis which extends beyond the the purview of this study.

CONTRIBUTORS

The bioassay of caprolactam was conducted from January 1977 to February 1979 by Litton Bionetics, Inc., Kensington, Maryland, under a subcontract to Tracor Jitco, Inc., the prime contractor for the NCI Carcinogenesis Testing Program.

The bioassay was conducted under the supervision of Dr. E. Gordon (1,7), principal investigator. Doses of the test chemical were selected by Drs. W. MacDonald (2), J. Robens (2,3), Cipriano Cueto (4,2), R. Schueler (2), and E. Gordon (1,7). Mr. D. Kinsel (1), and Ms. J. Sheldon (1) were in charge of animal care, and Mr. G. North (1) supervised the preparation of the feed mixtures and collected samples of the diets for analysis. Drs. G. Parker and R. Cardy (1), pathologists, directed the necropsies and performed the histopathologic examinations. The pathology report and selected slides were evaluated by the NCI Pathology Working Group as described in Ward et al. (1978). The diagnoses represent a consensus of contracting pathologists and the NCI Pathology Working Group with final approval by the NCI Pathology Working Group.

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute, Rockville, Maryland (5). The statistical analyses were performed by Dr. J. R. Joiner (2) and Ms. S. Vatsan (2), using methods selected for the bioassay program by Dr. J. J. Gart (8). Chemicals used in this bioassay were analyzed at Midwest Research Institute (6), and dosed feed mixtures were analyzed by Mr. H. Paulin (1).

This report was prepared at Tracor Jitco (2) and reviewed by NTP. Those responsible for the report at Tracor Jitco were Dr. L. A. Campbell, Acting Director of the Bioassay Program; Dr. S. S. Olin, Associate Director; Dr. M. A. Stedham, pathologist; Dr. D. J. Beach, reports manager; Dr. A. C.

Jacobs, bioscience writer; and Dr. W. D. Theriault and Ms. M. W. Glasser, technical editors.

The following scientists at NCI/NTP (4) were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. J. Fielding Douglas, Dr. Richard A. Griesemer, Dr. Charles K. Grieshaber, Dr. Larry Hart, Dr. Joseph Haseman, Dr. James Huff, Dr. C. W. Jameson, Dr. Mary Kornreich, Dr. Ernest E. McConnell, Dr. John A. Moore, Dr. Sherman F. Stinson, Dr. Raymond Tennant, and Dr. Jerrold M. Ward (chemical manager).

On June 27, 1980, this report underwent peer-review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting began at 9 a.m. in Room 1331, Switzer Building, 330 C Street, S.W., Washington, D.C. Members of the Subcommittee are: Drs. Margaret Hitchcock (Chairperson), Curtis Harper, Thomas Shepard, and Alice Whittemore. Members of the Panel are: Drs. Norman Breslow, Joseph Highland, Charles Irving, Frank Mirer, Sheldon Murphy, Svend Nielsen, Bernard Schwetz, Roy Shore, James Swenberg, and Gary Williams. Drs. Highland, Schwetz, and Swenberg were unable to attend the review.

Dr. Hitchcock, as the primary reviewer for the report on the bioassay of caprolactam, agreed with the conclusion in the report that caprolactam was not carcinogenic under the test conditions. Possible shortcomings in the study included the factor of the animals being housed in rooms in which other bioassay studies were also being conducted, and the fact that the starting weights of the female mice were not matched. Dr. Hitchcock thought that the shortcomings were unlikely to affect the conclusions and considered the study to be valid.

As the secondary reviewer, Dr. Breslow agreed with the conclusion that caprolactam was not carcinogenic under the conditions of the bioassay. He had three general criticisms applicable to many of the reports, which he indicated should be dealt with routinely in the future, these being: (1) the control animals were described in the report as "matched," yet no basis for the matching was specified; (2) since the test for departure from linear trend, in contrast to the test for trend itself, failed to employ a continuity correction or an exact distribution, it could occasionally result in exaggerated statements of statistical significance; and, (3) the results of age-adjusted statistical analyses should be routinely contained in the reports.

Dr. Hitchcock moved that the report on the bioassay of caprolactam be accepted. Dr. Breslow seconded the motion and it was approved unanimously.

---

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SUMMARY

A carcinogenesis bioassay of caprolactam, a chemical intermediate used in the production of nylon 6, was conducted by feeding diets containing 3,750 or 7,500 ppm caprolactam to groups of 50 male or female F344 rats and 7,500 or 15,000 ppm to groups of 50 male or female B6C3F1 mice for 103 weeks. Control groups consisted of 50 undosed rats and 50 undosed mice of each sex.

Throughout the bioassay, mean body weight gains for dosed rats and mice of either sex were decreased when compared with those of the controls. No other compound-related effects were observed.

Under the conditions of this bioassay, caprolactam was not carcinogenic for F344 rats or B6C3F1 mice.

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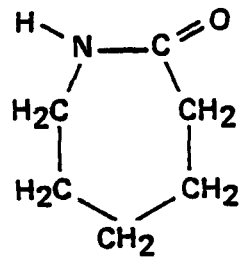
I. INTRODUCTION



CAPROLACTAM

Molecular formula:
$C_6 H_{11} NO$
Molecular weight:
113.16
Composition: C = 63.7%
H = 9.8%
N = 12.4%
O = 14.1%

Caprolactam (CAS No. 105-60-2) (NCI No. C50646) -- aminocaproic lactam; 2-oxohexamethylenimine — is the monomer used in the production of nylon-6, a fiber or resin used to make carpets, knit fabrics, hosiery, thread, hairbrushes, replacement parts for automobiles and machinery, flotation devices, and food packaging (IARC, 1979; Brady and Clauser, 1977). Nylon-6 resins have been approved by the U.S. Food and Drug Administration for use in food contact films, including those for irradiated, prepackaged foods (CFR, 1977). Approximately 918 million pounds of caprolactam were produced in the United States during 1978 (USITC, 1979).

Caprolactam is a solid at 25°C, but has significant vapor pressure (0.01 mm at 20°C). Highly soluble in water, it reportedly leaches out of clothing made from polyamide fibers when placed in a solution containing the same components as perspiration (Statsek and Ivanova, 1978). Transient irritation of the skin, eyes, nose, and throat have been reported in workers exposed to caprolactam dust or vapor at concentrations ranging from 10 to 100 ppm (Ferguson and Wheeler, 1973). Recommended threshold limit values for caprolactam are 1 mg/m^3 for the dust and 20 mg/m^3 for the vapor (ACGIH, 1975).

The LD_{50} values of caprolactam administered to rats and mice are presented in Table 1. Single, intraperitoneal injections of the test chemical at concentrations of 350 to 600 g/kg body weight reportedly caused tremors, convulsions, temperature depression, and bloody discharge from the eyes in rats, and the compound was excreted in the urine, partly as the lactam and partly as the -amino acid (Goldblatt et al., 1954; err et al., 1976. Exposure to caprolactam by inhalation for 24 days at concentrations of 120 to 150 mg/m^3 altered the functions of the kidney, the gonads, and the nervous system and

respiratory system (Gabrielyan et al., 1975) and reduced fertility in rats (Khadzhieva, 1969). Polycaprolactam (nylon 6) was tested by implanting intraperitoneally 10 mm diameter films into BD rats; four of six developed local sarcomas (Druckrey and Schmahl, 1952).

Caprolactam was tested by the Carcinogenesis Testing Program because of the large volume produced (nearly one billion pounds per year), because of the widespread use in food packaging materials and clothing, and because no carcinogenicity studies had been done.

Table 1. LD_{50} Values for Rats and Mice Administered Caprolactam

Species	Route of Administration	LD_{50} Value	Reference
Mouse (a)	Inhalation	0.45mg/liter	Lomonova, 1966
Mouse (a)	Intraperitoneal	0.58g/kg	Hohensee, 1951
Mouse (a)	Intravenous	0.48g/kg	Hohensee, 1951
Mouse (a)	Oral	1.2g/kg (LD_{100})	Hohensee, 1951
Mouse (B6C3F1 male)	Oral	2.07g/kg	NTP (1981)
Mouse (B6C3F1 female)	Oral	2.49g/kg	NTP (1981)
Mouse (a)	Subcutaneous	0.75g/kg	Hohensee, 1951
Rat (a)	Oral	1.6g/kg	Hohensee, 1951
Rat (F344 male)	Oral	1.65g/kg	NTP (1981)
Rat (F344 female)	Oral	1.21g/kg	NTP (1981)

(a) Strain not reported.

II. MATERIALS AND METHODS

A. Chemical

Caprolactam (CAS No. 105-60-2) was obtained from Dow Badische Company (Williamsburg, VA) in two batches. Lot No. DB 7-7-75 was used for the subchronic study and the first 68 weeks of the chronic studies, and Lot No. DB 6-23-78 was used for the rest of the chronic studies. The results of purity and identity analyses performed at Midwest Research Institute were consistent with the structure and literature values (Appendixes E and F), and results from thin-layer and vapor-phase chromatography indicated a single homogeneous compound.

Caprolactam was stored at 4°C in its original container.

B. Dietary Preparation

Test diets were formulated by mixing Purina® Lab Chow and the required amount of caprolactam in a Patterson-Kelly® twin-shell blender for 20 minutes (Table 2). The mixture was stored in the dark at 4°C for no longer than 2 weeks. Control diets consisted of Purina®Laboratory Chow.

In a study conducted at Midwest Research Institute (Appendix G), caprolactam (100,000 ppm) in dosed feed samples was found to be stable for 2 weeks at temperatures up to 45°C. During the chronic study, random samples containing target levels of 15,000, 7,5000, and 3,750 ppm caprolactam in feed were analyzed at Litton Bionetics, Inc. The mean concentrations were found to be 2.3%, 10.0%, and 8.0% below the theoretical level, respectively (Appendix H).

In followup stability studies at Litton Bionetics, Inc., a gradual decrease in the percent recovery of caprolactam from feed was detected after storage at room temperature (Appendix I). At 15,000 ppm, the recovery was 89.0% after 7 days compared with approximately 100% immediately after mixing. The decrease may be due to slow binding to feed components or to slow hydrolysis or degradation of the chemical. The fact that the Midwest stability

study did not detect the decrease in recovery probably is due to the higher concentration of caprolactam in feed used in that test.

C. Animals

Three-week old male and female F344 rats and B6C3F1 mice were obtained from the NCI Frederick Cancer Research Center, Frederick, Maryland, observed for 2 weeks, and then assigned to test groups according to a table of random numbers.

D. Animal Maintenance

The specifications and sources for materials used for animal maintenance are presented in Table 2. Rats were housed four per cage and mice five per cage in polycarbonate cages covered with nonwoven polyester filter sheets. Racks and filters were changed once every 2 weeks. Cages, Absorb-dri® hardwood chip bedding, and glass water bottles equipped with stainless steel sipper tubes were replaced two times per week. Tap water was acidified with hydrochloric acid to pH 2.5. Feed for the controls and the test diet were available ad libitum in stainless steel feed hoppers that were changed once per week. The animal rooms were maintained at 22°-26°C and 30%-70% humidity.

Air was filtered through AG-55 Ameriglass Roughing filters and then through HEPA-100 filters. Room air was changed 10 times per hour and fluorescent lighting provided illumination 12 hours per day.

During the chronic study, rats fed caprolactam were housed in a room in which feeding studies on bisphenol A (CAS 80-05-7) were being carried out; mice fed caprolactam were housed in a room in which feeding studies on the following chemicals were being conducted:

(CAS 80-05-7)	bisphenol A
(CAS 2432-99-7)	11-aminoundecanoic acid
(CAS 609-20-1)	2,6-dichloro-p-phenylenediamine (1,4-diamino-2,6-dichlorobenzene)

Table 2. Specifications and Sources of Materials Used for Animal Maintenance

Item	Specifications	Manufacturer or Supplier
Bedding	Absorb-dri® hardwood chips	Lab Products, Inc. Garfield, NJ
Cages	Polycarbonate	Lab Products, Inc. Garfield, NJ
Feed	Ralston Purina® Laboratory Chow	Ralston Purina Richmond, IN
Filters	AG-55 Ameriglass Roughing Filter	American Air Filter Louisville, KY
Filters	HEPA-100	American Air Filter Louisville, KY
Filter Sheets	Non-woven Polyester	Snow Filtration Cincinnati, Ohio

E. Acute Toxicity and 14-Day Repeated-Dose Studies

Single-dose acute toxicity and 14-day repeated-dose feed studies were conducted using F344 rats and B6C3F1 mice to determine the concentrations of caprolactam to be used in the subchronic studies. In the acute toxicity study, groups of five males and five females of each species were administered single doses of the test substance in corn oil by gavage in the amounts shown in Table 3. All surviving animals were killed after 14 days. Deaths occurred in male rats receiving 1,470 mg/kg or more caprolactam, in female rats receiving 1,000 mg/kg or more, and in mice receiving 2,150 mg/kg or more. The estimated LD_{50} values were 1,650 and 1,210 mg/kg for male and female F344 rats and 2,070 and 2,490 mg/kg for male and female B6C3F1 mice.

In the repeated-dose study, groups of five males and five females of each species were administered the test substance in the feed for 2 weeks at the concentrations shown in Table 4. All animals were killed after 2 weeks. No deaths occurred in either species at the doses tested. Pale, mottled kidneys occurred in all groups of dosed male rats in incidences of 60%-100%. No compound-related effects were observed in mice.

F. Subchronic Studies

Subchronic studies were conducted to determine the concentrations to be used in the chronic studies. Diets containing 0, 625, 1,250, 2,500, 5,000, or 7,500 ppm caprolactam were fed for 13 weeks to groups of 12 male and 12 female rats (Table 5), and groups of 10 male and 10 female mice received diets with 0, 5,000, 10,000, 15,000, 20,000, or 30,000 ppm (Table 6).

Clinical observations were made twice daily and animals were weighed weekly. At the end of the 91-day study survivors were killed, necropsies were performed on all animals, and tissues were taken for histopathologic analysis.

Rats: One of 12 male rats receiving 5,000 ppm became moribund and was killed. Weight gain depression (12% or less for males and 14% or less for females) was not dose related. Food consumption by rats fed 7,500 ppm as

Table 3. Dosage and Survival of Rats and Mice Administered A Single Dose of Caprolactam by Gavage

Dose (mg/kg)	Survival (a) Male	Female
Rats		
681	5/5	5/5
1,000	5/5	4/5
1,470	3/5	1/5
2,150	1/5	0/5
3,160	0/5	0/5
Mice		
1,000	5/5	5/5
1,470	5/5	5/5
2,150	2/5	3/5
3,160	0/5	1/5
4,640	- (b)	1/5

(a) Number surviving/number per group.
(b) Male mice were not tested at this dose.

Table 4. Dosage and Survival of Rats and Mice Fed Diets Containing Caprolactam for 14 Days

Dose (ppm)	Survival (a) Male	Female
Rats		
0	5/5	5/5
5,000	5/5	5/5
10,000	5/5	5/5
15,000	5/5	5/5
20,000	5/5	5/5
30,000	5/5	5/5
Mice		
0	5/5	5/5
5,000	5/5	5/5
10,000	5/5	5/5
15,000	5/5	5/5
20,000	5/5	5/5
30,000	5/5	5/5

(a) Number surviving/number per group.

Table 5. Dosage, Survival, and Mean Body Weight of Rats Fed Diets Containing Caprolactam for 13 Weeks

Dose (ppm)	Survival (a)	Mean Body Weights (grams) Initial	Final	Gain	Weight Change Relative to Controls (b) (percent)
Male					
0	12/12	132	318	186	
625	12/12	132	301	169	-9
1,250	12/12	132	308	176	-5
2,500	12/12	132	296	164	-12
5,000	11/12(c)	133	297	164	-12
7,500	12/12	132	303	171	-8
Female					
0	12/12	101	182	81	
625	12/12	101	183	82	+1
1,250	12/12	101	185	84	+4
2,500	12/12	101	174	73	-11
5,000	12/12	101	179	78	-4
7,500	12/12	101	171	70	-14

(a) Number surviving/number per group.

(b) Weight Change Relative to Controls =

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

(c) Moribund animal was killed.

Table 6. Dosage, Survival, and Mean Body Weights of Mice Fed Diets Containing Caprolactam for 13 Weeks

Dose (ppm)	Survival (a)	Mean Body Weights (grams) Initial	Final	Gain	Weight Change Relative to Controls (b) (percent)
Male					
0	10/10	20	31	11	
5,000	10/10	20	27	7	-36
10,000	10/10	20	28	8	-27
15,000	10/10	20	28	8	-27
20,000	10/10	20	28	8	-27
30,000	10/10	20	27	7	-36
Female					
0	10/10	18	26	8	
5,000	10/10	18	23	5	-38
10,000	10/10	18	22	4	-50
15,000	10/10	18	22	4	-50
20,000	9/10(c)	18	22	4	-50
30,000	8/10	18	21	3	-63

(a) Number surviving/number per group.

(b) Weight Change Relative to Controls =

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

(c) Death was accidental.

compared with controls was decreased 23% and 19% for males and females, respectively. No compound-related histopathologic effects were observed.

Based on decreased mean weight gain, doses selected for the chronic studies in rats were 3,750 and 7,500 ppm caprolactam in feed.

Mice: Two of the ten female mice that received 30,000 ppm caprolactam in feed died, and one female that received 20,000 ppm died as a result of an accident. No deaths occurred among the male mice. A depression in mean body weight gain was observed in all dosed mice, but mean body weight gain was no different for male mice fed 30,000 ppm (36%) than for those fed 5,000 ppm. Weight gain depression for females was dose related. No compound-related histopathologic effects were observed.

Based on deaths and decreased mean weight gains, doses selected for the chronic study in mice were 7,500 ppm and 15,000 ppm.

G. Design of Chronic Studies

The number of animals per group, doses administered, and durations of the chronic studies are shown in Table 7.

H. Clinical Examinations and Pathology

All animals were observed twice daily for signs of toxicity. Mean body weights of animals by cage were recorded every 2 weeks for the first 13 weeks and monthly thereafter. Clinical signs were recorded monthly. 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 tissues and organs 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, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenals, bladder, seminal

Table 7. Experimental Design of Chronic Feeding Studies with Caprolactam in Rats and Mice

Test Group	Initial No. of Animals		Dose (ppm)	Time on Study	
	Male	Female		Dosed (weeks)	Observed (weeks)
Rats					
Control	50	50	0	0	105
Low-Dose	50	50	3,750	103	2
High-Dose	50	50	7,500	103	2
Mice					
Control	50	50	0	0	105
Low-Dose	50	50	7,500	103	2
High-Dose	50	50	15,000	103	2

vesicles/prostate/testes or ovaries/uterus, nasal tissues, brain, pituitary, eyes, and spinal cord. Special staining techniques were utilized as necessary.

Necropsies were performed 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.

I. Data Recording and Statistical Analysis

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. One-tailed P values have been reported for all tests except the departure from linearity test, which is reported only when its two-tailed P value is less than 0.05.

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 (numerator) to the number of animals in which that site is examined (denominator). 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.

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970) was used to compare the tumor incidence of a control group with that of a group of dosed animals at each dose level. When results from two dosed groups are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality criterion (Miller, 1966) requires that the P values for any comparison be less than or equal to 0.025. When this correction is used, it is discussed in the narrative section, but it is not presented in the tables, where the Fisher exact P values are shown.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971), was also used. When a linear trend is assumed, this test determines if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend is a positive relationship. This method also provides a two-tailed test of departure from linear trend based on the difference between the chi square test for homogeneity and the Cochran-Armitage test without continuity correction.

The approximate 95% confidence interval for the relative risk of each dosed group compared with its control was calculated from the exact interval on the odds ratio (Gart, 1971).

A time-adjusted analysis was applied when numerous early deaths resulted from cases that were not associated with the formation of tumors. In this analysis, deaths that occurred before the first tumor was observed were excluded by basing the statistical tests on animals that survived at least 52 weeks unless a tumor was found at the anatomic site of interest before week 52. When such an early tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage test, etc.) were followed.

Life table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which an animal died naturally or was killed was entered as the time point of tumor observation. The methods of Cox and of Tarone were used for the statistical test of the groups. The statistical tests were one-tailed.

The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that, in approximately 95% of a large number of identical experiments, the true ratio of the risk in a dosed group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result has occurred ($P<0.025$ one-tailed test when the control incidence is not zero, $P<0.050$ when the control incidence is zero). When the lower limit is less than unity but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of the induction of tumors by the test chemical, which could not be detected under the conditions of this test.

III. RESULTS - RATS

A. Body Weights and Clinical Signs (Rats)

Throughout the study, mean body weights of dosed rats of either sex were lower than those of controls, and the decrements in mean body weight gain were dose related (Figure 1). Feed consumption was inversely related to dose. Feed consumption by high-dose rats of either sex was only 70%-80% that of the controls (Appendix J). No other compound-related clinical signs were reported.

B. Survival (Rats)

Estimates of the probabilities of survival for male and female rats administered caprolactam in feed at the doses of this bioassay, and those of the controls, are shown by the Kaplan and Meier curves in Figure 2. The survival among all groups in either sex was comparable. In male rats, 32/50 (64%) of the control group, 33/50 (66%) of the low-dose group, and 37/50 (74%) of the high-dose group lived to the end of the study at week 105. In females, 40/50 (80%) of the controls, 42/50 (84%) of the low-dose group, and 38/50 (76%) of the high-dose group lived to the end of the study at week 105.

C. Pathology (Rats)

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.

The various types of neoplasms occurring in dosed and control rats did not appear to be related to chemical administration. The large number of degenerative, proliferative, and inflammatory lesions encountered in dosed and control animals were of the type and occurred at a frequency commonly

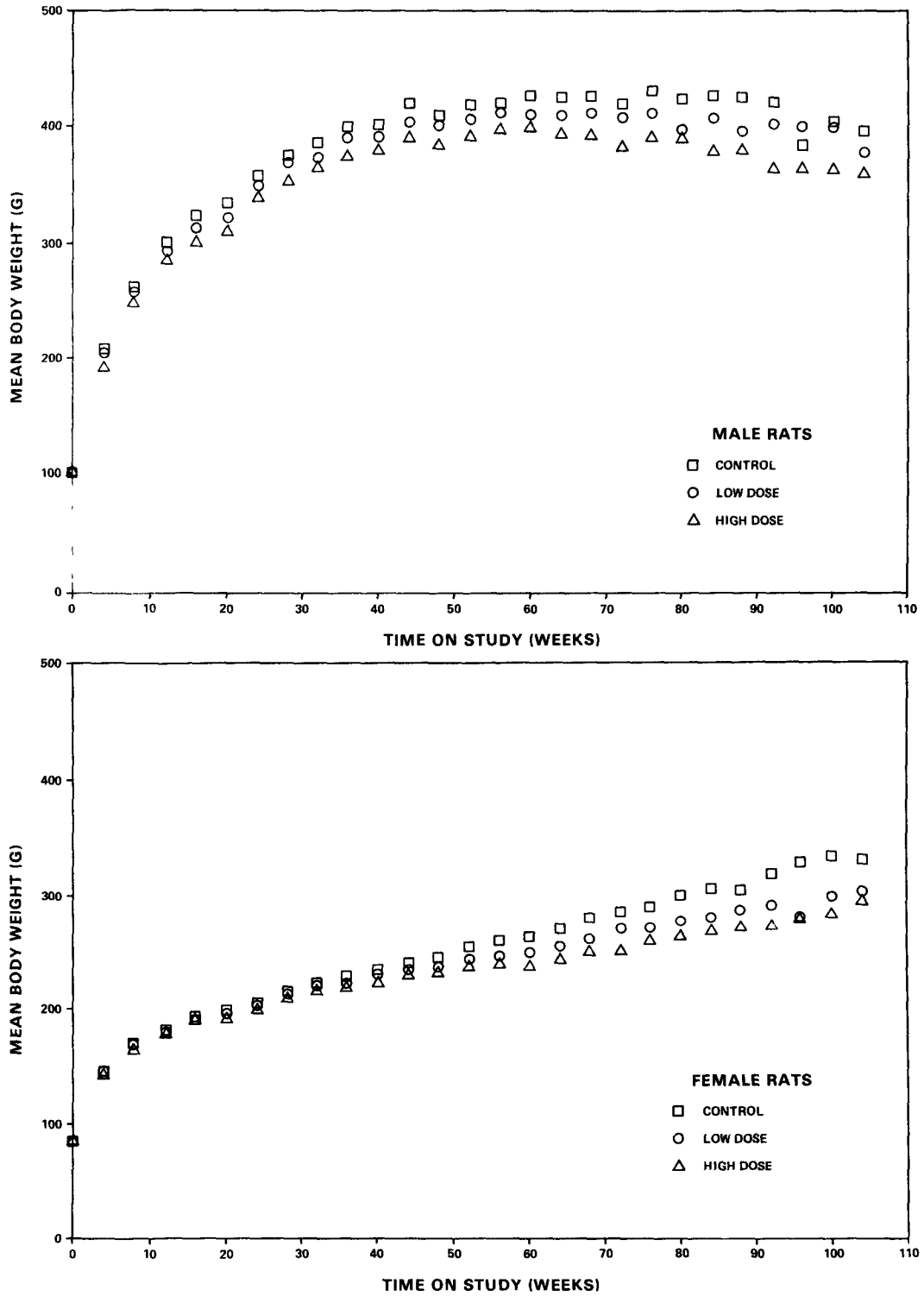


Figure 1. Growth Curves for Rats Fed Diets Containing Caprolactam

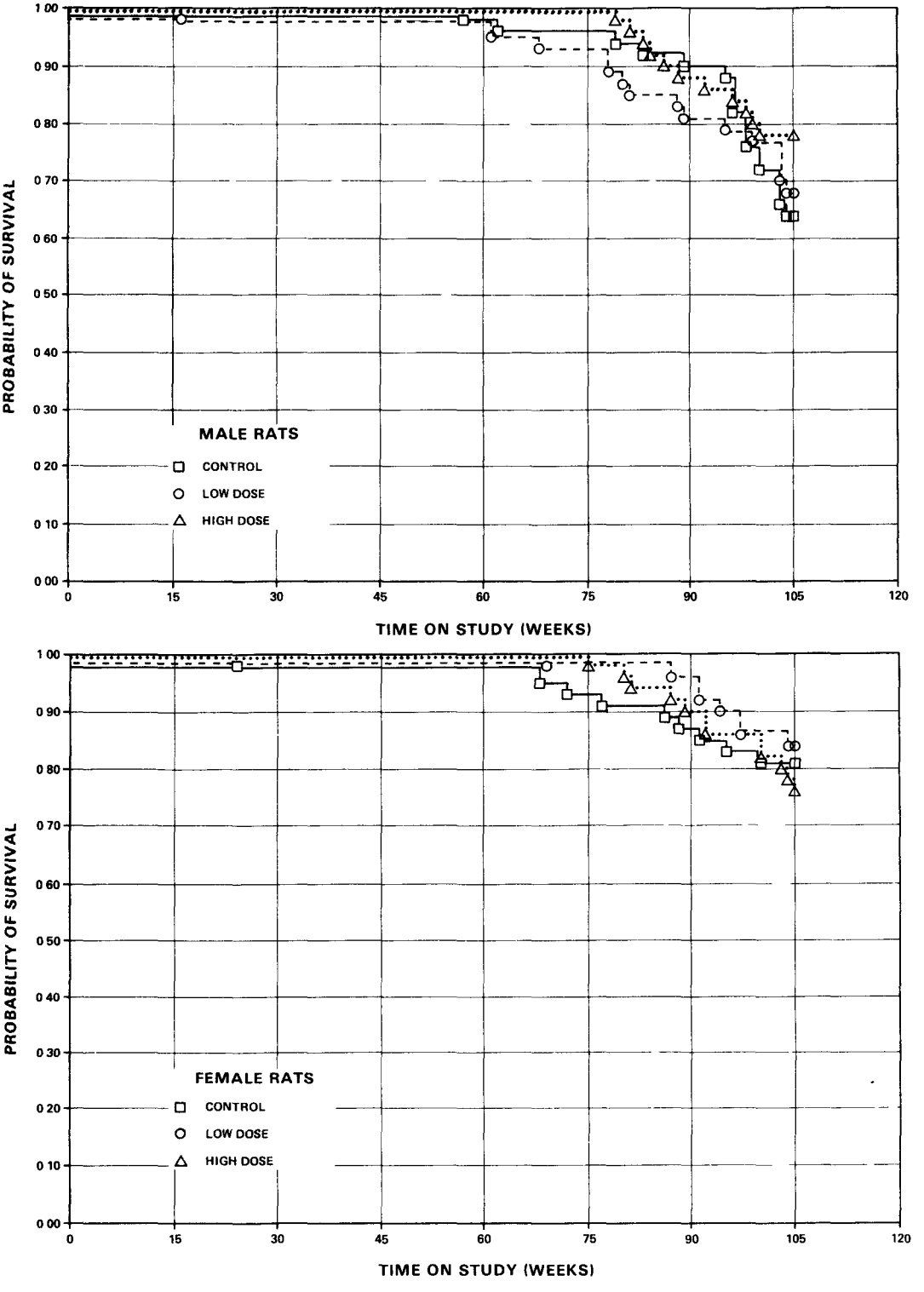


Figure 2. Survival Curves for Rats Fed Diets Containing Caprolactam

encountered in aging F344 rats and none are believed to be related to treatment. Toxic lesions were not seen in any tissue.

The results of histopathologic examination indicated that caprolactam was not carcinogenic or toxic to F344 rats under the conditions of this bioassay.

D. Statistical Analyses of Results (Rats)

Tables 8 and 9 contain the statistical analyses of those primary tumors that occurred in at least two animals of one group and with an incidence of at least 5% in one or more groups. Survival in all groups was comparable.

Interstitial-cell tumors of the testis were observed in increased proportions in the dosed groups compared with the control group (41/49, 84% in the controls; 43/50, 86% in the low-dose; and 48/50, 96% in the high-dose group). The Cochran-Armitage test for linear trend is statistically significant in the positive direction (P=0.038). The Fisher exact test comparing the high-dose group and the control group indicates a value of P=0.043, which is above the value of P=0.025 required by the Bonferroni inequality criterion for an overall significance of P=0.05 when two dosed groups are compared with a common control group. This tumor commonly occurred in historical control groups at levels above 80%.

Carcinomas of the pituitary were observed in increased proportion in the high-dose group of male rats (0/46, 0% in the controls; 0/49, 0% in the low-dose; and 3/47, 6% in the high-dose group). The Cochran-Armitage test for linear trend is statistically significant in the positive direction (P=0.037). The Fisher exact tests are not significant in either the male or female groups when compared with the control groups.

Papillary adenocarcinomas of the mammary gland were observed in increased proportion in the low-dose group of male rats compared with the control group (0/50, 0% in the controls; 3/50, 6% in the low-dose; and 0/50, 0% in the high-dose group) and this increase resulted in a departure from linear trend of P=0.014. In females, the incidence of papillary adenocarcinomas of the mammary gland was observed in decreasing proportions (4/49, 8% in the controls; 1/50, 2% in the low-dose; and 0/50, 0% in the high-dose group). The Cochran-Armitage test for linear trend is statistically significant in

the negative direction (P=0.024). The Fisher exact tests are not significant in either the male or female groups.

Fibromas of the subcutaneous tissue were observed in decreased proportions in the dosed groups of male rats compared with the control group (5/50, 10% in the controls; 3/50, 6% in the low-dose; and 0/50, 0% in the high-dose group). The Cochran-Armitage test for linear trend is statistically significant in the negative direction (P=0.023). The Fisher exact test between the high-dose group and the control group indicates a significantly lower (P=0.028) incidence in the high-dose group than in the controls, but this value is above the value of P=0.025 required by the Bonferroni inequality criterion for an overall significance of P=0.050 when two dosed groups are compared with a common control.

Only three low-dose male rats and one control female rat failed to survive longer than 52 weeks on study, so time-adjusted statistics were not done. Life table analysis, using the time to observation of the various tumors, did not materially change the previously mentioned results.

The tumors of the subcutaneous tissue were observed at a smaller incidence in the high-dose male rats than in the controls to the extent that the upper limit of the relative risk was less than one. With this exception, the value of one is included in each of the 95% confidence intervals for relative risk and indicates the absence of significant positive results; each of the intervals has an upper limit greater than one, indicating the theoretical possibility of tumor induction by caprolactam, which could not be detected under the conditions of this test.

Table 8. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing Caprolactam (a)

Topography: Morphology	Control	Low Dose	High Dose
Subcutaneous Tissue:			
Fibroma (b)	5/50(10)	3/50(6)	0/50(0)
P Values (c),(d)	P=0.023(N)	N.S.	P=0.028(N)
Relative Risk (Control) (e)		0.600	0.000
Lower Limit		0.098	0.000
Upper Limit		2.910	0.793
Weeks to First Observed Tumor	95	105	--
Subcutaneous Tissue: Fibroma or			
Fibrosarcoma (b)	6/50(12)	4/50(8)	1/50(2)
P Values (c),(d)	P=0.042(N)	N.S.	N.S.
Relative Risk (Control) (e)		0.667	0.167
Lower Limit		0.147	0.004
Upper Limit		2.635	1.302
Weeks to First Observed Tumor	95	105	105
Hematopoietic System:			
Leukemia, NOS (b)	13/50(26)	10/50(20)	16/50(32)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.769	1.231
Lower Limit		0.334	0.624
Upper Limit		1.715	2.474
Weeks to First Observed Tumor	62	78	79

Table 8. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing Caprolactam (a)

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Hematopoietic System: All Leukemias (b)	13/50(26)	11/50(22)	16/50(32)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.846	1.231
Lower Limit		0.381	0.624
Upper Limit		1.844	2.474
Weeks to First Observed Tumor	62	16	79
Hematopoietic System: Leukemia or Lymphoma (b)	13/50(26)	11/50(22)	17/50(34)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.846	1.308
Lower Limit		0.381	0.674
Upper Limit		1.844	2.597
Weeks to First Observed Tumor	62	16	79
Liver: Hepatocellular Carcinoma (b)	1/50(2)	3/49(6)	2/50(4)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		3.061	2.000
Lower Limit		0.256	0.108
Upper Limit		157.341	115.621
Weeks to First Observed Tumor	105	95	105

Table 8. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing Caprolactam (a)

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma or Neoplastic Nodule (b)	1/50(2)	5/49(10)	2/50(4)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		5.102	2.000
Lower Limit		0.601	0.108
Upper Limit		236.025	115.621
Weeks to First Observed Tumor	105	95	105
Pituitary: Carcinoma, NOS (b)	0/46(0)	0/49(0)	3/47(6)
P Values (c),(d)	P=0.037	N.S.	N.S.
Relative Risk (Control) (e)		--	Infinite
Lower Limit		--	0.590
Upper Limit		--	Infinite
Weeks to First Observed Tumor	--	--	105
Pituitary: Adenoma, NOS (b)	10/46(22)	11/49(22)	8/47(17)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.033	0.783
Lower Limit		0.442	0.295
Upper Limit		2.453	2.002
Weeks to First Observed Tumor	96	105	105

Table 8. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing Caprolactam (a)

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Pituitary: Adenoma or Carcinoma(b)	10/46(22)	11/49(22)	11/47(23)
P Values (c), (d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.033	1.077
Lower Limit		0.442	0.461
Upper Limit		2.453	2.549
Weeks to First Observed Tumor	96	105	105
Adrenal: Pheochromocytoma (b)	10/49(20)	8/50(16)	6/49(12)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.784	0.600
Lower Limit		0.294	0.194
Upper Limit		2.017	1.673
Weeks to First Observed Tumor	96	81	105
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant (b)	10/49(20)	8/50(16)	7/49(14)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.784	0.700
Lower Limit		0.294	0.246
Upper Limit		2.017	1.865
Weeks to First Observed Tumor	96	81	105

Table 8. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing Caprolactam (a)
(continued)

Topography: Morphology	Control	Low Dose	High Dose
Thyroid: C-Cell Adenoma (b)	3/46(7)	1/45(2)	5/49(10)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.341	1.565
Lower Limit		0.007	0.324
Upper Limit		4.054	9.581
Weeks to First Observed Tumor	105	105	104
Thyroid: C-Cell Adenoma or Carcinoma (b)	3/46(7)	1/45(2)	6/49(12)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.341	1.878
Lower Limit		0.007	0.428
Upper Limit		4.054	11.019
Weeks to First Observed Tumor	105	105	104
Mammary Gland: Papillary Adenocarcinoma (b)	0/50(0)	3/50(6)	0/50(0)
P Values (c),(d)	N.S.	N.S.	N.S.
Departure from Linear Trend (f)	P=0.014		
Relative Risk (Control) (e)		Infinite	--
Lower Limit		0.601	--
Upper Limit		Infinite	--
Weeks to First Observed Tumor	--	105	--

Table 8. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing Caprolactam (a)

(continued)

Topography: Morphology	Control	Low Dose	High Dose
Testis: Interstitial-Cell Tumor (b)	41/49(84)	43/50(86)	48/50(96)
P Values (c),(d)	P=0.038	N.S.	P=0.043
Relative Risk (Control) (e)		1.028	1.147
Lower Limit		0.859	0.984
Upper Limit		1.221	1.241
Weeks to First Observed Tumor	79	80	83

(a) Dosed groups received doses of 3,750 or 7,500 ppm in feed.
(b) Number of tumor-bearing animals/number of animals examined at site (percent).
(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.
(d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.
(e) The 95 percent confidence interval of the relative risk between each dosed group and the control group.
(f) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

Table 9. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing Caprolactam (a)

Topography: Morphology	Control	Low Dose	High Dose
Hematopoietic System:			
Leukemia, NOS (b)	10/49(20)	9/50(18)	11/50(22)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.882	1.078
Lower Limit		0.348	0.459
Upper Limit		2.203	2.570
Weeks to First Observed Tumor	68	69	75
Hematopoietic System: Leukemia or Lymphomas (b)	10/49(20)	10/50(20)	11/50(22)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.980	1.078
Lower Limit		0.403	0.459
Upper Limit		2.387	2.570
Weeks to First Observed Tumor	68	69	75
Pituitary:			
Adenoma, NOS (b)	22/49(45)	23/49(47)	15/47(32)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.045	0.711
Lower Limit		0.653	0.397
Upper Limit		1.676	1.246
Weeks to First Observed Tumor	86	91	105

Table 9. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing Caprolactam (a)
(continued)

Topography: Morphology	Control	Low Dose	High Dose
Pituitary: Adenoma, NOS or Carcinoma, NOS (b)	24/49(49)	24/49(49)	16/47(34)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.000	0.695
Lower Limit		0.643	0.403
Upper Limit		1.556	1.177
Weeks to First Observed Tumor	86	91	89
Adrenal: Cortical Adenoma (b)	4/48(8)	3/50(6)	2/50(4)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.720	0.480
Lower Limit		0.111	0.045
Upper Limit		4.035	3.183
Weeks to First Observed Tumor	105	105	104
Adrenal: Pheochromocytoma (b)	2/48(4)	4/50(8)	3/50(6)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.920	1.440
Lower Limit		0.290	0.173
Upper Limit		20.456	16.632
Weeks to First Observed Tumor	105	105	100

Table 9. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing Caprolactam (a) (continued)

Topography: Morphology	Control	Low Dose	High Dose
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant (b)	2/48(4)	5/50(10)	3/50(6)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		2.400	1.440
Lower Limit		0.416	0.173
Upper Limit		24.269	16.632
Weeks to First Observed Tumor	105	105	100
Thyroid: Follicular-Cell Adenoma or Carcinoma (b)	0/44(0)	1/46(2)	3/46(7)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		Infinite	Infinite
Lower Limit		0.051	0.578
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	104	92
Thyroid: C-Cell Adenoma (b)	2/44(5)	4/46(9)	6/46(13)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.913	2.870
Lower Limit		0.290	0.548
Upper Limit		20.310	27.866
Weeks to First Observed Tumor	105	105	81

Table 9. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing Caprolactam (a)
(continued)

Topography: Morphology	Control	Low Dose	High Dose
Mammary Gland: Adenoma, NOS (b)	3/49(6)	1/50(2)	1/50(2)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.327	0.327
Lower Limit		0.006	0.006
Upper Limit		3.903	3.903
Weeks to First Observed Tumor	105	105	105
Mammary Gland: Papillary Adenocarcinoma (b)	4/49(8)	1/50(2)	0/50(0)
P Values (c),(d)	P=0.024(N)	N.S.	N.S.
Relative Risk (Control) (e)		0.245	0.000
Lower Limit		0.005	0.000
Upper Limit		2.362	1.057
Weeks to First Observed Tumor	72	105	--
Mammary Gland: Fibroadenoma (b)	5/49(10)	3/50(6)	4/50(8)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.588	0.784
Lower Limit		0.096	0.165
Upper Limit		2.851	3.428
Weeks to First Observed Tumor	101	105	92

Table 9. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing Caprolactam (a)
(continued)

Topography: Morphology	Control	Low Dose	High Dose
Uterus: Endometrial Stromal Polyp (b)	12/49(24)	20/50(40)	15/50(30)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.633	1.225
Lower Limit		0.860	0.600
Upper Limit		3.230	2.561
Weeks to First Observed Tumor	105	87	75

(a) Dosed groups received doses of 3,750 or 7,500 ppm in feed.
(b) Number of tumor-bearing animals/number of animals examined at site (percent).
(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.
(d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.
(e) The 95 percent confidence interval of the relative risk between each dosed group and the control group.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

Throughout the bioassay, mean body weights of dosed mice of either sex were lower than those of the controls (Figure 3). The presence of the test chemical in feed had no effect on feed consumption (Appendix J).

B. Survival (Mice)

Estimates of the probabilities of survival for male and female mice administered caprolactam in feed at the doses of this bioassay, and those of the controls, are shown by the Kaplan and Meier curves in Figure 4. The result of Tarone's test for dose-related trend in mortality indicates no significant difference in survival of the three groups of male mice. In females, a significant trend (P=0.032) occurred in a negative direction due to shorter survival in the control group than in the high-dose group. In male mice, 40/50 (80%) of the control group, 48/50 (96%) of the low-dose group, and 43/50 (86%) of the high-dose group lived to the end of the study at week 105. In females, 38/50 (76%) of the control group, 41/50 (82%) of the low-dose group, and 46/50 (92%) of the high-dose group lived to the end of the study at week 105.

C. Pathology (Mice)

Histopathologic findings on neoplasms in mice are summarized in Appendix B, Tables B1 and B2; findings on nonneoplastic lesions are summarized in Appendix D, Tables D1 and D2.

A variety of neoplasms occurred in both the control and dosed mice, but no increased incidences of any types of neoplasms were seen in dosed mice. The observed neoplasms were typical of those seen in this strain of mouse.

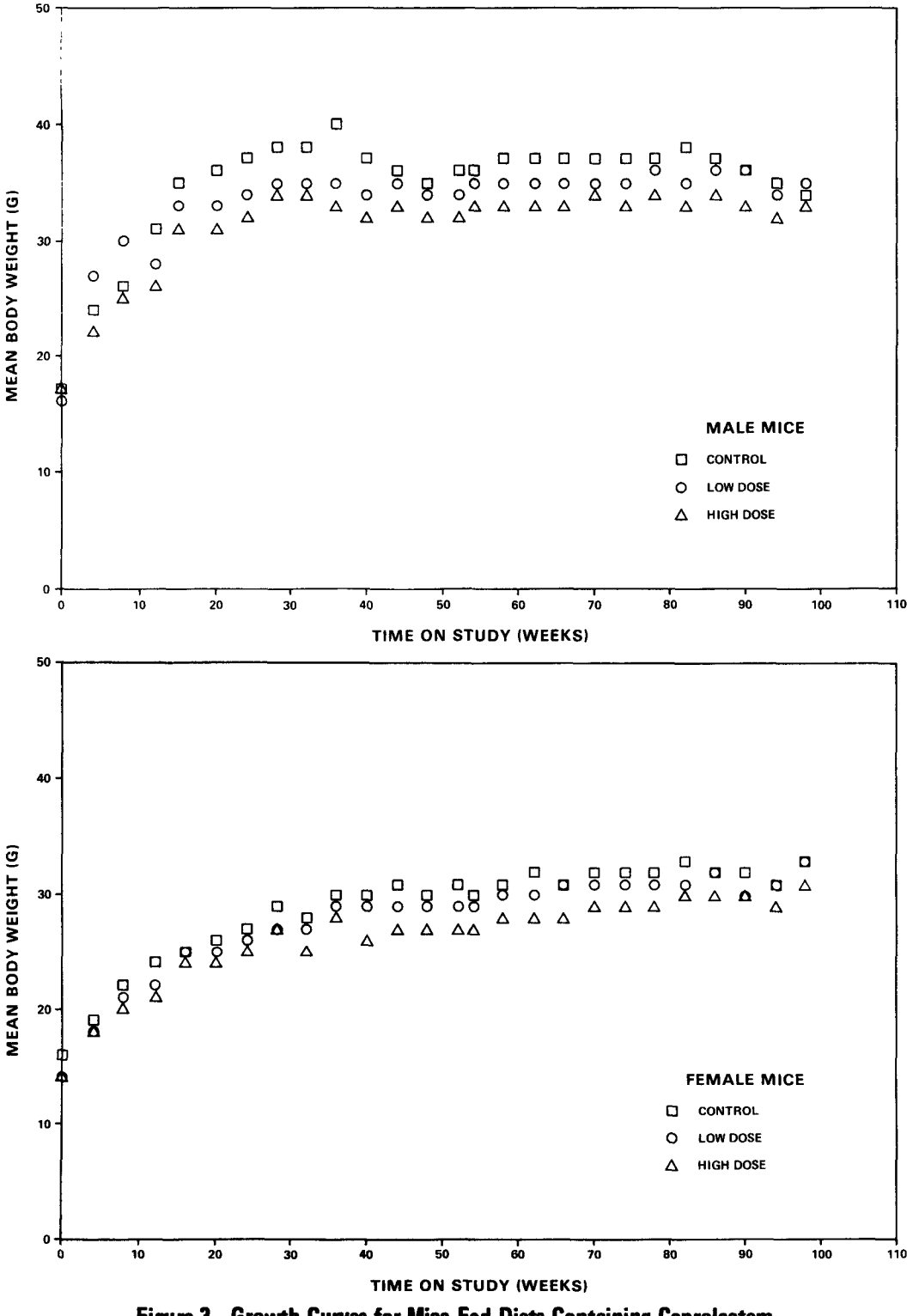


Figure 3. Growth Curves for Mice Fed Diets Containing Caprolactam

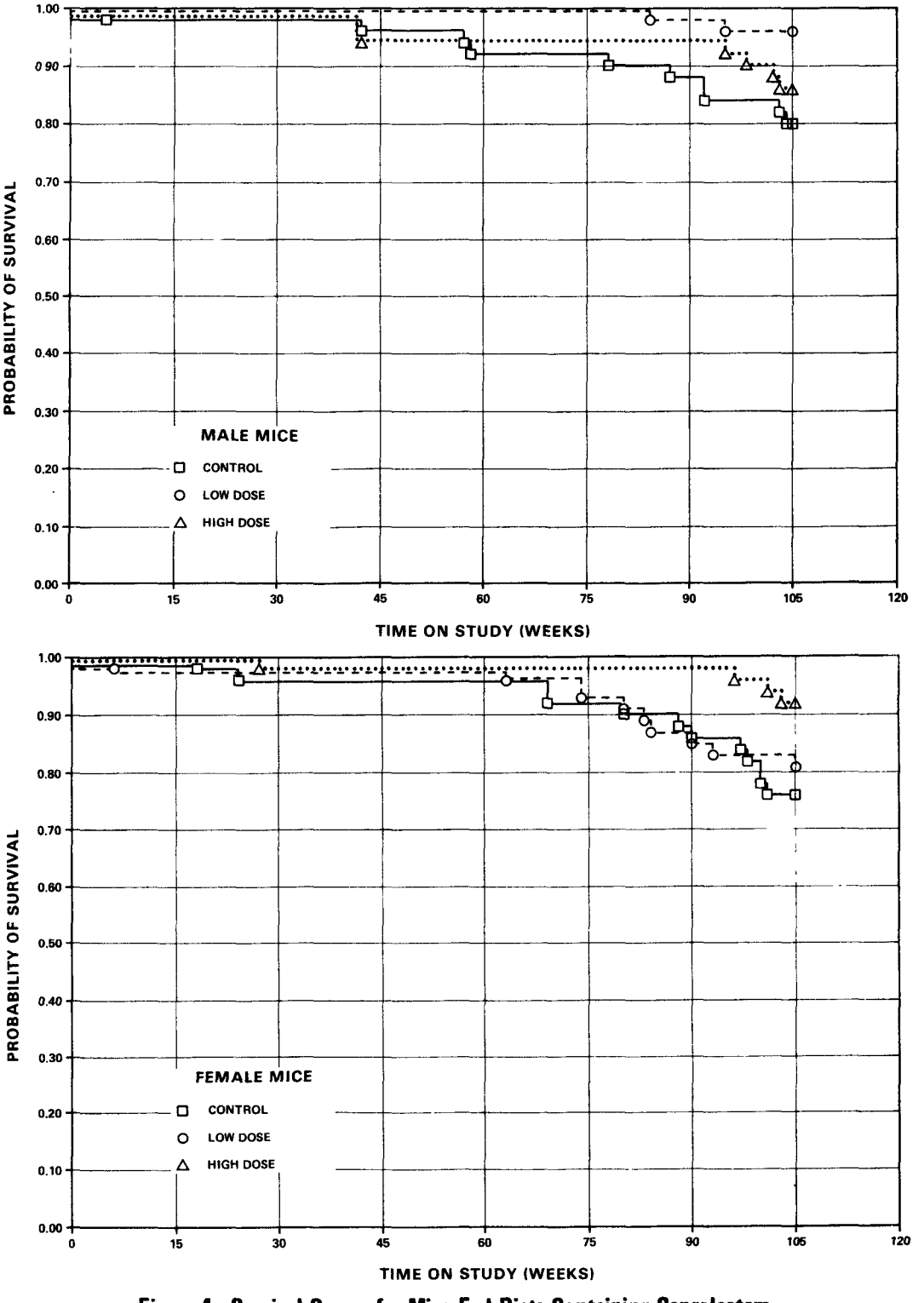


Figure 4. Survival Curves for Mice Fed Diets Containing Caprolactam

Degenerative changes were found in mice, but no increase in the severity or frequency of these lesions was observed in dosed versus control animals. No toxic lesions were seen.

Results of histopathologic examination indicated that caprolactam was not carcinogenic or toxic to B6C3F1 mice under the conditions of this bioassay.

D. Statistical Analyses of Results (Mice)

Tables 10 and 11 contain the statistical analyses of those primary tumors that occurred in at least two animals of one group and with an incidence of at least 5% in one or more groups.

Alveolar/bronchiolar adenomas of the lung in female mice were observed to occur in decreasing proportions (3/50, 6% in the controls; 0/49, 0% in the low-dose; 0/50, 0% in the high-dose). The Cochran-Armitage test for linear trend is statistically significant in the negative direction (P=0.038). The Fisher exact tests are not significant. In male mice, this tumor was not observed in a statistically significant proportion.

Lymphomas or leukemia of the hematopoietic system in the female mice were found to occur in decreased proportion in the high-dose group compared with the control group (21/50, 42% in the controls, 23/49, 47% in the low-dose; 12/50, 24% in the high-dose). The Cochran-Armitage test for linear trend is statistically significant in the negative direction (P=0.040). The Fisher exact test comparing the high-dose group and the control group indicates a value of P=0.044, which is above the value of P=0.025 required by the Bonferroni inequality criterion for an overall significance of P=0.05 when two dosed groups are compared with a common control group. In male mice, this tumor was not observed in statistically significant proportions.

Time-adjusted tests, eliminating those mice that died before 52 weeks on study, did not alter the previously discussed conclusions. Life table analysis, using the time observation of the various tumors, did not materially change the results.

In summary, there was no site at which an increase in tumor incidence could be associated unequivocally with the application of the chemical. In each of the 95% confidence intervals for relative risk, the value of less than one is included and indicates the absence of significant positive results. It should also be noted that each of the intervals has an upper limit greater than one, indicating the theoretical possibility of tumor induction by caprolactam, which could not be detected under the conditions of this test.

Table 10. Analyses of the Incidence of Primary Tumors in Male Mice Fed Diets Containing Caprolactam (a)

Topography: Morphology	Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma (b)	3/50(6)	3/50(6)	2/49(4)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.000	0.680
Lower Limit		0.140	0.059
Upper Limit		7.133	5.680
Weeks to First Observed Tumor	105	105	105
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma (b)	4/50(8)	5/50(10)	4/49(8)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.250	1.020
Lower Limit		0.286	0.201
Upper Limit		5.954	5.183
Weeks to First Observed Tumor	105	105	105
Hematopoietic System: Malignant Lymphoma, NOS (b)	9/50(18)	6/50(12)	4/50(8)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.667	0.444
Lower Limit		0.211	0.106
Upper Limit		1.935	1.478
Weeks to First Observed Tumor	103	95	95

Table 10. Analyses of the Incidence of Primary Tumors in Male Mice Fed Diets Containing Caprolactam (a)
(continued)

Topography: Morphology	Control	Low Dose	High Dose
Hematopoietic System: All Lymphomas (b)	9/50(18)	6/50(12)	5/50(8)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.667	0.556
Lower Limit		0.211	0.157
Upper Limit		1.935	1.708
Weeks to First Observed Tumor	103	95	95
Hematopoietic System: Lymphoma or Leukemia (b)	9/50(18)	6/50(12)	6/50(12)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.667	0.667
Lower Limit		0.211	0.211
Upper Limit		1.935	1.935
Weeks to First Observed Tumor	103	95	95
Liver: Hepatocellular Adenoma (b)	3/50(6)	1/50(2)	4/49(8)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.333	1.361
Lower Limit		0.006	0.243
Upper Limit		3.983	8.854
Weeks to First Observed Tumor	105	105	105

Table 10. Analyses of the Incidence of Primary Tumors in Male Mice Fed Diets Containing Caprolactam (a)
(continued)

Topography: Morphology	Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma (b)	5/50(10)	9/50(18)	6/49(12)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.800	1.224
Lower Limit		0.586	0.333
Upper Limit		6.377	4.751
Weeks to First Observed Tumor	78	84	103
Liver: Hepatocellular Adenoma or Carcinoma (b)	8/50(16)	10/50(20)	10/49(20)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.250	1.276
Lower Limit		0.485	0.496
Upper Limit		3.342	3.405
Weeks to First Observed Tumor	78	84	103

(a) Dosed groups received doses of 7,500 or 15,000 ppm in feed.
(b) Number of tumor-bearing animals/number of animals examined at site (percent).
(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.
(d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.
(e) The 95 percent confidence interval of the relative risk between each dosed group and the control group.

Table 11. Analyses of the Incidence of Primary Tumors in Female Mice Fed Diets Containing Caprolactam (a)

Topography: Morphology	Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma (b)	3/50(6)	0/49(0)	0/50(0)
P Values (c),(d)	P=0.038(N)	N.S.	N.S.
Relative Risk (Control) (e)		0.000	0.000
Lower Limit		0.000	0.000
Upper Limit		1.696	1.663
Weeks to First Observed Tumor	105	--	--
Hematopoietic System: Malignant Lymphoma, Histiocytic Type (b)	1/50(2)	4/49(8)	0/50(0)
P Values (c),(d)	N.S.	N.S.	N.S.
Departure From Linear Trend (f)	P=0.023		
Relative Risk (Control) (e)		4.082	0.000
Lower Limit		0.423	0.000
Upper Limit		196.655	18.658
Weeks to First Observed Tumor	90	80	--
Hematopoietic System: Malignant Lymphoma, NOS (b)	15/50(30)	17/49(35)	12/50(24)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.156	0.800
Lower Limit		0.616	0.382
Upper Limit		2.190	1.637
Weeks to First Observed Tumor	100	63	101

Table 11. Analyses of the Incidence of Primary Tumors in Female Mice Fed Diets Containing Caprolactam (a)
(continued)

Topography: Morphology	Control	Low Dose	High Dose
Hematopoietic System: All Lymphomas (b)	17/50(34)	21/49(43)	12/50(24)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.261	0.706
Lower Limit		0.727	0.346
Upper Limit		2.204	1.397
Weeks to First Observed Tumor	88	63	101
Hematopoietic System: Leukemia, NOS (b)	4/50(8)	2/49(4)	0/50(0)
P Values (c),(d)	P=0.038(N)	N.S.	N.S.
Relative Risk (Control) (e)		0.510	0.000
Lower Limit		0.048	0.000
Upper Limit		3.383	1.079
Weeks to First Observed Tumor	69	93	--
Hematopoietic System: All Leukemias (b)	4/50(8)	2/49(4)	0/50(0)
P Values (c),(d)	P=0.038(N)	N.S.	N.S.
Relative Risk (Control) (e)		0.510	0.000
Lower Limit		0.048	0.000
Upper Limit		3.383	1.079
Weeks to First Observed Tumor	69	93	--

Table 11. Analyses of the Incidence of Primary Tumors in Female Mice Fed Diets Containing Caprolactam (a)
(continued)

Topography: Morphology	Control	Low Dose	High Dose
Hematopoietic System: Lymphoma or Leukemia (b)	21/50(42)	23/49(47)	12/50(24)
P Values (c),(d)	P=0.040(N)	N.S.	P=0.044(N)
Relative Risk (Control) (e)		1.118	0.571
Lower Limit		0.689	0.291
Upper Limit		1.814	1.074
Weeks to First Observed Tumor	69	63	101
Circulatory System: Hemangiosarcoma (b)	3/50(6)	0/49(0)	1/50(2)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.000	0.333
Lower Limit		0.000	0.006
Upper Limit		1.696	3.983
Weeks to First Observed Tumor	69	--	105

(a) Dosed groups received doses of 7,500 or 15,000 ppm in feed.
(b) Number of tumor-bearing animals/number of animals examined at site (percent).
(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.
(d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.
(e) The 95 percent confidence interval of the relative risk between each dosed group and the control group.
(f) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

V. DISCUSSION

No evidence of neoplastic or nonneoplastic lesions associated with oral administration of caprolactam was demonstrated by histopathologic examination of rats and mice in this study. Dose-related decrements in mean body weight gains indicate that it is highly likely that animals in this study were receiving the maximum tolerated doses of caprolactam.

A review by the International Agency for Research Against Cancer of the biological data relevant to evaluation of the carcinogenic risk of caprolactam concluded that "Data from one experimental study with nylon 6, and the absence of both animal and human data on caprolactam, preclude a definite assessment of caprolactam and of its polymer" (IARC, 1979). In the single study of nylon 6, intraperitoneal implantation of nylon 6 induced local sarcomas (Druckrey and Schmahl, 1952).

VI. CONCLUSION

Under the conditions of this bioassay, caprolactam was not carcinogenic for F344 rats or B6C3F1 mice.

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Appendix A
Summary of the Incidence of Neoplasms in Rats Fed Diets Containing Caprolactam

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS FED DIETS CONTAINING CAPROLACTAM

	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)
SQUAMOUS CELL CARCINOMA			1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
SARCOMA, NOS		1 (2%)	
FIBROMA	5 (10%)	3 (6%)	
FIBROSARCOMA	1 (2%)	1 (2%)	1 (2%)
LIPOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS			1 (2%)
LEUKEMIA,NOS	13 (26%)	10 (20%)	16 (32%)
GRANULOCYTIC LEUKEMIA		1 (2%)	
#THYMUS	(33)	(32)	(30)
CARCINOMA,NOS		1 (3%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(50)
NEOPLASTIC NODULE		2 (4%)	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HEPATOCELLULAR CARCINOMA	1 (2%)	3 (6%)	2 (4%)
SARCOMA, NOS, METASTATIC		1 (2%)	
#PANCREAS	(49)	(48)	(49)
ACINAR-CELL ADENOMA		1 (2%)	
#DUODENAL MUCOSA	(50)	(49)	(48)
CYSTADENOCARCINOMA, NOS	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
PHEOCHROMOCYTOMA, METASTATIC			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(49)	(47)
CARCINOMA,NOS			3 (6%)
ADENOMA, NOS	10 (22%)	11 (22%)	8 (17%)
#ADRENAL	(49)	(50)	(49)
CORTICAL ADENOMA	1 (2%)		
CORTICAL CARCINOMA		2 (4%)	
PHEOCHROMOCYTOMA	10 (20%)	8 (16%)	6 (12%)
PHEOCHROMOCYTOMA, MALIGNANT			1 (2%)
GANGLIONEUROMA			1 (2%)
#THYROID	(46)	(45)	(49)
C-CELL ADENOMA	3 (7%)	1 (2%)	5 (10%)
C-CELL CARCINOMA			1 (2%)
#PANCREATIC ISLETS	(49)	(48)	(49)
ISLET-CELL ADENOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)		
ADENOCARCINOMA, NOS	1 (2%)		
PAPILLARY ADENOCARCINOMA		3 (6%)	
FIBROADENOMA	1 (2%)	1 (2%)	1 (2%)
*PREPUTIAL GLAND	(50)	(50)	(50)
CARCINOMA,NOS	2 (4%)	2 (4%)	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
SQUAMOUS CELL CARCINOMA			1 (2%)
ADENOMA, NOS			2 (4%)
#TESTIS	(49)	(50)	(50)
INTERSTITIAL-CELL TUMOR	41 (84%)	43 (86%)	48 (96%)
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
GLIOMA, NOS	2 (4%)		
MEDULLOBLASTOMA	1 (2%)		
SPECIAL SENSE ORGANS			
*ZYMBAL'S GLAND	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (2%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)		
*TUNICA VAGINALIS	(50)	(50)	(50)
MESOTHELIOMA, NOS			2 (4%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
MESOTHELIOMA, NOS			1 (2%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	6	3	4
MORIBUND SACRIFICE	12	12	9
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED		2	
TERMINAL SACRIFICE	32	33	37
ANIMAL MISSING			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	48	46	50
TOTAL PRIMARY TUMORS	96	97	102
TOTAL ANIMALS WITH BENIGN TUMORS	43	44	48
TOTAL BENIGN TUMORS	72	70	71
TOTAL ANIMALS WITH MALIGNANT TUMORS	20	22	25
TOTAL MALIGNANT TUMORS	24	25	28
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	1
TOTAL SECONDARY TUMORS		1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		2	3
TOTAL UNCERTAIN TUMORS		2	3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

@ INCLUDES AUTOLYZED ANIMALS

* 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 CAPROLACTAM

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(49)	(50)	(50)
BASAL-CELL TUMOR			1 (2%)
*SUBCUT TISSUE	(49)	(50)	(50)
FIBROMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(49)	(50)	(50)
UNDIFFERENTIATED CARCINOMA METAS	1 (2%)		
PAPILLARY ADENOCARCINOMA, METAST	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(49)	(50)	(50)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
LEUKEMIA,NOS	10 (20%)	9 (18%)	11 (22%)
#MANDIBULAR L. NODE	(48)	(49)	(48)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(48)	(50)	(50)
UNDIFFERENTIATED CARCINOMA METAS	1 (2%)		

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#PANCREAS	(48)	(50)	(50)
UNDIFFERENTIATED CARCINOMA	1 (2%)		
#JEJUNUM	(48)	(50)	(50)
ADENOCARCINOMA, NOS	1 (2%)		
SARCOMA, NOS	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(49)	(50)	(50)
TUBULAR-CELL ADENOCARCINOMA		1 (2%)	
#KIDNEY/PELVIS	(49)	(50)	(50)
PAPILLOMA, NOS		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(49)	(47)
CARCINOMA,NOS	2 (4%)	1 (2%)	1 (2%)
ADENOMA, NOS	22 (45%)	23 (47%)	15 (32%)
#ADRENAL	(48)	(50)	(50)
UNDIFFERENTIATED CARCINOMA METAS	1 (2%)		
CORTICAL ADENOMA	4 (8%)	3 (6%)	2 (4%)
PHEOCHROMOCYTOMA	2 (4%)	4 (8%)	3 (6%)
PHEOCHROMOCYTOMA, MALIGNANT		1 (2%)	
#THYROID	(44)	(46)	(46)
CARCINOMA,NOS		1 (2%)	
FOLLICULAR-CELL ADENOMA			1 (2%)
FOLLICULAR-CELL CARCINOMA		1 (2%)	2 (4%)
C-CELL ADENOMA	2 (5%)	4 (9%)	6 (13%)
#PARATHYROID	(30)	(27)	(27)
ADENOMA, NOS	1 (3%)		
#PANCREATIC ISLETS	(48)	(50)	(50)
ISLET-CELL ADENOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(49)	(50)	(50)
ADENOMA, NOS	3 (6%)	1 (2%)	1 (2%)

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
PAPILLARY ADENOCARCINOMA	4 (8%)	1 (2%)	
CYSTADENOMA, NOS	1 (2%)	1 (2%)	1 (2%)
PAPILLARY CYSTADENOMA, NOS		1 (2%)	
FIBROSARCOMA			1 (2%)
FIBROADENOMA	5 (10%)	3 (6%)	4 (8%)
*CLITORAL GLAND	(49)	(50)	(50)
CARCINOMA,NOS	1 (2%)	1 (2%)	
SQUAMOUS CELL CARCINOMA	1 (2%)	1 (2%)	
ADENOMA, NOS	1 (2%)		
#UTERUS	(49)	(50)	(50)
LEIOMYOSARCOMA			1 (2%)
ENDOMETRIAL STROMAL POLYP	12 (24%)	20 (40%)	15 (30%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(49)	(50)	(50)
MENINGIOMA	1 (2%)		
#BRAIN	(49)	(50)	(50)
UNDIFFERENTIATED CARCINOMA METAS	1 (2%)		
SPECIAL SENSE ORGANS			
*ZYMBAL'S GLAND	(49)	(50)	(50)
SQUAMOUS CELL CARCINOMA			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	4	4	2
MORIBUND SACRIFICE	5	4	10
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	40	42	38
ANIMAL MISSING			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	45	46	38
TOTAL PRIMARY TUMORS	76	80	66
TOTAL ANIMALS WITH BENIGN TUMORS	37	40	32
TOTAL BENIGN TUMORS	54	62	49
TOTAL ANIMALS WITH MALIGNANT TUMORS	20	16	17
TOTAL MALIGNANT TUMORS	22	18	17
TOTAL ANIMALS WITH SECONDARY TUMORS#	2		1
TOTAL SECONDARY TUMORS	5		1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

@ INCLUDES AUTOLYZED ANIMALS

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

Appendix B

Summary of the Incidence of Neoplasms in Mice Fed Diets Containing Caprolactam

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE FED DIETS CONTAINING CAPROLACTAM

	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			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(49)
HEPATOCELLULAR CARCINOMA, METAST			1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (6%)	3 (6%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	2 (4%)	2 (4%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	6 (12%)	6 (12%)	3 (6%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
LEUKEMIA,NOS			1 (2%)
#SPLEEN	(48)	(50)	(49)
MALIGNANT LYMPHOMA, NOS	1 (2%)		1 (2%)
#MESENTERIC L. NODE	(35)	(37)	(41)
MALIGNANT LYMPHOMA, NOS	1 (3%)		
#ILEUM	(44)	(49)	(48)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(49)
HEPATOCELLULAR ADENOMA	3 (6%)	1 (2%)	4 (8%)

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HEPATOCELLULAR CARCINOMA	5 (10%)	9 (18%)	6 (12%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PANCREATIC ISLETS	(50)	(49)	(48)
ISLET-CELL ADENOMA	1 (2%)	1 (2%)	
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
ADENOMA, NOS		1 (2%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
TAIL			
FIBROMA	1		

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATHS	9	1	5
MORIBUND SACRIFICE	1	1	2
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	40	48	43
ANIMAL MISSING			
a INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	21	18	19
TOTAL PRIMARY TUMORS	23	23	21
TOTAL ANIMALS WITH BENIGN TUMORS	8	6	7
TOTAL BENIGN TUMORS	8	6	7
TOTAL ANIMALS WITH MALIGNANT TUMORS	14	16	13
TOTAL MALIGNANT TUMORS	15	17	14
TOTAL ANIMALS WITH SECONDARY TUMORS#			1
TOTAL SECONDARY TUMORS			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 CAPROLACTAM

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(50)	(49)	(50)
SARCOMA, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(49)	(50)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (6%)		
CYSTADENOCARCINOMA, METASTATIC	1 (2%)		
OSTEOSARCOMA, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(49)	(50)
MALIGNANT LYMPHOMA, NOS	11 (22%)	13 (27%)	8 (16%)
MALIG.LYMPHOMA, UNDIFFER-TYPE	1 (2%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)	4 (8%)	
LEUKEMIA,NOS	4 (8%)	2 (4%)	
#SPLEEN	(48)	(49)	(50)
MALIGNANT LYMPHOMA, NOS	2 (4%)	2 (4%)	
#MESENTERIC L. NODE	(41)	(36)	(39)
CYSTADENOCARCINOMA, METASTATIC	1 (2%)		
MALIGNANT LYMPHOMA, NOS		1 (3%)	1 (3%)
#LIVER	(50)	(49)	(50)
MALIGNANT LYMPHOMA, NOS	2 (4%)	1 (2%)	
#SMALL INTESTINE	(44)	(46)	(49)
MALIGNANT LYMPHOMA, NOS			1 (2%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#JEJUNUM	(44)	(46)	(49)
MALIGNANT LYMPHOMA, NOS			1 (2%)
#KIDNEY	(50)	(49)	(50)
MALIGNANT LYMPHOMA, NOS			1 (2%)
CIRCULATORY SYSTEM			
#SPLEEN	(48)	(49)	(50)
HEMANGIOSARCOMA			1 (2%)
#LIVER	(50)	(49)	(50)
HEMANGIOSARCOMA	1 (2%)		
#UTERUS	(50)	(49)	(50)
HEMANGIOSARCOMA	2 (4%)		
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(50)
HEPATOCELLULAR ADENOMA			1 (2%)
HEPATOCELLULAR CARCINOMA	1 (2%)	1 (2%)	
CYSTADENOCARCINOMA, INVASIVE	1 (2%)		
#DUODENUM	(44)	(46)	(49)
CYSTADENOCARCINOMA, INVASIVE	1 (2%)		
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(42)	(45)
ADENOMA, NOS	2 (4%)	1 (2%)	
#THYROID	(45)	(45)	(45)
FOLLICULAR-CELL ADENOMA	1 (2%)		1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(49)	(50)
ADENOCARCINOMA, NOS	1 (2%)		

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#OVARY	(45)	(45)	(45)
CYSTADENOCARCINOMA, NOS	1 (2%)		
GRANULOSA-CELL TUMOR	1 (2%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(49)	(50)
ADENOMA, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*LUMBAR VERTEBRA	(50)	(49)	(50)
OSTEOSARCOMA			1 (2%)
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
THIGH			
SQUAMOUS CELL CARCINOMA	1		
SITE UNKNOWN			
SQUAMOUS CELL CARCINOMA	1		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATHə	8	7	2
MORIBUND SACRIFICE	4	2	2
SCHEDULED SACRIFICE		1	
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	38	40	46
ANIMAL MISSING			

ə INCLUDES AUTOLYZED ANIMALS

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	31	25	16
TOTAL PRIMARY TUMORS	36	27	16
TOTAL ANIMALS WITH BENIGN TUMORS	6	2	2
TOTAL BENIGN TUMORS	6	2	2
TOTAL ANIMALS WITH MALIGNANT TUMORS	28	24	14
TOTAL MALIGNANT TUMORS	29	25	14
TOTAL ANIMALS WITH SECONDARY TUMORS#	2		1
TOTAL SECONDARY TUMORS	5		1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1		
TOTAL UNCERTAIN TUMORS	1		
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

Appendix C

Summary of the Incidence of Nonneoplastic Lesions in Rats Fed Diets Containing Caprolactam

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS FED DIETS CONTAINING CAPROLACTAM

	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%)
CUTANEOUS HORN	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
STEATITIS		1 (2%)	
NECROSIS, FAT	1 (2%)		
RESPIRATORY SYSTEM			
#TRACHEA	(44)	(42)	(45)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
#LUNG/BRONCHUS	(50)	(50)	(50)
ABSCESS, NOS			1 (2%)
#LUNG	(50)	(50)	(50)
ATELECTASIS	2 (4%)	1 (2%)	
CONGESTION, NOS	2 (4%)	5 (10%)	1 (2%)
HEMORRHAGE		1 (2%)	
INFLAMMATION, INTERSTITIAL	1 (2%)	3 (6%)	1 (2%)
INFLAMMATION, NECROTIZING			1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
PNEUMONIA, CHRONIC MURINE		1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)	1 (2%)	
HYPERPLASIA, ADENOMATOUS		1 (2%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(49)	(49)	(49)
HYPERPLASIA, NOS		3 (6%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
MYELOFIBROSIS			1 (2%)
HYPERPLASIA, GRANULOCYTIC			1 (2%)
#SPLEEN	(50)	(49)	(50)
CONGESTION, NOS		1 (2%)	
NECROSIS, NOS		1 (2%)	
HEMATOPOIESIS	2 (4%)		
#SPLENIC CAPSULE	(50)	(49)	(50)
HYPERPLASIA, NOS	1 (2%)		
#LYMPH NODE	(49)	(48)	(47)
FOREIGN BODY, NOS			1 (2%)
INFLAMMATION, GRANULOMATOUS			1 (2%)
MASTOCYTOSIS			1 (2%)
#MANDIBULAR L. NODE	(49)	(48)	(47)
PLASMACYTOSIS		1 (2%)	1 (2%)
MASTOCYTOSIS			1 (2%)
#MESENTERIC L. NODE	(49)	(48)	(47)
HYPERPLASIA, NOS	1 (2%)		
#ILEUM	(50)	(49)	(48)
HYPERPLASIA, LYMPHOID	1 (2%)		
#COLON	(40)	(46)	(48)
HYPERPLASIA, LYMPHOID			1 (2%)
#THYMUS	(33)	(32)	(30)
HYPERPLASIA, EPITHELIAL	1 (3%)		1 (3%)
CIRCULATORY SYSTEM			
#MANDIBULAR L. NODE	(49)	(48)	(47)
LYMPHANGIECTASIS	1 (2%)		1 (2%)
#MESENTERIC L. NODE	(49)	(48)	(47)
LYMPHANGIECTASIS	1 (2%)	1 (2%)	
#HEART	(50)	(50)	(50)
PERIARTERITIS		1 (2%)	
#HEART/ATRIUM	(50)	(50)	(50)
THROMBOSIS, NOS		2 (4%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#MYOCARDIUM	(50)	(50)	(50)
DEGENERATION, NOS	28 (56%)	27 (54%)	23 (46%)
*PULMONARY ARTERY	(50)	(50)	(50)
MINERALIZATION	4 (8%)	5 (10%)	2 (4%)
*PANCREATIC ARTERY,	(50)	(50)	(50)
DEGENERATION, NOS		1 (2%)	
*VEIN OF NECK	(50)	(50)	(50)
THROMBOSIS, NOS			1 (2%)
*JUGULAR VEIN	(50)	(50)	(50)
MINERALIZATION		1 (2%)	
#PANCREAS	(49)	(48)	(49)
PERIARTERITIS		2 (4%)	1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(50)	(48)
ATROPHY, NOS		1 (2%)	
#LIVER	(50)	(49)	(50)
EMBRYONAL DUCT CYST	1 (2%)		
INFLAMMATION, NECROTIZING		1 (2%)	
GRANULOMA, NOS	8 (16%)	7 (14%)	11 (22%)
CHOLANGIOFIBROSIS	36 (72%)	31 (63%)	15 (30%)
HEPATITIS, TOXIC		1 (2%)	
DEGENERATION, CYSTIC	1 (2%)		
NECROSIS, FOCAL			1 (2%)
NECROSIS, COAGULATIVE	1 (2%)		
METAMORPHOSIS FATTY	1 (2%)	1 (2%)	
BASOPHILIC CYTO CHANGE	2 (4%)		2 (4%)
FOCAL CELLULAR CHANGE	9 (18%)	11 (22%)	6 (12%)
ANGIECTASIS	2 (4%)	1 (2%)	
#LIVER/CENTRILOBULAR	(50)	(49)	(50)
NECROSIS, NOS		1 (2%)	
#BILE DUCT	(50)	(49)	(50)
CYST, NOS	1 (2%)		
INFLAMMATION, NOS			2 (4%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, NOS	2 (4%)	1 (2%)	6 (12%)
#PANCREAS	(49)	(48)	(49)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
GRANULOMA, NOS			1 (2%)
NECROSIS, NOS		1 (2%)	
#PANCREATIC ACINUS	(49)	(48)	(49)
CYTOPLASMIC VACUOLIZATION	1 (2%)		1 (2%)
ATROPHY, NOS	11 (22%)	9 (19%)	5 (10%)
ATROPHY, FOCAL			1 (2%)
#STOMACH	(49)	(50)	(50)
EDEMA, NOS		1 (2%)	
ULCER, NOS		1 (2%)	1 (2%)
INFLAMMATION, NECROTIZING		1 (2%)	
#DUODENUM	(50)	(49)	(48)
ATROPHY, FOCAL		1 (2%)	
#ILEUM	(50)	(49)	(48)
INFLAMMATION, CHRONIC		1 (2%)	
#COLON	(40)	(46)	(48)
ULCER, FOCAL			1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (3%)		
NEMATODIASIS		1 (2%)	
#CECUM	(40)	(46)	(48)
CYST, NOS		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
MINERALIZATION		1 (2%)	
HYDRONEPHROSIS	1 (2%)		
CYST, NOS		1 (2%)	
PYELONEPHRITIS SUPPURATIVE			1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
NEPHROPATHY	45 (90%)	40 (80%)	48 (96%)
DEGENERATION, HYALINE		1 (2%)	
INFARCT, NOS			1 (2%)
#KIDNEY/TUBULE	(50)	(50)	(50)
MINERALIZATION		1 (2%)	5 (10%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DEGENERATION, NOS			1 (2%)
DEGENERATION, HYALINE		1 (2%)	
PIGMENTATION, NOS	40 (80%)	39 (78%)	45 (90%)
#KIDNEY/PELVIS	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL		1 (2%)	
#URINARY BLADDER	(42)	(48)	(43)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)	1 (2%)	1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		2 (5%)
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(49)	(47)
CYST, NOS	2 (4%)	2 (4%)	
CYTOPLASMIC VACUOLIZATION	2 (4%)		
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)	
#ADRENAL	(49)	(50)	(49)
HEMORRHAGE		2 (4%)	
FOCAL CELLULAR CHANGE			1 (2%)
ANGIECTASIS	2 (4%)		3 (6%)
#ADRENAL/CAPSULE	(49)	(50)	(49)
INFLAMMATION, NOS		1 (2%)	
#ADRENAL CORTEX	(49)	(50)	(49)
NECROSIS, FOCAL			1 (2%)
FOCAL CELLULAR CHANGE	1 (2%)		1 (2%)
#ADRENAL MEDULLA	(49)	(50)	(49)
NECROSIS, NOS		1 (2%)	
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)	
#THYROID	(46)	(45)	(49)
ATROPHY, FOCAL		1 (2%)	
HYPERPLASIA, C-CELL	1 (2%)	2 (4%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
GALACTOCELE	1 (2%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION ACUTE AND CHRONIC	1 (2%)		
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, FOCAL		1 (2%)	
LACTATION	22 (44%)	9 (18%)	8 (16%)
*MAMMARY DUCT	(50)	(50)	(50)
HYPERPLASIA, NOS			1 (2%)
*PREPUTIAL GLAND	(50)	(50)	(50)
DILATATION/DUCTS			1 (2%)
ABSCESS, NOS	1 (2%)		2 (4%)
#PROSTATE	(40)	(46)	(45)
INFLAMMATION, ACUTE	1 (3%)		
ABSCESS, NOS	4 (10%)	2 (4%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
HYPERPLASIA, FOCAL	1 (3%)		
*SEMINAL VESICLE	(50)	(50)	(50)
INFLAMMATION, ACUTE	1 (2%)		
#TESTIS	(49)	(50)	(50)
MINERALIZATION		1 (2%)	
CYST, NOS			1 (2%)
HEMORRHAGE			2 (4%)
ATROPHY, NOS	6 (12%)		
HYPERPLASIA, INTERSTITIAL CELL		1 (2%)	1 (2%)
#TESTIS/TUBULE	(49)	(50)	(50)
DEGENERATION, NOS		1 (2%)	
*EPIDIDYMIS	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
DEGENERATION, NOS		1 (2%)	2 (4%)
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
PERIVASCULAR CUFFING			1 (2%)
INFARCT HEMORRHAGIC		1 (2%)	
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
SYNECHIA, POSTERIOR	1 (2%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CATARACT	2 (4%)		3 (6%)
*EYE/RETINA	(50)	(50)	(50)
ATROPHY, NOS	2 (4%)		
*EYE/CONJUNCTIVA	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(50)	(50)	(50)
NECROSIS, FAT		1 (2%)	
INFARCT, NOS	2 (4%)	3 (6%)	4 (8%)
*TUNICA VAGINALIS	(50)	(50)	(50)
HYPERPLASIA, MESOTHELIAL	1 (2%)		
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
STEATITIS	2		
INFLAMMATION, ACUTE/CHRONIC		1	
NECROSIS, FAT			1
SPECIAL MORPHOLOGY SUMMARY			
NONE			

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 CAPROLACTAM

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#TRACHEA	(45)	(49)	(45)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
#LUNG	(49)	(50)	(50)
ATELECTASIS			2 (4%)
CONGESTION, NOS	1 (2%)	1 (2%)	1 (2%)
EDEMA, NOS		1 (2%)	
HEMORRHAGE	1 (2%)	1 (2%)	2 (4%)
INFLAMMATION, INTERSTITIAL	1 (2%)	1 (2%)	
PNEUMONIA, CHRONIC MURINE		2 (4%)	2 (4%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(49)	(50)	(50)
LYMPHOID DEPLETION			1 (2%)
#BONE MARROW	(47)	(49)	(48)
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)		
#SPLEEN	(47)	(50)	(50)
INFLAMMATION, GRANULOMATOUS	1 (2%)		
GRANULOMA, NOS	1 (2%)		
HEMATOPOIESIS	1 (2%)		
#LYMPH NODE	(48)	(49)	(48)
HEMOSIDEROSIS			1 (2%)
#MESENTERIC L. NODE	(48)	(49)	(48)
FOREIGN BODY, NOS	1 (2%)		

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
GRANULOMA, NOS			1 (2%)
LYMPHADENOPATHY	1 (2%)		
#COLON	(45)	(42)	(47)
HYPERPLASIA, LYMPHOID	1 (2%)		
#THYMUS	(37)	(42)	(27)
CYST, NOS	1 (3%)	1 (2%)	
HYPERPLASIA, LYMPHOID	1 (3%)		
CIRCULATORY SYSTEM			
#MYOCARDIUM	(49)	(50)	(49)
DEGENERATION, NOS	14 (29%)	21 (42%)	9 (18%)
*PULMONARY ARTERY	(49)	(50)	(50)
MINERALIZATION	1 (2%)	2 (4%)	1 (2%)
*PULMONARY VEIN	(49)	(50)	(50)
MINERALIZATION	1 (2%)		
#PANCREAS	(48)	(50)	(50)
PERIARTERITIS	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(48)	(50)	(50)
GRANULOMA, NOS	28 (58%)	34 (68%)	33 (66%)
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)		
CHOLANGIOFIBROSIS	10 (21%)	4 (8%)	8 (16%)
HEPATITIS, TOXIC			1 (2%)
NECROSIS, FOCAL	1 (2%)		
METAMORPHOSIS FATTY	1 (2%)		1 (2%)
BASOPHILIC CYTO CHANGE	3 (6%)	4 (8%)	2 (4%)
FOCAL CELLULAR CHANGE	3 (6%)	3 (6%)	4 (8%)
ANGIECTASIS		1 (2%)	1 (2%)
#HEPATIC LOBULE	(48)	(50)	(50)
METAMORPHOSIS FATTY			1 (2%)
#LIVER/CENTRILOBULAR	(48)	(50)	(50)
METAMORPHOSIS FATTY			1 (2%)
#BILE DUCT	(48)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, NOS		1 (2%)	
#PANCREAS	(48)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
ATROPHY, NOS	1 (2%)		
#PANCREATIC ACINUS	(48)	(50)	(50)
ATROPHY, NOS	11 (23%)	8 (16%)	11 (22%)
ATROPHY, FOCAL		1 (2%)	
#STOMACH	(49)	(50)	(50)
EPIDERMAL INCLUSION CYST	1 (2%)		
ULCER, NOS		1 (2%)	
#GASTRIC MUCOSA	(49)	(50)	(50)
CYST, NOS	1 (2%)		
#GASTRIC FUNDAL GLAND	(49)	(50)	(50)
DILATATION, NOS			4 (8%)
#DUODENUM	(48)	(50)	(50)
INFLAMMATION, NECROTIZING	1 (2%)		
#ILEUM	(48)	(50)	(50)
ULCER, NOS			1 (2%)
#COLON	(45)	(42)	(47)
NEMATODIASIS	2 (4%)		1 (2%)
URINARY SYSTEM			
#KIDNEY	(49)	(50)	(50)
MINERALIZATION		2 (4%)	2 (4%)
CYST, NOS	1 (2%)		2 (4%)
NEPHROPATHY	26 (53%)	27 (54%)	23 (46%)
DEGENERATION, HYALINE			1 (2%)
#RENAL PAPILLA	(49)	(50)	(50)
MINERALIZATION			1 (2%)
#KIDNEY/TUBULE	(49)	(50)	(50)
MINERALIZATION	4 (8%)	5 (10%)	2 (4%)
DEGENERATION, HYALINE			1 (2%)
NECROSIS, FOCAL			1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
PIGMENTATION, NOS	42 (86%)	43 (86%)	48 (96%)
#KIDNEY/PELVIS	(49)	(50)	(50)
DILATATION, NOS			1 (2%)
#URINARY BLADDER	(49)	(50)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR	13 (27%)	10 (20%)	6 (12%)
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(49)	(47)
CYST, NOS	12 (24%)	12 (24%)	14 (30%)
HYPERPLASIA, NOS		1 (2%)	1 (2%)
HYPERPLASIA, FOCAL		1 (2%)	3 (6%)
ANGIECTASIS	3 (6%)		
#ADRENAL	(48)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
NECROSIS, FOCAL			1 (2%)
ANGIECTASIS	2 (4%)		4 (8%)
#ADRENAL CORTEX	(48)	(50)	(50)
CYST, NOS		1 (2%)	
FOCAL CELLULAR CHANGE	9 (19%)	3 (6%)	2 (4%)
#THYROID	(44)	(46)	(46)
ATROPHY, FOCAL		1 (2%)	
HYPERPLASIA, C-CELL	9 (20%)	4 (9%)	3 (7%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(49)	(50)	(50)
GALACTOCELE	1 (2%)		
HYPERPLASIA, FOCAL	1 (2%)		
LACTATION	30 (61%)	28 (56%)	27 (54%)
*CLITORAL GLAND	(49)	(50)	(50)
ABSCESS, NOS	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
*VAGINA	(49)	(50)	(50)
CYST, NOS			1 (2%)
#UTERUS	(49)	(50)	(50)
PROLAPSE		1 (2%)	1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HEMORRHAGIC CYST	1 (2%)		
HYPERPLASIA, STROMAL		1 (2%)	
FIBROSING ADENOSIS	24 (49%)	29 (58%)	15 (30%)
#UTERUS/ENDOMETRIUM	(49)	(50)	(50)
FIBROSIS	4 (8%)	1 (2%)	2 (4%)
HYPERPLASIA, NOS		3 (6%)	2 (4%)
HYPERPLASIA, CYSTIC	5 (10%)	2 (4%)	9 (18%)
#OVARY	(47)	(50)	(50)
CYST, NOS	1 (2%)	1 (2%)	1 (2%)
CORPUS LUTEUM CYST		1 (2%)	
PAROVARIAN CYST			1 (2%)
INFLAMMATION, GRANULOMATOUS	1 (2%)		
NERVOUS SYSTEM			
#BRAIN	(49)	(50)	(50)
PERIVASCULAR CUFFING			1 (2%)
SPECIAL SENSE ORGANS			
*EYE	(49)	(50)	(50)
INFLAMMATION, CHRONIC		2 (4%)	
CATARACT		5 (10%)	2 (4%)
*EYE/CORNEA	(49)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)
*EYEBALL TUNICA VASCU	(49)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)
*EYE/RETINA	(49)	(50)	(50)
ATROPHY, NOS		3 (6%)	1 (2%)
*EYE/CONJUNCTIVA	(49)	(50)	(50)
INFLAMMATION, ACUTE			1 (2%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*MESENTERY	(49)	(50)	(50)
NECROSIS, HEMORRHAGIC		1 (2%)	
INFARCT, NOS	1 (2%)	2 (4%)	4 (8%)
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
INFLAMMATION, FOCAL	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 Caprolactam

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE FED DIETS CONTAINING CAPROLACTAM

	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)
INFLAMMATION ACTIVE CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)		
HYPERKERATOSIS			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(49)
CONGESTION, NOS	1 (2%)	1 (2%)	
HEMORRHAGE	14 (28%)	16 (32%)	12 (24%)
INFLAMMATION, INTERSTITIAL			2 (4%)
INFLAMMATION, ACUTE		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	7 (14%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(48)	(48)	(46)
MYELOFIBROSIS	1 (2%)		
HYPERPLASIA, HEMATOPOIETIC	1 (2%)		
#SPLEEN	(48)	(50)	(49)
HEMORRHAGE		1 (2%)	
LYMPHOID DEPLETION		1 (2%)	
HEMATOPOIESIS	1 (2%)		
#LYMPH NODE	(35)	(37)	(41)
HEMOSIDEROSIS	4 (11%)	7 (19%)	9 (22%)
PLASMACYTOSIS	1 (3%)		
MASTOCYTOSIS	1 (3%)		
#MANDIBULAR L. NODE	(35)	(37)	(41)
HEMOSIDEROSIS	6 (17%)	7 (19%)	14 (34%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
PLASMACYTOSIS	8 (23%)	10 (27%)	16 (39%)
#MEDIASTINAL L.NODE	(35)	(37)	(41)
HEMOSIDEROSIS	2 (6%)	1 (3%)	1 (2%)
PLASMACYTOSIS	1 (3%)		1 (2%)
#MESENTERIC L. NODE	(35)	(37)	(41)
HEMORRHAGE	9 (26%)	12 (32%)	6 (15%)
HEMOSIDEROSIS	3 (9%)		
HISTIOCYTOSIS	1 (3%)		
HYPERPLASIA, LYMPHOID	1 (3%)		
*INTESTINAL TRACT	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID			1 (2%)
#SMALL INTESTINE	(44)	(49)	(48)
HYPERPLASIA, LYMPHOID		1 (2%)	
#DUODENUM	(44)	(49)	(48)
LEUKOCYTOSIS, EOSINOPHILIC	1 (2%)		
HYPERPLASIA, LYMPHOID	1 (2%)		
#JEJUNUM	(44)	(49)	(48)
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)
#ILEUM	(44)	(49)	(48)
HYPERPLASIA, LYMPHOID		1 (2%)	
#THYMUS	(21)	(27)	(27)
INVOLUTION, NOS	1 (5%)		
CIRCULATORY SYSTEM			
#HEART	(50)	(50)	(49)
MINERALIZATION		2 (4%)	
INFLAMMATION, CHRONIC	1 (2%)		
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(49)	(48)
INFLAMMATION, CHRONIC			1 (2%)
#LIVER	(50)	(50)	(49)
CYST, NOS		1 (2%)	

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TORSION	1 (2%)		
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, SUPPURATIVE	1 (2%)		
INFLAMMATION, ACUTE	1 (2%)	1 (2%)	2 (4%)
INFLAMMATION ACTIVE CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)	1 (2%)	
INFLAMMATION, GRANULOMATOUS	1 (2%)		
NECROSIS, NOS	1 (2%)		1 (2%)
NECROSIS, COAGULATIVE	2 (4%)		
NECROSIS, CENTRAL			1 (2%)
METAMORPHOSIS FATTY	1 (2%)		
BASOPHILIC CYTO CHANGE	1 (2%)		
GROUND-GLASS CYTO CHANGE	4 (8%)	1 (2%)	1 (2%)
#LIVER/CENTRILOBULAR	(50)	(50)	(49)
NECROSIS, COAGULATIVE			1 (2%)
#PANCREAS	(50)	(49)	(48)
INFLAMMATION, CHRONIC	1 (2%)		
#PANCREATIC ACINUS	(50)	(49)	(48)
ATROPHY, NOS	1 (2%)	1 (2%)	1 (2%)
#STOMACH	(50)	(50)	(50)
MINERALIZATION			1 (2%)
#COLON	(46)	(49)	(47)
NEMATODIASIS			2 (4%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
MINERALIZATION			1 (2%)
CYST, NOS	2 (4%)		
INFLAMMATION, CHRONIC	39 (78%)	41 (82%)	35 (70%)
DEGENERATION, HYALINE			1 (2%)
NEPHROSIS, NOS	2 (4%)		
GLOMERULOSCLEROSIS, NOS		1 (2%)	
NECROSIS, FAT	1 (2%)		
#KIDNEY/TUBULE	(50)	(50)	(50)
CYTOPLASMIC VACUOLIZATION	1 (2%)		
#URINARY BLADDER	(49)	(40)	(46)
MINERALIZATION			1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, CHRONIC	15 (31%)	10 (25%)	3 (7%)
HYPERPLASIA, EPITHELIAL	2 (4%)		1 (2%)
#U. BLADDER/MUCOSA	(49)	(40)	(46)
INFLAMMATION, SUPPURATIVE	1 (2%)		
#U.BLADDER/SEROSA	(49)	(40)	(46)
INFLAMMATION, CHRONIC	1 (2%)		
*URETHRA	(50)	(50)	(50)
HEMORRHAGE	2 (4%)	3 (6%)	3 (6%)
ENDOCRINE SYSTEM			
#PARATHYROID	(16)	(16)	(15)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (6%)	
REPRODUCTIVE SYSTEM			
*PREPUCE	(50)	(50)	(50)
INFLAMMATION ACTIVE CHRONIC	1 (2%)		
*PREPUTIAL GLAND	(50)	(50)	(50)
INFLAMMATION ACTIVE CHRONIC	1 (2%)		
#PROSTATE	(49)	(47)	(46)
INFLAMMATION, NOS	1 (2%)		
INFLAMMATION, SUPPURATIVE	2 (4%)		
INFLAMMATION, CHRONIC	2 (4%)		
#TESTIS	(50)	(50)	(49)
MINERALIZATION	8 (16%)	10 (20%)	2 (4%)
INFLAMMATION ACTIVE CHRONIC	1 (2%)		
GRANULOMA, SPERMATIC		1 (2%)	
*EPIDIDYMIS	(50)	(50)	(50)
INFLAMMATION ACTIVE CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)		1 (2%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(50)	(50)	(48)
HEMORRHAGE	1 (2%)		

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
PIGMENTATION, NOS			1 (2%)
#BRAIN	(50)	(50)	(48)
MINERALIZATION	3 (6%)	1 (2%)	1 (2%)
HEMORRHAGE		1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*STERNUM	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
INFLAMMATION ACTIVE CHRONIC	1 (2%)		
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
ECTOPIA		1 (2%)	
*ABDOMINAL CAVITY	(50)	(50)	(50)
NECROSIS, FAT		2 (4%)	
*PELVIS	(50)	(50)	(50)
NECROSIS, FAT			1 (2%)
*PLEURA	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
*EPICARDIUM	(50)	(50)	(50)
INFLAMMATION ACTIVE CHRONIC	1 (2%)		
*MESENTERY	(50)	(50)	(50)
INFLAMMATION ACTIVE CHRONIC	1 (2%)		
ALL OTHER SYSTEMS			
NONE			

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED			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 CAPROLACTAM

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(50)
MINERALIZATION	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)		
HYPERKERATOSIS		1 (2%)	
RESPIRATORY SYSTEM			
*LARYNX	(50)	(49)	(50)
INFLAMMATION ACTIVE CHRONIC			1 (2%)
#LUNG	(50)	(49)	(50)
MINERALIZATION	1 (2%)		1 (2%)
CONGESTION, NOS	2 (4%)	1 (2%)	1 (2%)
HEMORRHAGE	16 (32%)	9 (18%)	11 (22%)
LYMPHOCYTIC INFLAMMATORY INFILTR			3 (6%)
INFLAMMATION, INTERSTITIAL	1 (2%)		
INFLAMMATION, CHRONIC	2 (4%)	3 (6%)	3 (6%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(45)	(48)	(48)
NECROSIS, NOS	1 (2%)		
HYPERPLASIA, NOS		1 (2%)	
MYELOFIBROSIS	36 (80%)	39 (81%)	44 (92%)
HYPERPLASIA, HEMATOPOIETIC	1 (2%)		
#SPLEEN	(48)	(49)	(50)
INFLAMMATION, CHRONIC			1 (2%)
LYMPHOCYTOSIS			1 (2%)
HEMATOPOIESIS	2 (4%)	5 (10%)	
#LYMPH NODE	(41)	(36)	(39)
HEMOSIDEROSIS	5 (12%)	1 (3%)	5 (13%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HISTIOCYTOSIS	1 (2%)		
PLASMACYTOSIS	1 (2%)		
HYPERPLASIA, LYMPHOID	1 (2%)		
#MANDIBULAR L. NODE	(41)	(36)	(39)
HEMORRHAGE	1 (2%)		1 (3%)
HEMOSIDEROSIS	12 (29%)	14 (39%)	19 (49%)
LYMPHOCYTOSIS	1 (2%)		1 (3%)
PLASMACYTOSIS	10 (24%)	9 (25%)	11 (28%)
#MEDIASTINAL L.NODE	(41)	(36)	(39)
HEMOSIDEROSIS	1 (2%)	2 (6%)	1 (3%)
PLASMACYTOSIS	2 (5%)	1 (3%)	
#LUMBAR LYMPH NODE	(41)	(36)	(39)
INFLAMMATION, ACUTE	1 (2%)		
HEMATOPOIESIS	1 (2%)		
#MESENTERIC L. NODE	(41)	(36)	(39)
HEMORRHAGE	1 (2%)	1 (3%)	1 (3%)
HEMOSIDEROSIS	1 (2%)		
#RENAL LYMPH NODE	(41)	(36)	(39)
HISTIOCYTOSIS	1 (2%)		
PLASMACYTOSIS	1 (2%)		
#LUNG	(50)	(49)	(50)
LEUKOCYTOSIS, NEUTROPHILIC	1 (2%)		
#LIVER	(50)	(49)	(50)
LEUKOCYTOSIS, NEUTROPHILIC	1 (2%)		
HEMATOPOIESIS	1 (2%)	1 (2%)	
#ADRENAL	(50)	(49)	(50)
HEMATOPOIESIS	1 (2%)		
#THYMUS	(24)	(28)	(33)
LYMPHOID DEPLETION	1 (4%)		
CIRCULATORY SYSTEM			
#HEART	(50)	(48)	(48)
MINERALIZATION			1 (2%)
#MYOCARDIUM	(50)	(48)	(48)
MINERALIZATION	1 (2%)		

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(49)	(47)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
NECROSIS, NOS		1 (2%)	
#LIVER	(50)	(49)	(50)
MINERALIZATION		1 (2%)	
INFLAMMATION, MULTIFOCAL		1 (2%)	
INFLAMMATION, ACUTE	6 (12%)	11 (22%)	18 (36%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
INFLAMMATION, CHRONIC	11 (22%)	7 (14%)	5 (10%)
GRANULOMA, NOS			1 (2%)
DEGENERATION, NOS	1 (2%)		
NECROSIS, FOCAL		1 (2%)	
NECROSIS, COAGULATIVE	6 (12%)		
NECROSIS, CENTRAL	1 (2%)		
CYTOPLASMIC VACUOLIZATION	1 (2%)		
BASOPHILIC CYTO CHANGE		1 (2%)	
GROUND-GLASS CYTO CHANGE	1 (2%)		1 (2%)
ANGIECTASIS	1 (2%)		
*GALLBLADDER	(50)	(49)	(50)
CYST, NOS			1 (2%)
#PANCREAS	(47)	(48)	(50)
CYST, NOS	1 (2%)		1 (2%)
INFLAMMATION ACTIVE CHRONIC	1 (2%)		
CYTOPLASMIC VACUOLIZATION	1 (2%)		3 (6%)
#PANCREATIC ACINUS	(47)	(48)	(50)
ATROPHY, NOS	2 (4%)	1 (2%)	1 (2%)
#STOMACH	(49)	(48)	(49)
MINERALIZATION	2 (4%)	1 (2%)	
INFLAMMATION ACTIVE CHRONIC	1 (2%)		
#DUODENUM	(44)	(46)	(49)
HAMARTOMA		1 (2%)	
#COLON	(48)	(46)	(47)
NEMATODIASIS	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(50)	(49)	(50)
MINERALIZATION	2 (4%)		

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, NOS	1 (2%)		
INFLAMMATION, CHRONIC	32 (64%)	33 (67%)	37 (74%)
INFLAMMATION, OSSIFYING	1 (2%)		
FIBROSIS, DIFFUSE	1 (2%)		
DEGENERATION, HYALINE	1 (2%)		
GLOMERULOSCLEROSIS, NOS			1 (2%)
#KIDNEY/GLOMERULUS	(50)	(49)	(50)
NEPHROSIS, NOS	1 (2%)		
#KIDNEY/TUBULE	(50)	(49)	(50)
MINERALIZATION	1 (2%)		
DEGENERATION, HYALINE		1 (2%)	
PIGMENTATION, NOS	1 (2%)		
#URINARY BLADDER	(49)	(47)	(45)
HEMORRHAGE		1 (2%)	
INFLAMMATION, CHRONIC	30 (61%)	23 (49%)	27 (60%)
ENDOCRINE SYSTEM			
#ADRENAL	(50)	(49)	(50)
CYTOPLASMIC CHANGE, NOS			1 (2%)
#THYROID	(45)	(45)	(45)
INFLAMMATION, ACUTE		1 (2%)	
#PARATHYROID	(19)	(16)	(22)
HYPERPLASIA, NOS			1 (5%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(49)	(50)
DILATATION/DUCTS	1 (2%)		
FIBROSIS	1 (2%)		
#UTERUS	(50)	(49)	(50)
CYST, NOS	1 (2%)		
CONGESTION, NOS		1 (2%)	
HEMORRHAGE	1 (2%)	1 (2%)	
INFLAMMATION, SUPPURATIVE	2 (4%)	1 (2%)	
ABSCESS, NOS	1 (2%)		
#UTERUS/ENDOMETRIUM	(50)	(49)	(50)
HYPERPLASIA, NOS	1 (2%)		

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, CYSTIC	27 (54%)	32 (65%)	30 (60%)
#OVARY	(45)	(45)	(45)
MINERALIZATION		1 (2%)	
CYST, NOS		2 (4%)	
PAROVARIAN CYST	4 (9%)	9 (20%)	7 (16%)
HEMOPRHAGE	1 (2%)	1 (2%)	
HEMATOMA, NOS		1 (2%)	
ABSCESS, NOS	1 (2%)		
NERVOUS SYSTEM			
#BRAIN/MENINGES	(50)	(49)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)		
PIGMENTATION, NOS		1 (2%)	
#CEREBELLUM	(50)	(49)	(50)
HEMORRHAGE			1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(50)	(49)	(50)
CYST, NOS		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(49)	(50)
INFLAMMATION, CHRONIC			1 (2%)
SPECIAL MORPHOLOGY SUMMARY			
AUTOLYSIS/NO NECROPSY		1	

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

Appendix E

Analysis of Caprolactam (Lot No. DB 7-7-75)
Midwest Research Institute

Appendix E

Analysis of Caprolactam (Lot No. DB-7-7-75)

A. ELEMENTAL ANALYSIS

Element	C	H	N
Theory	63.68	9.80	12.39
Determined	63.77	9.74	12.38
	63.90	9.98	12.62

B. MELTING POINT

Determined	Literature Values
m.p. 64° to 67°C (Dupont 900 DTA)	m.p. 68° to 70°C (Tokura et al., 1965)
69.3° to 71.3°C (visual capillary)	

C. THIN-LAYER CHROMATOGRAPHY

Plates: Silica gel F-254 — Ref. Standard: Acetanilide
Amount Spotted: 100 and 300μg — Visualization: Iodine vapor; ninhydrin

System 1: Ethanol, 100%
R_f: 0.73
R_{st}: 0.86

No ninhydrin-positive impurities.

System 2: Ethyl acetate, 100%
R_f: 0.14
R_{st}: 0.24

D. VAPOR-PHASE CHROMATOGRAPHY

Instrument: Tracor MT 220
Column: 5% Carbowax 20M-TPA on 60/80 Gas Chrom Q, 1.8 m x 4 mm I.D.
Detection: Flame ionization
Oven Temperature Program: 100°C, 5 min; 100 to 200°C at 10°C/min
Results: One homogeneous peak, retention time, 13.0 min.

E. SPECTRAL DATA

(1) Infrared:
Instrument: Beckman IR-12
Cell: 0.15% KBr pellet
Results: See Figure 5

Identical to literature spectrum (Sadtler Standard Spectra)

(2) Ultraviolet/Visible
Instrument: Cary 118
No absorbance between 350 and 800 nm (visible region).

No maximum between 210 and 350 nm (ultraviolet region).
Strong absorbance at the solvent cutoff (210 nm)
Concentration: 1.0 mg/ml
Solvent: 95% ethanol

No literature reference found

(3) Nuclear Magnetic Resonance:
Instrument: Varian HA-100
Solvent: $CDCl_3$ with internal tetramethylsilane
Assignment (See Figure 6)
(a) δ1.68 (c) δ3.15
(b) δ2.41 (d) δ7.28
Integration Ratios:
(a) 6.42 (c) 1.74
(b) 1.85 (d) 0.64

Identical to literature spectrum (Sadtler Standard spectra).

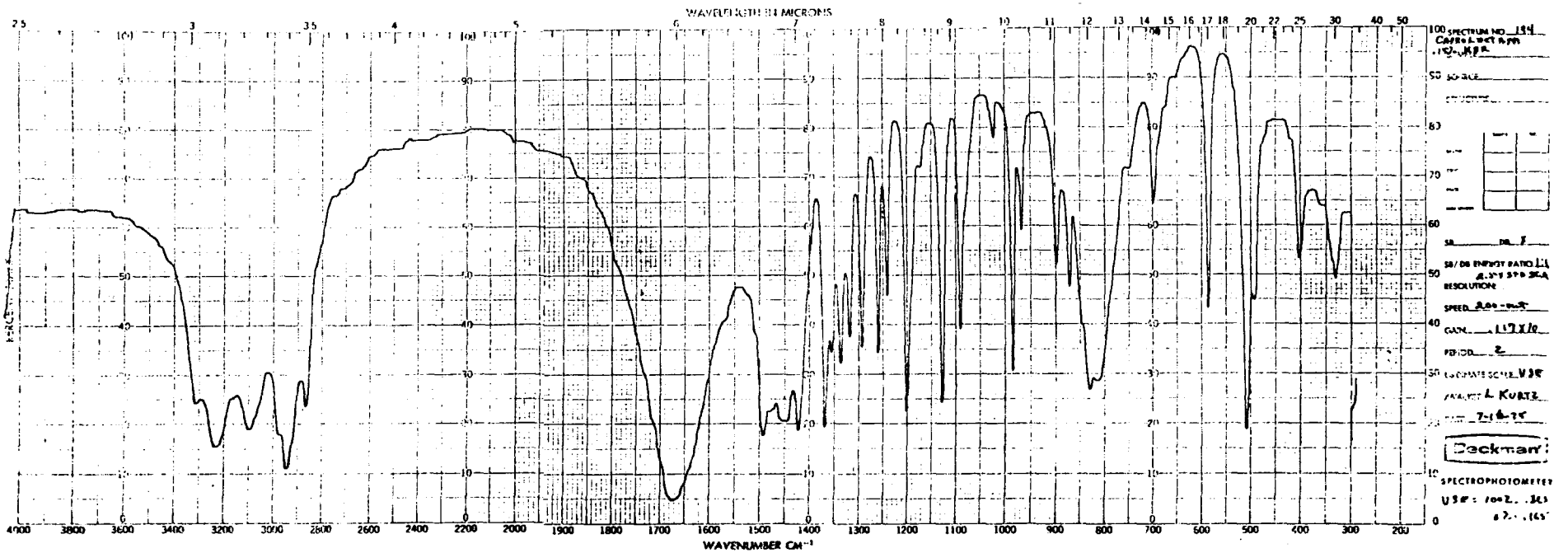

Figure 5. Infrared Absorption Spectrum of Caprolactam (Lot No. DB7-7-75)

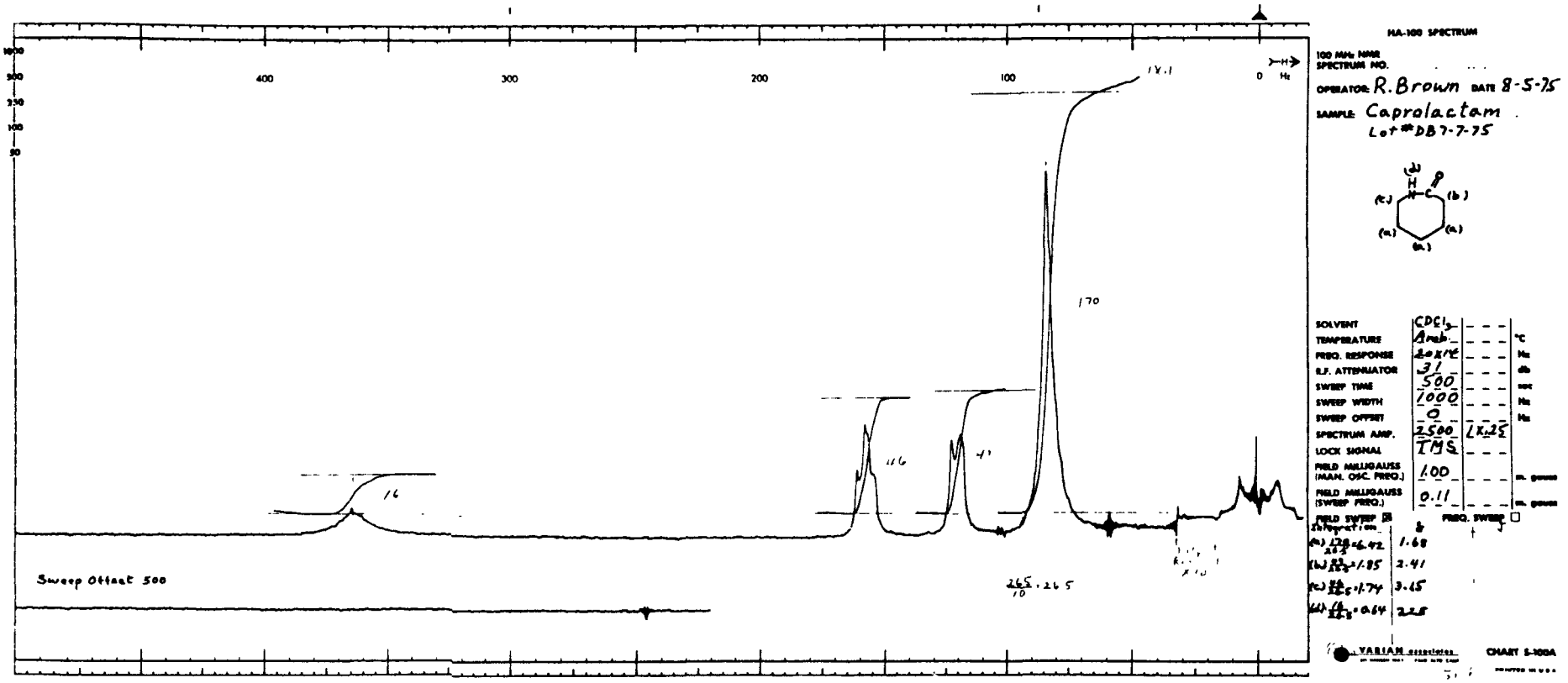

Figure 6. Nuclear Magnetic Resonance Spectrum of Caprolactam (Lot No. DB7-7-75)

Appendix F

Analysis of Caprolactam

(Lot No. DB 6-23-78)

APPENDIX F

Analysis of Caprolactam (Lot No. DB 6-23-78)

A. ELEMENTAL ANALYSIS

Element	C	H	N
Theory	63.68	9.80	12.39
Determined	63.47	10.43	12.23
	63.59	10.05	12.30

B. THIN-LAYER CHROMATOGRAPHY

Plates: Silica Gel 60 F-254
Amount Spotted: 100 and 300 μg (10 μg/μl in chloroform)
Ref. Standard: Acetanilide, 10 μg (10 μg/μl in chloroform)
Visualization: Ultraviolet, 254 nm; iodine vapor

1. System 1: Ethanol (100%)

R_f: 0.64 (major)
R_{st}: 0.82

2. System 2: Ethyl acetate (100%)

R_f: 0.15 major
R_{st}: 0.22

C. VAPOR PHASE CHROMATOGRAPHY

Instrument: Varian 3740
Detector: Flame ionization
Inlet Temperature: 200°C
Detector Temperature: 250°C
Carrier Gas: Nitrogen
Carrier Flow Rate: 70 cc/min

1. System 1

Column: 20% SP 2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m x 4 mm ID, glass
Oven Temperature Program: 100°C, 5 min; 100 to 170°C at 10°C/min

Sample Injected: Solution (5 μl) of 1% caprolactam in dichloromethane and 0.5% to check for overloading
Results: Single homogeneous peak with a retention time of 12.5 min

2. System 2

Column: 10% Carbowax 20M-TPA on 80/100 Chromosorb W(AW), 1.8 m x 4 mm ID, glass
Oven Temperature Program: 100°C, 5 min; 100 to 200°C at 10°C/min

Sample Injected: Solution (5 μl) of 1% caprolactam in dichloromethane and 0.5% to check for overloading
Results: Single homogeneous peak with a retention time of 18.1 min

D. SPECTRAL DATA

1. Infrared

Instrument: Beckman IR-12
Cell: 1% KBr pellet
Results: See Figure 7

Consistent with literature spectrum (Sadtler Standard Spectra)

2. Ultraviolet/Visible

Instrument: Cary 118

No absorbance between 350 and 800 nm (visible region). No maximum between 220 and 350 nm (ultraviolet region) but increase in absorbance toward the solvent cutoff.

Concentration: 0.1%
Solvent: 95% ethanol

No literature reference found; spectrum consistent with the the structure.

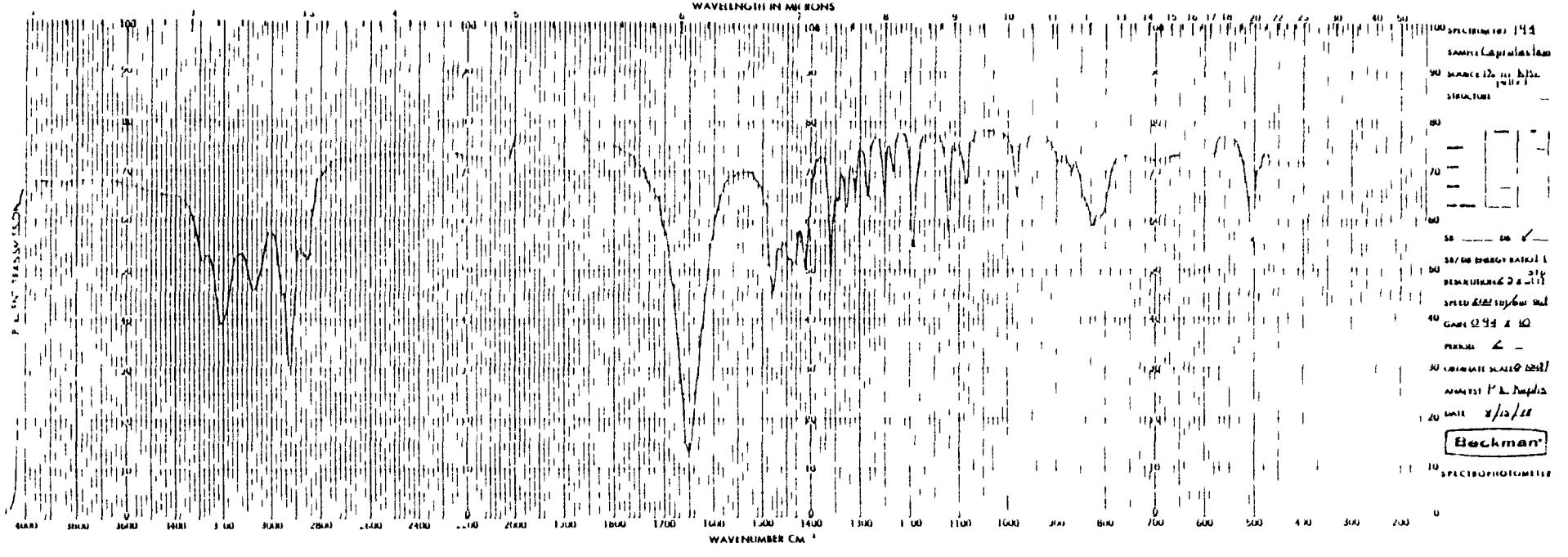

Figure 7. Infrared Absorption Spectrum of Caprolactam (Lot No. DB6-23-78)

(3) Nuclear Magnetic Resonance

Instrument: EM-360A
Solvent: Deuterated chloroform with internal tetramethylsilane

Consistent with literature spectrum (Sadtler Standard Spectra)

Assignments: (see Figure 8)

(a) δ 1.72 ppm
(b) δ 2.44 ppm
(c) δ 3.20 ppm
(d) δ 8.05 ppm
(e) δ 3.56 ppm

Integration Ratios:

(a) 6.10
(b) 2.03
(c) 1.87
(d) 0.89
(e) $<$ 0.05 (impurity)

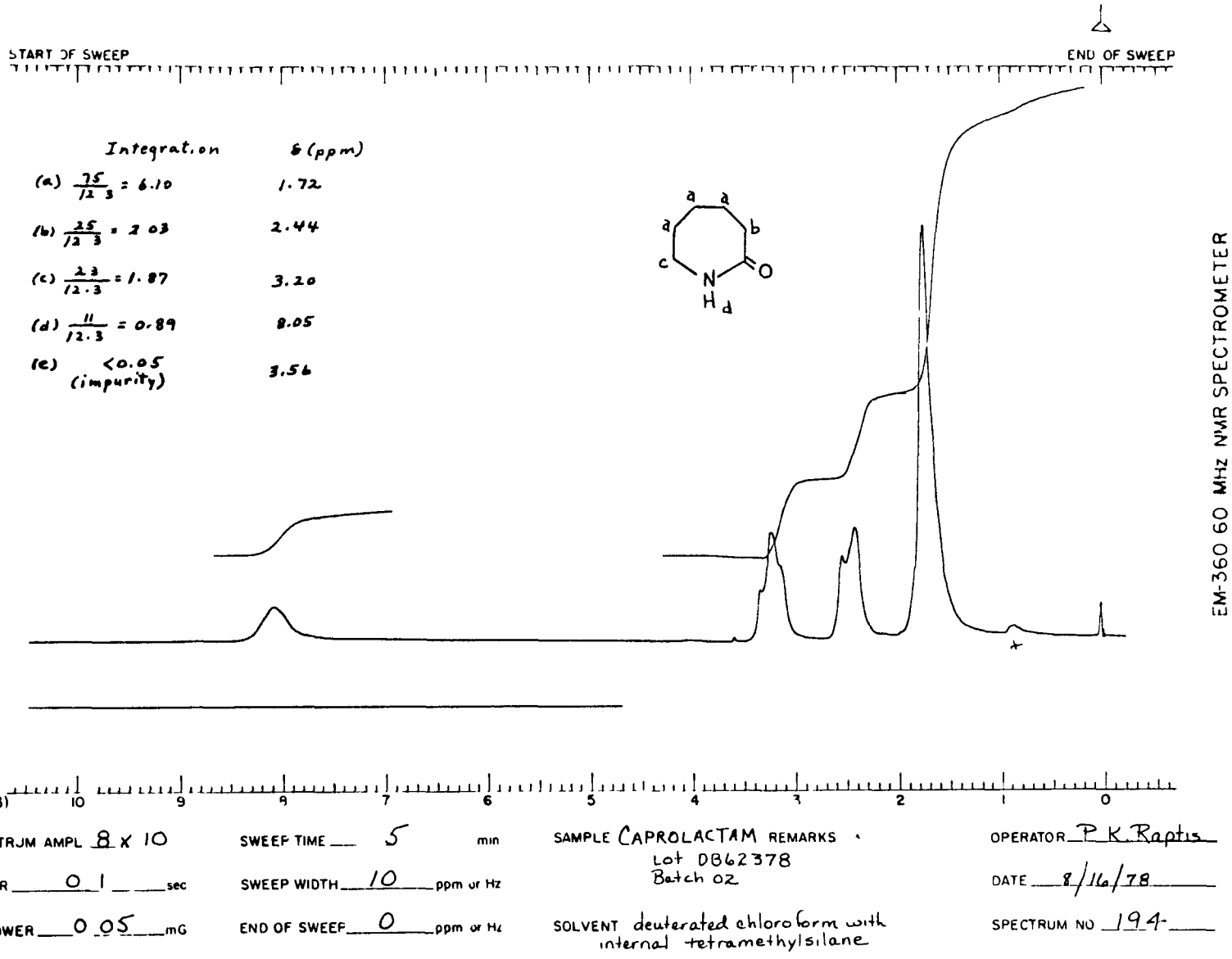

Figure 8. Nuclear Magnetic Resonance Spectrum (Lot No. DB6-23-78)

Appendix G

Stability Analysis of Caprolactam

in Formulated Diets

Midwest Research Institute

Appendix G

Stability Analysis of Caprolactam in Formulated Diets
Midwest Research Institute

1. Mixing and Storage: Caprolactam (2.4730 g) and Wayne Lab-Blox® Rodent Feed (22.5614 g) were mixed in a mortar. Samples of the mixture were stored for 2 weeks at -20°C, 5°C, 25°C, or 45°C, and then analyzed by the vapor-phase chromatographic method outlined below.

2. Extraction and Analysis: Two-gram samples of the mixtures were mixed with 50 ml of methanol in an ultrasonic vibratory bath for 30 seconds and then triturated for 1 minute using a Polytron high-speed blender. The mixture was centrifuged and the supernatant solution was decanted into a 100-ml volumetric flask. This extraction procedure was repeated on the feed residue. The methanolic supernatants were combined, and the total was made up to volume with additional methanol. This constituted the test solution used for the vapor-phase chromatography.

Instrument: Tracor MT-220

Column: 1.5% OV-210 + 1.5% OV-225 on gas Chrom Q, 80/100 mesh, 1.8 m x 4 mm I.D., glass

Detection: Flame ionization

Temperatures: Inlet - 245°C
Oven - 170°C isothermal
Detector - 275°C

Retention time of compound: 2.2 minutes

3. Results:

Sample (°C)	Average % Compound Recovered (a)
-20	10.0±0.1
5	10.0±0.1
25	9.9±0.1
45	9.9±0.1

(a)Spiked recovery yield was 99.6±0.5%. Theoretical recovery yield was 9.9%.

4. Conclusion: Caprolactam mixed with feed is stable for 2 weeks at temperatures of up to 45°C.

Appendix H

Analyses of Formulated Diets for Concentrations of Caprolactam

Appendix H

Analyses of Formulated Diets for Concentrations of Caprolactam

Method

A two-gram subsample was extracted with 50 ml of methanol by shaking for 10 minutes in an automatic shaker. The extract was clarified by centrifugation for 10 minutes at 1,350 rpm and decanted into a glass bottle. A second extraction was performed with 50 ml of methanol in the same manner. The two extracts were combined and mixed well. An aliquot of the extract was diluted with a solution containing dibenzofuran as an internal standard. Standards were prepared using control feed and treated in the same manner. Samples were analyzed in duplicate by gas-liquid chromatography under the following conditions:

Instruments: Hewlett-Packard 5840A with 7672 Auto Liquid Sampler.

Detector:	Flame ionization
Column temperature:	185°C
Inlet temperature:	250°C
Detector Temperature:	250°C
Carrier gas:	Nitrogen
Carrier flow rate:	20ml/min
Column:	10% FFAP on 80/100 Supelcoport, 1.8m x2mm ID, glass, silanized.

Theoretical Dietary Level(ppm)	No. of Samples	Sample Analytical mean (ppm)	Coefficient of Variation (%)	Range (ppm)
3,750	7	3,450.3	9.7	2,957 - 3,950
7,500	13	6,734.0	17.4	4,801 - 8,041
15,000	19	14,651.2	7.1	11,575 - 15,901

Because of the gradual decrease in percent recovery of caprolactam from feed upon storage (see Appendix I), only those samples that were analyzed within 1 week if held at room temperature or 2 weeks if held at -20°C were considered valid.

Appendix I

Stability Study of Caprolactam
in Feed

Litton Bionetics, Inc.

Appendix I

Stability Study of Caprolactam in Feed (Litton Bionetics, Inc.)

Method: See Appendix H.

Days After Mixing (a)	Concentration Found (b)	Percent of Theoretical (b)
1	14,972	99.8
4	13,899	92.6
7	13,353	89.0
14	12,384	82.6

(a) Stored at ambient temperature (Day 1 at -20°C)
(b) Theoretical: 15,000 ppm

Days After Mixing (a)	Concentration Found (b)	Percent of Theoretical(b)
1	14,972	99.8
4	14,627	97.5
7	14,752	98.3
14	14,361	95.7

(a) Stored at -20°C.
(b) Theoretical: 15,000 ppm

Appendix J

Daily Feed Consumption (Grams) Per Animal In Rats And Mice Fed Diets Containing Caprolactam In The Chronic Study

Appendix J

Daily Feed Consumption (Grams) Per Animal In Rats and Mice Fed Diets Containing Caprolactam in the Chronic Study (a)

Species	Week (b)	Males			Females		
		Control	Low Dose	High Dose	Control	Low Dose	High Dose
Rat	4	23	23	20	16	15	14
"	16	25	22	21	16	15	12
"	40	32	26	26	18	15	15
"	64	25	24	24	20	16	15
"	80	33	31	29	23	21	18
"	100	35	30	23	27	25	18
Mouse	4	5	4	4	4	4	4
"	16	8	6	6	7	6	5
"	40	4	3	4	4	4	5
"	64	6	6	6	7	7	7
"	80	5	4	5	5	5	6
"	100	4	4	5	6	5	6

(a) Estimated from weekly group feeder weighings

$$\text{Daily feed consumption per animal} = \frac{\text{Total feed consumption}}{\text{No. of days X No. of animals}}$$

(b) Representative weeks were selected.

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