NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 207

CARCINOGENESIS BIOASSAY OF CYTEMBENA

(CAS NO. 21739-91-3)

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

NTP Technical Report

on the

CARCINOGENESIS BIOASSAY

of

CYTEMBENA

(CAS No. 21739-91-3)

National Cancer Institute
NATIONAL TOXICOLOGY PROGRAM
P. O. Box 12233
Research Triangle Park
North Carolina 27709
and
Bethesda, Maryland 20205

NTP-80-27
NIH Publication No. 81-1763

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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CARCINOGENESIS BIOASSAY OF
CYTEMBENA
(CAS NO. 21739-91-3)

FOREWORD

This report presents the results of the bioassay of cytembena conducted January 1977-January 1979 for the Carcinogenesis Testing Program, National Cancer Institute (NCI)/ National Toxicology Program (NTP). 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 the test chemical is not a carcinogen inasmuch as the experiments are conducted under a limited set of conditions. A positive result demonstrates that the 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 purview of this study.

CONTRIBUTORS

This bioassay of cytembena was conducted by Southern Research Institute, Birmingham, Alabama, under a subcontract to Tracor Jitco, Inc., Rockville, Maryland, prime contractor for the NCI Carcinogenesis Testing Program. The persons responsible for selecting the protocols used in this bioassay were Drs. J. F. Robens (1,2) and C. Cueto (3,4). The principal investigator was Dr. J. D. Prejean (5). Ms. C. Prejean (5) and Ms. H. Prince (5) were responsible for data management, and Ms. J. Belzer (5) was the supervisor of animal care. Histopathologic examinations were performed by Drs. R. B. Thompson, H. D. Giles, and J. C. Peckham (5). 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 (6). Statistical analyses were performed by Dr. J. R. Joiner (1) and Ms. S. Vatsan (1), using methods selected for the bioassay program by Dr. J. J. Gart (7).

Chemicals used in this bioassay were analyzed at Midwest Research Institute (8) and Southern Research Institute (5), and dose solutions containing the test chemical were analyzed at Southern Research Institute by Ms. R. James (5). The results of these analyses were reviewed by Dr. S. S. Olin (1).

This report was prepared at Tracor Jitco in collaboration with Southern Research Institute and NCI. Those responsible for the report at Tracor Jitco (1) were Dr. L. A. Campbell, Acting Director of the Bioassay Program; Dr. S. S. Olin, Associate Director; Dr. R. L. Schueler, 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 (3) were responsible for evaluating the bioassay, interpreting the results, and reporting the findings: Dr. J. Fielding Douglas, Dr. Richard A. Griesemer. Dr. Charles K. Grieshaber (chemical manager), Dr. Larry Hart, Dr. William V. Hartwell, Dr. Joseph Haseman, Dr. James E. Huff, Dr. C. W. Jameson, Dr. Ernest E. McConnell, Dr. John A. Moore, Dr. Raymond Tennant, and Dr. Jerrold M. Ward.

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. Breslow, as the primary reviewer for the report on the bioassay of cytembena, agreed with the conclusion of the report that cytembena was carcinogenic to the F344 rat, producing mesotheliomas in males and fibroadenomas in the mammary gland of females. Cytembena was not demonstrated to be carcinogenic in the B6C3F1 mouse. However, he noted that early mortality may have compromised the sensitivity of the assay in male mice for detection of late occurring tumors. Problems of interpretation of the results from this study are caused by early mortality observed in both male rats and male mice. Since no adjustment of cumulative incidence data for intercurrent mortality was reported, the stated incidence figures probably represent underestimates. Moreover, in rats the mortality was clearly dose related, and not taking into account time of tumor occurrence may have obscured associations between dose and cancer occurring at other sites.

As the secondary reviewer, Dr. Shepard agreed with Dr. Breslow's critique.

Dr. Breslow moved that the report on the bioassay of Cytembena be accepted contingent on the inclusion of statistical analyses of tumor incidences which account for differential mortality. (This has been done by the inclusion of life table analyses in this report.) The motion was seconded by Dr. Whittemore and approved unanimously.

(1) Tracor Jitco, Inc., 1776 East Jefferson Street, Rockville, Maryland 20852.
(2) Now with Bureau of Veterinary Medicine, Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland 20851.
(3) Carcinogenesis Testing Program, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20205; National Toxicology Program, Research Triangle Park, Box 12233, North Carolina 27709.
(4) Now with Tracor Jitco, Inc., 1776 East Jefferson St., Rockville Maryland 20852.
(5) Southern Research Institute, 2000 Ninth Avenue South, Birmingham, Alabama 35205.
(6) EG&G Mason Research Institute, 1530 East Jefferson Street, Rockville, Maryland 20852.
(7) Mathematical Statistics and Applied Mathematics Section, Biometry Branch, Field Studies and Statistics, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20205.
(8) Midwest Research Institute, 425 Volker Boulevard, Kansas City, Missouri 64110.

SUMMARY

A carcinogenesis bioassay of cytembena, a cytostatic agent, was conducted by injecting intraperitoneally 7 or 14 mg/kg into groups of 50 male and 50 female F344 rats and 12 or 24 mg/kg into groups of 50 male or 50 female B6C3F1 mice three times per week for 104 weeks. Groups of 50 rats and 50 mice of both sexes served as vehicle and untreated controls.

Mean body weights of dosed and vehicle-control rats were comparable throughout the bioassay. Mean body weights of dosed and vehicle-control mice were comparable for the first 73 weeks of the bioassay; mean body weight of the high-dose male mice was slightly lower than that of the vehicle controls after 73 weeks, and that of the high-dose female mice was lower after week 87.

In dosed male rats, mesotheliomas in the tunica vaginalis and malignant mesotheliomas in multiple organs occurred with dose-related trends and at incidences in each of the dosed groups which were significantly higher than those in the vehicle control rats.

In dosed female rats, fibroadenomas in the mammary gland occurred with a dose-related trend and at a significantly higher incidence in the high-dose group than in the vehicle control rats.

Under the conditions of this bioassay, cytembena was carcinogenic for male and female F344 rats, causing increased incidences of mesotheliomas in the tunica vaginalis and in multiple organs of males and fibroadenomas in the mammary gland of females. Cytembena was not carcinogenic for male or female B6C3F1 mice.

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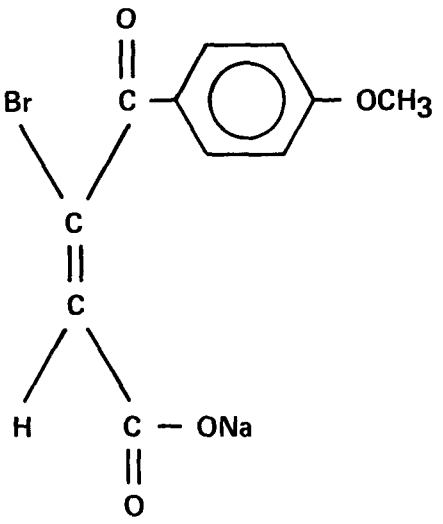

$C_{11}H_8BrO_4Na$
Mol. Wt. = 307

CYTEMBENA

Cytembena (CAS No. 21739-91-3) -- NSC 104801; cytembene; 2-butenoic acid, 3-bromo-4-(4-methoxyphenyl)-4-oxo-, sodium salt, (E) -- is a cytostatic agent that showed promising results in the remission of ovarian, uterine, and breast tumors in initial clinical studies in Czechoslovakia (Dvorak et al., 1965; Dvorak et al., 1971; Dvorak and Bauer, 1971; and Matejovsky, 1971). After the present bioassay was in progress, clinical trials of cytembena were discontinued by the NCI, Division of Cancer Treatment, because no apparant antineoplastic effects were demonstrated in the tests conducted in the United States (Edmonson et al., 1977; Baker et al., 1976; Falkson and Falkson, 1976; and DCT Newsletter, 1977).

The following LD_{50} values were reported (Jelinek et al., 1969) for H-Rosice mice and W-Rosice rats:

SPECIES	ROUTE	LD_{50} (mg/kg)
Mouse	Subcutaneous	52
"	Intraperitoneal	50
"	Intravenous	98
Rat	Subcutaneous	155
"	Intraperitoneal	155
"	Intravenous	245

Cytembena is nephrotoxic in rats, mice, and rhesus monkeys. Urinary protein and glucose excretion, increased urine volumes, and decreased urine osmolalities were found in male and female Sprague-Dawley rats given a single intraperitoneal dose of 50 mg/kg cytembena (Berndt, 1977). Cellular necrosis and desquamation of the distal tubular epithelium were found in rhesus monkeys injected intraveneously with 25 mg/kg cytembena per day for 5 days (Gralla et al., 1975). Renal mitochondrial swelling and disruption were observed in male Swiss-Webster mice 24 hours after a single intravenous injection of 100 mg/kg cytembena (Gralla et al., 1975).

Administration of 50 mg/kg ^{14}C-labelled cytembena to Sprague-Dawley rats by gavage or by the subcutaneous or dermal routes resulted in the highest concentration of radioactivity localized in the kidney after 24 hours (Mitoma et al., 1977). Over 70% of the cytembena administered to rats was excreted in 24 hours, whereas in humans only 8% of the dose was excreted in 15 hours (Grafnetterova et al., 1971).

The inhibitory effect of cytembena on the in vitro growth of three mammalian cell lines (L-1210, Wl-L2, and Yoshida) has been attributed to the inhibitory effect of cytembena on DNA biosynthesis (Jackson et al., 1975). Cytembena is a direct inhibitor of the final stage of replicative DNA synthesis in permeable L-cells (Berger and Weber, 1977). Low, dose-dependent increases in abnormal metaphases and chromosomal breaks were found in the bone marrow cells taken from Wistar rats, ICR Swiss mice, and cancer patients that had been administered cytembena. The frequency of abnormal metaphases and chromosomal breaks was two to three times higher in the rodents than in humans after intraperitoneal injections of 20 mg/kg cytembena (Goetz, 1976). Cytembena was found to be weakly positive in a dominant-lethal assay in S strain mice (Sykora and Gandalovicova, 1978).

Cytembena was tested by the Carcinogenesis Testing Program because of its potential use as an antineoplastic agent in humans.

II. MATERIALS AND METHODS

A. Chemical

The cytembena (CAS 21739-91-3) used in this bioassay was manufactured by Aldrich Chemical Company (Milwaukee, WI) and supplied by the Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland. The compound was obtained in two batches -- Lot No. KL-110127 was used in the subchronic studies, and Lot No. MF-II-250 was used in the chronic studies. Identity and purity analyses, performed by Midwest Research Institute and Southern Research Institute, are presented in Appendixes E and F. Results of the elemental analysis of Lot No. MF-II-250 were consistent with the theoretical composition, and the ultraviolet spectrum was comparable with that reported previously (Stanford Research Institute Report, 1972 and 1975). The infrared and ultraviolet spectra of the two batches were consistent with each other. Results of titration of the carboxylate anion with 0.1N HCl indicated a purity of 99.4%±1.0 (δ)% for Lot No. KL-110127.

B. Dose Preparation and Administration

For the subchronic study and each month during the first 18 months of the chronic study, the amount of cytembena needed for each dose level for the entire month was weighed and placed in labeled 2-ml plastic beakers with snap-on lids. The beakers were then placed in plastic bags which were sealed and stored at 5°C until needed. The saline vehicle (9,000 ppm NaCl in water, Travenol Laboratory, Inc., Deerfield, IL) was measured monthly into labeled injection bottles and stored at 5°C. For the final 7 months of the chronic study, the desired amounts of compound and vehicle were measured just before mixing, eliminating the storage period.

On each injection day, the appropriate amounts of the vehicle and compound were hand homogenized using a Potter-Elvenjem tissue grinder with a Teflon® pestle, poured into an injection bottle, and capped. The method of sample homogenization was modified during the sixth month of the chronic study because the analytical concentration varied by ±40% from the desired concentrations during weeks 18-21. During the next 5 months, samples were

sonicated for 10 minutes; subsequently, hand homogenization using warm saline was found to be the best method of mixing the compound and vehicle. The compound-vehicle solutions were administered by intraperitoneal injection using disposable 1- or 3-ml syringes and 23 gauge 1/4-inch needles. A new needle and syringe were used for each injection.

Each month, dosage mixtures were analyzed at Southern Research Institute using ultraviolet absorption spectroscopy as described in Appendix G. From week 22 to week 104, the mean concentration of 11 samples containing a theoretical level of 5,600 ppm was 5,520±200 ppm and represented the 14 mg/kg dose administered to rats. The mean concentration of 12 samples containing a theoretical level of 2,400 ppm was 2,350±120 ppm, which represented the 24 mg/kg administration to mice.

C. Animals

Four-week old F344 rats and 4- to 5-week-old B6C3F1 mice were obtained from the NCI Frederick Cancer Research Center, Frederick, Maryland. The rats and mice were acclimated for 10 days and assigned to test groups according to a table of random numbers.

D. Animal Maintenance

Groups of five rats or mice were housed in suspended, solid bottom, polycarbonate cages (Lab Products, Garfield, NJ) covered with Reemay spun-bonded polyester disposable filters (DuPont style #2024; Snow Filtration; Cincinnati, Ohio). All animals were housed in the same room, and the room was not used for animals on test for other chemicals. Beta® Chips bedding (Northeastern Products Corporation, Warrensburg, NY) was used for days 1-328, 420-465, and 651-714, and from day 726 until the end of the studies. Sawdust (P.W.I. Inc, Lowville, NY) was used for days 329-419, 466-650, and 715-725. Cages and bedding were changed twice per week, feed hoppers once per week, and racks, cage filters, and room air filters once every 2 weeks. Wayne® Lab-Blox (Allied Mills, Inc., Chicago, IL) in metal

feeders (Lab Products, Inc.) and tap water through an Edstrom automatic watering system (Edstrom Industries, Inc., Waterford, Wis.) were supplied ad libitum.

The animal room was maintained at 21°-23°C and relative humidity was 30%-50%. Incoming air was filtered through fiberglass roughing filters (Airguard Industries, Inc., Louisville, KY) and changed 15 times per hour. Fluorescent lighting was provided 12 hours per day.

E. Subchronic Studies

In subchronic studies, groups of 10 male and 10 female rats were administered cytembena by intraperitoneal injection at doses of 0, 1.8, 3.6, 7.2, 14, or 29 mg/kg in saline three times per week for 90 days. Each rat received 2.5 ml/kg body weight. Groups of 10 male and 10 female mice were administered cytembena by intraperitoneal injection at doses of 0, 3.0, 6.0, 12, 24, or 48 mg/kg in saline three times per week for 90 days. Each mouse received 10.0 ml/kg body weight. After 90 days, the rats and mice were killed and necropsied. A complete histopathologic examination was performed on the tissues of animals administered the highest dose and on the control animals. Doses, survival, and mean body weights of rats and mice are shown in Tables 1 and 2.

Rats: No deaths occurred. Male and female rats receiving 14 mg/kg had depressions in weight gain of 12% and 13%, respectively, relative to the controls, and depression in weight gain at all other doses, including the highest dose of 29 mg/kg body weight, was less than 10%. In rats injected with 29 mg/kg, subchronic peritonitis was found in 1/10 males, moderate to severe lymphoid depletion from the mesenteric lymph nodes was detected in 2/10 males and 5/10 females, and mild centrolobular hepatic degeneration was found in 5/10 males. No compound-related lesions were found in rats injected with 14 mg/kg or less. Doses of 14 and 7 mg/kg cytembena were selected for rats in the chronic studies due to concern about possible cumulative effects at higher doses.

Mice: Deaths occurred in 1/10 males and 1/10 females injected with 6.0 mg/kg, in 1/10 males injected with 3.0 mg/kg, and in 1/10 male and 1/10

Table 1. Doses, Survival, and Mean Body Weights of Rats Administered Cytembena in Saline by Intraperitoneal Injection for 90 days

Dose (a) (mg/kg)	Survival (b)	Mean Body Weights (grams) Initial	Final	Gain	Weight Change Relative to Controls(%) (c)
Rats - Male					
0(d)	10/10	68	307	239	
1.8	10/10	69	294	225	-5.8
3.6	10/10	78	315	237	-0.8
7.2	10/10	66	305	239	0
14.0	10/10	64	275	211	-11.7
29.0	10/10	80	315	235	-1.7
Rats - Female					
0(d)	10/10	60	181	121	
1.8	10/10	61	183	122	+0.8
3.6	10/10	65	186	121	0
7.2	10/10	71	186	115	-5.0
14.0	10/10	72	177	105	-13.0
29.0	10/10	66	183	117	-3.3

(a) Doses were administered in saline at 2.5 ml/kg body weight, 3 times per week.
(b) Number surviving/number per group.
(c) Weight change relative to controls =

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

(d) Vehicle controls received saline alone.

Table 2. Doses, Survival, and Mean Body Weights of Mice Administered Cytembena in Saline by Intraperitoneal Injection for 90 days

Dose (a) (mg/kg)	Survival (b)	Mean Body Weights (grams) Initial	Final	Gain	Weight Change Relative to Controls(%) (c)
Mice - Male					
0(d)	9/10	19	34	15	
3.0	9/10	19	34	15	0
6.0	9/10	18	34	16	+6.7
12.0	10/10	20	36	16	+6.7
24.0	10/10	19	33	14	-6.7
48.0	10/10	19	34	15	0
Mice - Female					
0(d)	9/10	15	27	12	
3.0	10/10	15	28	13	+8.3
6.0	9/10	14	26	12	0
12.0	10/10	17	27	10	-16.7
24.0	10/10	15	27	12	0
48.0	10/10	15	27	12	0

(a) Doses were administered in saline at 10.0 ml/kg body weight, 3 times per week.
(b) Number surviving/number per group.
(c) Weight change relative to controls =

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

(d) Vehicle controls received saline alone.

female vehicle controls. Weight gains of all dosed mice were comparable with those of the corresponding vehicle controls except for the females dosed with 12 mg/kg. Among the mice injected with 48 mg/kg, mild subchronic fibrinous peritonitis was found in 7/10 males and 7/10 females, splenic capsular fibrosis in 2/10 females, and moderate to severe lymphoid atrophy in 2/8 males. No compound-related lesions were observed among the mice receiving 24 mg/kg or less. Because fibrinous peritonitis could develop at higher doses, doses of 24 and 12 mg/kg were selected for mice in the chronic studies.

F. Chronic Studies

The test groups, doses administered, and durations of the chronic studies are shown in Table 3.

G. Clinical Examinations and Pathology

Animals were observed twice daily and observations of sick, tumor-bearing, and moribund animals were recorded. Animals were weighed at 4-week intervals. Moribund animals and those that survived to the end of the bioassay were killed using carbon dioxide and necropsied.

Gross and microscopic examinations were performed on major tissues, major organs, and all gross lesions from killed animals and from animals found dead. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Sections from the following tissues were examined microscopically: brain, pituitary, thymus, spleen, thyroid, parathyroid, lung, trachea, heart, esophagus, stomach (pylorus and fundus), duodenum, jejunum, ileum, large intestine, pancreas, adrenal, kidney, liver, skin, mammary gland, entire gonads, urinary bladder, prostate or uterus, seminal vesicles, and femur with marrow. The external ears, eyes, harderian glands, preputial gland, lymph nodes (mandibular, mesenteric, cervical, and axillary), diaphragm, abdominal wall, trigeminal ganglion, rectum, vagina, vertebrae, and gall bladder (mice only) were taken periodically but not on a routine basis. Special staining techniques were utilized as necessary.

Table 3. Experimental Design of Chronic Intraperitoneal Injection Studies with Cytembena in Rats and Mice

Sex, Species and Test Group	Initial No. of Animals	Dose (a) (mg/kg)	Time on Study	
			Dosed (weeks)	Observed (weeks)
Male Rats				
Untreated Control	50	0	0	104-105
Vehicle Control (b)	50	0	0	104-105
Low-Dose	50	7	104	0-1
High-Dose	50	14	104	0-1
Female Rats				
Untreated Control	50	0	0	104-105
Vehicle Control (b)	50	0	0	104-105
Low-Dose	50	7	104	0-1
High-Dose	50	14	104	0-1
Male Mice				
Untreated Control	50	0	0	104-105
Vehicle Control (b)	50	0	0	104-105
Low-Dose	50	12	104	0-1
High-Dose	50	24	104	0-1
Female Mice				
Untreated Control	50	0	0	104-105
Vehicle Control (b)	50	0	0	104-105
Low-Dose	50	12	104	0-1
High-Dose	50	24	104	0-1

(a) Doses were administered in saline at 2.5 ml/kg body weight, 3 times per week for rats. Mice received 10.0 ml/kg body weight, 3 times per week.
(b) The vehicle was saline (9,000 ppm NaCl in water).

Necropsies were performed on all animals found dead, unless precluded in whole or in part by autolysis or cannibalization. Thus, the number of animals for 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.

H. Data Recording and Statistical Analyses

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 are reported for all tests except for 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 for two dosed groups are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 is made. The Bonferroni test for inequality (Miller, 1966) requires that the P value for any comparison be less than or equal to 0.025. When this correction was used, it is discussed in the narrative section. 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. Under the assumption of a linear trend, 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 dose relationship. This method also provides a two-tailed test of departure from linear trend.

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).

A time-adjusted analysis was applied when numerous early deaths resulted from causes 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 tests, etc.) were followed.

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). 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)

Mean body weights of dosed and vehicle-control rats were comparable throughout the bioassay (Figure 1). Dose-related clinical signs included: abdominal distension in 14/50 high-dose males compared with 0/50 low-dose males and 3/50 vehicle-controls; scrotal cyanosis in 16/50 high-dose males and 22/50 low-dose males, compared with 4/50 vehicle controls; and abdominal distension in 19/50 high-dose females compared with 1/50 in both low-dose and vehicle controls.

B. Survival (Rats)

Estimates of the probabilities of survival for male and female rats administered cytembena by intraperitoneal injection at the doses of this bioassay, and those of the controls, are shown by the Kaplan and Meier curves in Figure 2. The Tarone test for a positive dose-related trend in mortality is significant ($P<0.001$) in the males due to shortened survival in the dosed groups. The survival in all four groups of female rats is comparable.

In male rats, 35/50 (70%) of the untreated-control group, 29/50 (58%) of the vehicle-control group, and 12/50 (24%) of each of the dosed groups lived to the end of the study at 104-105 weeks. In females, 34/50 (68%) of the untreated-control group, 30/50 (60%) of the vehicle-control group, 33/50 (66%) of the low-dose group, and 28/50 (56%) of the high-dose group lived to the end of the study at 104-105 weeks.

A sufficient number of female rats were at risk for the development of late-appearing tumors, but some late tumor development may have been reduced in the dosed male groups due to shortened survival time.

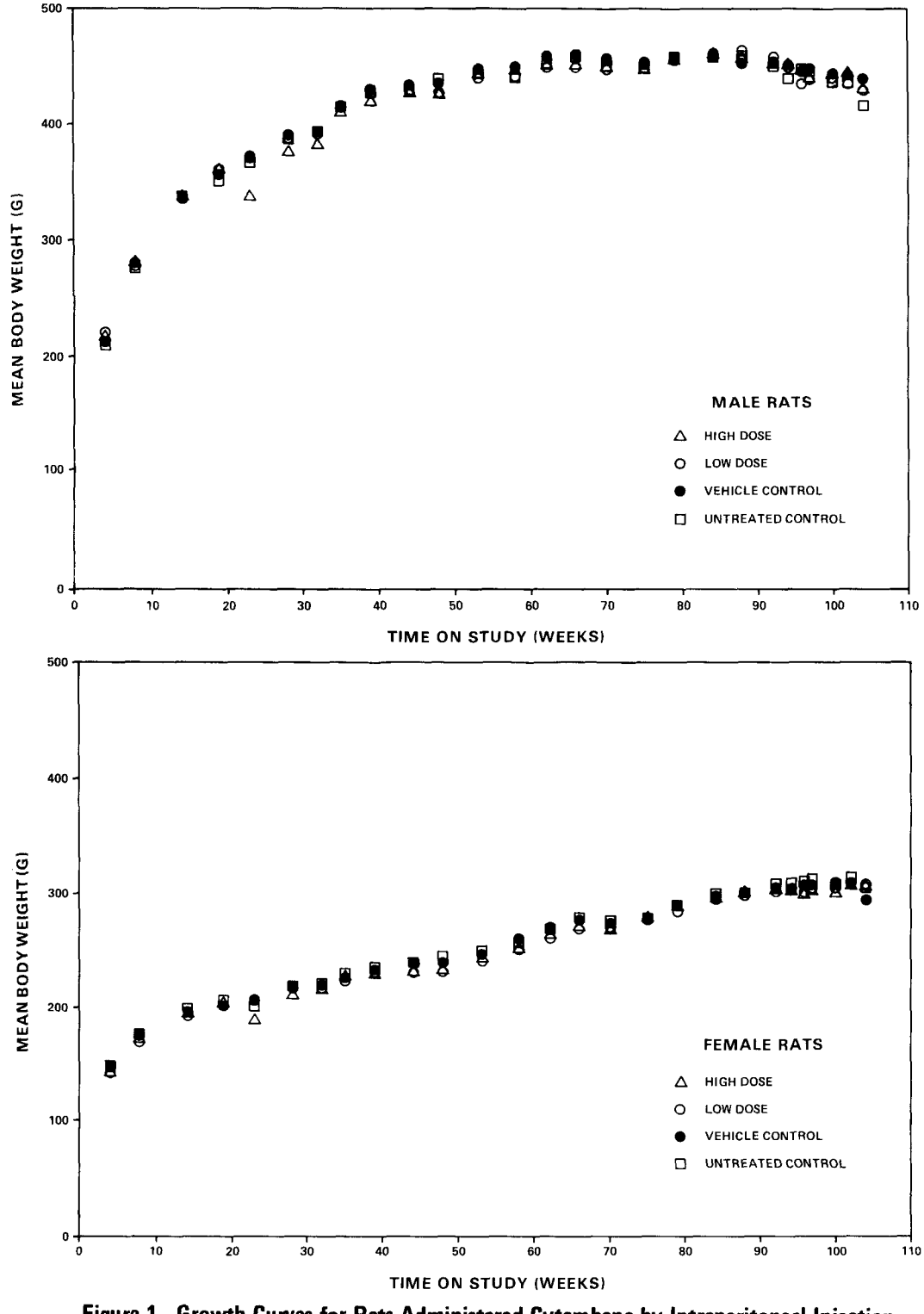

Figure 1. Growth Curves for Rats Administered Cytembena by Intraperitoneal Injection

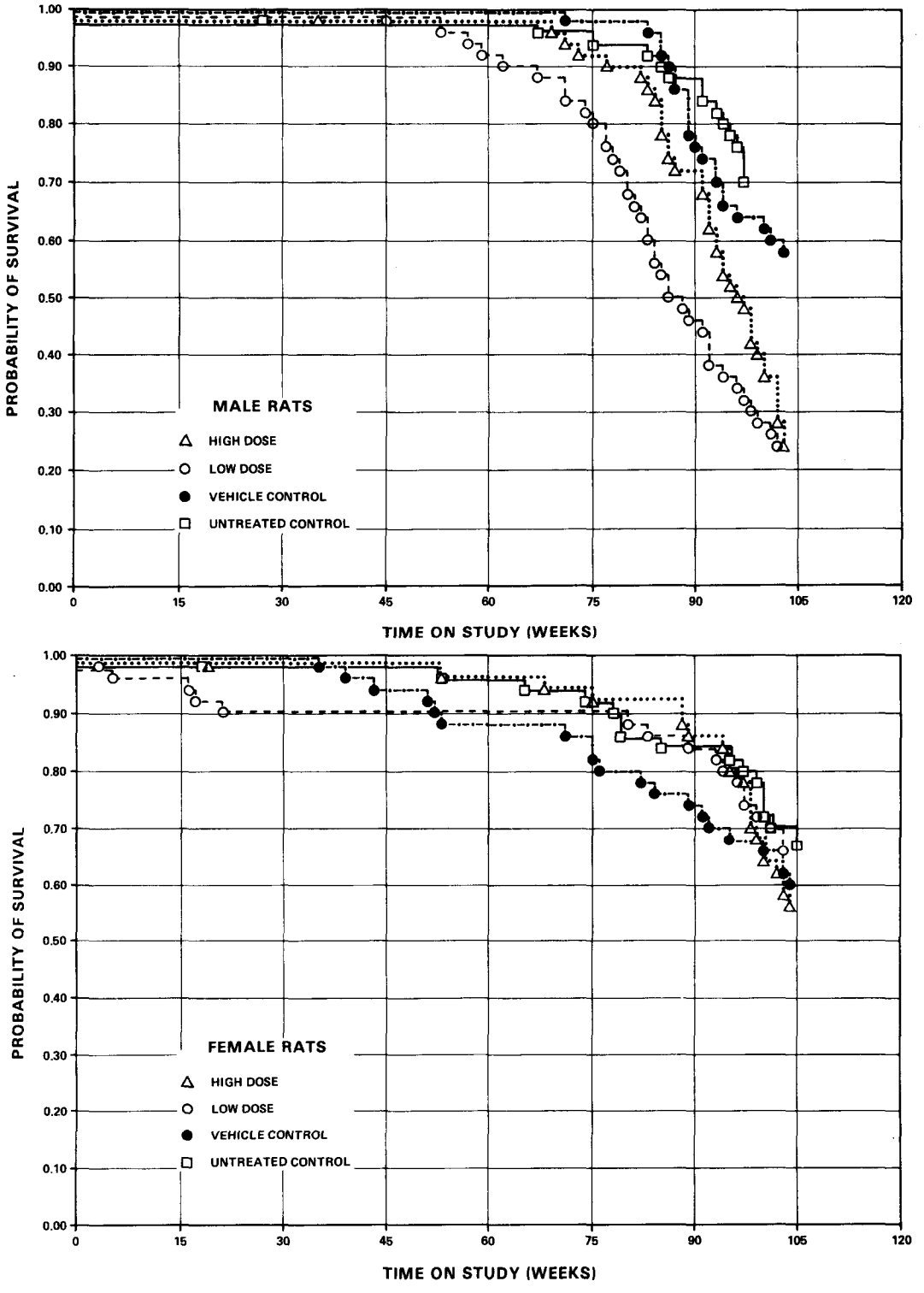

Figure 2. Survival Curves for Rats Administered Cytembena by Intraperitoneal Injection

C. Pathology (Rats)

Histopathologic findings on neoplasms in rats are tabulated in Appendix A, Tables A1 and A2; findings on nonneoplastic lesions are tabulated in Appendix C, Tables C1 and C2.

A variety of neoplasms were seen both in the control groups (untreated and vehicle controls administered buffered saline) and compound-treated groups. Other types of neoplasms occurred only, or with a greater frequency in rats of dosed groups as compared with controls; however, these lesions are not uncommon in this strain of rat.

Neoplastic, proliferative, and inflammatory lesions found in the abdominal cavity and mesothelium are listed in Table 4. An increased incidence of mesothelial tumors occurred in dosed male rats. The increased incidence of these tumors appeared to be related to chemical administration.

Malignant mesotheliomas involved the serosal surfaces of most of the abdominal organs including the spleen, pancreas, mesentery, urinary bladder, seminal vesicles, prostate, testicles (tunica vaginalis and epididymis), peritoneum, abdominal wall, and diaphragm. Grossly, abdominal distention was frequently observed. This distention resulted from accumulation of large quantities of dark brown peritoneal fluid. Most serous surfaces manifested a rough, granular appearance. The mesentery was usually thickened and nodular.

Histologically, most mesotheliomas were of the papillary type. There were numerous villous or papillary projections on the serous surface of affected organs. The stromal element of the villi consisted of connective tissue cells. The villi or projections were covered by prominent mesothelial cells. The cell nuclei had moderately dense stippled chromatin and were uniformly round to oval. Most nuclei had one or two small nucleoli. The cytoplasm was distinct and abundant. Mitotic figures were commonly seen. There was frequent invasion of the abdominal wall and diaphragm. Invasive cells were usually cuboidal or polygonal and sometimes formed pseudoglandular acini. These cells were usually more pleomorphic and were arranged in solid nests or cords.

Table 4. Neoplastic, Proliferative, and Inflammatory Lesions Found in the Abdominal Cavity and Mesothelium in Rats Following Administration of Cytembena

Tissue-Tumor	Dosage Groups (a)							
	Male				Female			
	U	V	L	H	U	V	L	H
No. of Animals Examined	50	50	50	50	49	49	50	50
Abdominal Cavity:								
Mesothelioma, Malignant (b)	0	3	26	26	0	0	0	2
Sarcoma, NOS (b)	0	0	1	0	1	0	0	1
Liposarcoma (b)	0	0	1	0	0	0	0	0
Tunica Vaginalis (Testis):								
Mesothelioma, NOS (b)	1	0	11	10				
Mesentery:								
Lipoma (b)	1	0	2	2				
Sarcoma, NOS (b)					0	0	0	1
Mineralization (b)					0	0	1	2
Hemorrhage (b)	1	0	0	0	0	0	0	1
Inflammation, Suppurative (b)	1	0	0	0	0	0	1	0
Inflammation, Acute/Chronic (b)	1	1	0	1	0	0	0	1
Inflammation, Chronic (Focal or Diffuse) (b)	3	4	4	8	5	8	14	17
Necrosis, Fat (b)	0	1	0	0	0	0	5	8
Metaplasia, Osseous (b)					0	0	0	2
Abscess, Chronic (b)					0	1	0	0

(a) U = untreated, V = vehicle control, L = low-dose, H = high-dose rats.
(b) Value represents number of animals affected.

The incidence of inflammatory lesions observed in the abdominal cavity appeared to be related to drug administration and was highest in female rats (14/50, low-dose group and 17/50, high-dose group).

In addition to the mesotheliomas in male rats, there was an increased number of proliferative and neoplastic lesions of the mammary glands in the dosed female F344 rats (Table 5).

A high incidence of atypical mammary gland fibroadenomas was observed in the female rats. These neoplasms were characterized by numerous cystic ducts with extensive periductular fibrosis and cystic glandular hyperplasia. Many of the ducts contained numerous intraductular papillary growths. Epithelial cells covering the papillary projections often showed piling up of cell nuclei. In some areas, there were dilated periductular acini. The epithelial cells lining these spaces stained deeply basophilic and frequently showed a loss of normal cellular orientation or polarity. Some mitotic activity was observed in these areas. The variable degrees of cellular atypia were suggestive of early malignant transformation or change. It was concluded that these lesions represented a variant of mammary fibroadenomas. The examining pathologist concluded that the lesions should be coded as fibroadenomas rather than adenocarcinomas. These lesions appeared to be compound and dosage related and were primarily observed in the high- and low-dose female rats. There was also an increase in the number of cystic ducts, cystic hyperplasia, epithelial hyperplasia, and lobular hyperplasia in the mammary tissue of dosed female F344 rats.

In addition to the neoplastic and nonneoplastic lesions noted previously, a number of degenerative, proliferative, and inflammatory changes were also encountered in the dosed and control groups (Appendix C). These nonneoplastic lesions are commonly seen in aged F344 rats.

The pathologists concluded that, under the conditions of this bioassay, cytembena was carcinogenic for F344 rats, inducing mesotheliomas in male rats and mammary neoplasms in females.

Table 5. Incidence of Proliferative and Neoplastic Lesions of the Mammary Glands in F344 Rats Following Administration of Cytembena

Tissue-Lesion	Dosage Groups (a)							
	Male				Female			
	U	V	L	H	U	V	L	H
No. of Animals Examined	50	50	50	50	49	49	50	50
Adenocarcinoma, NOS (b)	0	0	0	1	1	1	0	2
Fibroadenoma (b)	3	0	2	2	17	13	22	36
Cystic Ducts (b)	2	3	3	3	25	17	25	32
Cystic Hyperplasia (b)					8	5	14	18
Epithelial Hyperplasia (Glandular) (b)					0	0	1	0
Epithelial Hyperplasia (Ducts) (b)					0	0	3	1
Lobular Hyperplasia, NOS (b)	0	1	0	0	0	0	2	3

(a) U-untreated, V-vehicle control, L-low-dose, H-high-dose rats.
(b) Value represents number of animals affected.

D. Statistical Analyses of Results (Rats)

Tables 6 and 7 contain the statistical analysis of those primary tumors that occurred in at least two animals of one group and at an incidence of at least 5% in one or more than one group. Statistical tests have been used to compare each dosed group with the vehicle-control group, since the test conditions of the dosed groups are more comparable with those of the vehicle-control group than with the conditions found in the untreated-control group. The incidences of tumors in the untreated-control group are given in Appendix A and are comparable with those in the vehicle-control group.

There were dose-related trends in the incidences of male rats with mesotheliomas in the tunica vaginalis ($P=0.003$) and with malignant mesotheliomas in multiple organs ($P<0.001$). Both tumors appear in significantly higher incidences ($P<0.001$) in each of the dosed groups than in the control group. Figure 3 contains the Kaplan-Meier curves for the probability of survival without observation of mesotheliomas in the tunica vaginalis or in multiple organs in male rats. Lifetable analyses indicated a statistically significant ($P<0.001$) increased tumor incidence in the dosed groups when compared with the vehicle control. The curves include those animals in which tumors were observed at the termination of the study.

In female rats, a significant trend ($P<0.001$) relative to increased dose and a significantly higher incidence ($P<0.001$) of fibroadenomas in the mammary gland are present in the high-dose group when compared with controls. The analysis of data by lifetable methods indicated a significant ($P<0.001$) increase in fibroadenomas of the mammary gland in the high-dose female rats, and a significant ($P<0.001$) increasing trend in these tumors.

The results of the Cochran-Armitage test indicate significant positive dose-related trends in the incidences of either hepatocellular adenomas or neoplastic nodules in the liver ($P=0.027$) and of lipomas in the mesentery ($P=0.038$) of female rats. The Fisher exact tests are not significant in either instance.

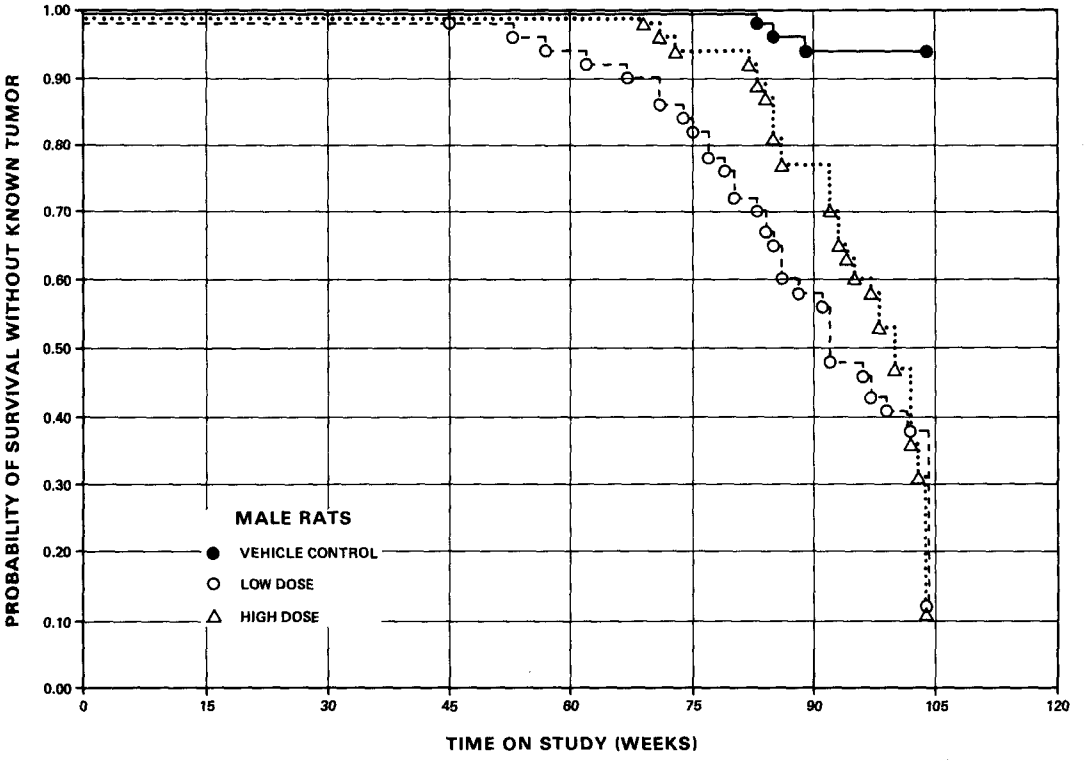

Figure 3. Probability of Survival Without Observed Mesotheliomas in Male Rats Administered Cytembena by Intraperitoneal Injection

In summary of the statistical analysis, there is a dose-related increase in the incidence of mesotheliomas in the tunica vaginalis and in multiple organs of male rats. The incidence of fibroadenomas in the mammary gland of females is also related to administration of cytembena.

Table 6. Analyses of the Incidence of Primary Tumors in Male Rats Administered Cytembena by Intraperitoneal Injection (a)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Subcutaneous Tissue: Fibroma or Fibrosarcoma (b)	3/50 (6)	0/50 (0)	2/50 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.000	0.667
Lower Limit		0.000	0.058
Upper Limit		1.663	5.570
Weeks to First Observed Tumor	89	--	83
Hematopoietic System: Undifferentiated Leukemia (b)	20/50 (40)	12/50 (24)	22/50 (44)
P Values (c,d)	N.S.	N.S.	N.S.
Departure from Linear Trend (f)	P=0.030		
Relative Risk (Matched Control) (e)		0.600	1.100
Lower Limit		0.303	0.664
Upper Limit		1.141	1.829
Weeks to First Observed Tumor	85	53	85
Hematopoietic System: All Leukemias (b)	20/50 (40)	12/50 (24)	22/50 (44)
P Values (c,d)	N.S.	N.S.	N.S.
Departure from Linear Trend (f)	P=0.030		
Relative Risk (Matched Control) (e)		0.600	1.100
Lower Limit		0.303	0.664
Upper Limit		1.141	1.829
Weeks to First Observed Tumor	85	53	85
Pituitary: Adenoma, NOS (b)	8/50 (16)	3/50 (6)	5/50 (10)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.375	0.625
Lower Limit		0.067	0.172
Upper Limit		1.460	2.011
Weeks to First Observed Tumor	87	96	93

Table 6. Analyses of the Incidence of Primary Tumors in Male Rats Administered Cytembena by Intraperitoneal Injection (a) (continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Adrenal: Pheochromocytoma (b)	10/50 (20)	6/50 (12)	6/49 (12)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.600	0.612
Lower Limit		0.194	0.198
Upper Limit		1.676	1.708
Weeks to First Observed Tumor	89	82	69
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant(b)	12/50 (24)	7/50 (14)	7/49 (14)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.583	0.595
Lower Limit		0.212	0.217
Upper Limit		1.467	1.495
Weeks to First Observed Tumor	89	82	69
Thyroid: Follicular-cell Adenoma or Carcinoma (b)	3/50 (6)	1/49 (2)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.340	1.000
Lower Limit		0.007	0.140
Upper Limit		4.062	7.133
Weeks to First Observed Tumor	105	104	92
Thyroid: C-cell Adenoma (b)	2/50 (4)	3/49 (6)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		1.531	1.500
Lower Limit		0.183	0.180
Upper Limit		17.671	17.329
Weeks to First Observed Tumor	85	92	86

Table 6. Analyses of the Incidence of Primary Tumors in Male Rats Administered Cytembena by Intraperitoneal Injection (a) (continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Thyroid: C-cell Carcinoma (b)	3/50 (6)	1/49 (2)	1/50 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.340	0.333
Lower Limit		0.007	0.006
Upper Limit		4.062	3.983
Weeks to First Observed Tumor	89	91	103
Thyroid: C-cell Adenoma or Carcinoma (b)	5/50 (10)	4/49 (8)	4/50 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.816	0.800
Lower Limit		0.171	0.168
Upper Limit		3.567	3.499
Weeks to First Observed Tumor	85	91	86
Pancreatic Islets: Islet-cell Adenoma (b)	2/50 (4)	1/50 (2)	3/49 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.500	1.531
Lower Limit		0.009	0.183
Upper Limit		9.290	17.671
Weeks to First Observed Tumor	93	88	104
Pancreatic Islets: Islet-cell Carcinoma (b)	1/50 (2)	4/50 (8)	1/49 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		4.000	1.020
Lower Limit		0.415	0.013
Upper Limit		192.805	78.488
Weeks to First Observed Tumor	101	94	104

Table 6. Analyses of the Incidence of Primary Tumors in Male Rats Administered Cytembena by Intraperitoneal Injection (a) (continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Pancreatic Islets: Islet-cell Carcinoma or Adenoma (b)	3/50 (6)	5/50 (10)	4/49 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		1.667	1.361
Lower Limit		0.344	0.243
Upper Limit		10.225	8.854
Weeks to First Observed Tumor	93	88	104
Testis: Interstitial-cell Tumor (b)	47/50 (94)	41/50 (82)	47/50 (94)
P Values (c,d)	N.S.	N.S.	N.S.
Departure from Linear Trend (f)	P=0.021		
Relative Risk (Matched Control) (e)		0.872	1.000
Lower Limit		0.785	0.908
Upper Limit		1.030	1.101
Weeks to First Observed Tumor	71	57	71
Mesentery: Mesothelioma (b)	0/50 (0)	3/49 (6)	0/47 (0)
P Values (c,d)	N.S.	N.S.	N.S.
Departure from Linear Trend (f)	P=0.014		
Relative Risk (Matched Control) (e)		Infinite	--
Lower Limit		0.614	--
Upper Limit		Infinite	--
Weeks to First Observed Tumor	--	104	--
Tunica Vaginalis: Mesothelioma, NOS (b)	0/50 (0)	11/50 (22)	10/50 (20)
P Values (c,d)	P=0.003	P<0.001	P=0.001
Departure from Linear Trend (f)	P=0.044		
Relative Risk (Matched Control) (e)		Infinite	Infinite
Lower Limit		3.320	2.974
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	53	69

Table 6. Analyses of the Incidence of Primary Tumors in Male Rats Administered Cytembena by Intraperitoneal Injection (a) (continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Multiple Organs: Mesothelioma, Malignant (b)	3/50 (6)	26/50 (52)	26/50 (52)
P Values (c,d)	P<0.001	P<0.001	P<0.001
Departure from Linear Trend (f)	P=0.006		
Relative Risk (Matched Control) (e)		8.667	8.667
Lower Limit		2.930	2.930
Upper Limit		41.137	41.137
Weeks to First Observed Tumor	83	45	73

(a) Dosed groups received doses of 7 or 14 mg/kg by intraperitoneal injection.
(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 vehicle-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 7. Analyses of the Incidence of Primary Tumors in Female Rats Administered Cytembena by Intraperitoneal Injection (a)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Hematopoietic System:			
Undifferentiated Leukemia (b)	8/49 (16)	8/50 (16)	8/50 (16)
P Values (c)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (d)		0.980	0.980
Lower Limit		0.349	0.349
Upper Limit		2.757	2.757
Weeks to First Observed Tumor	71	21	94
Hematopoietic System: All			
Leukemias (b)	8/49 (16)	8/50 (16)	8/50 (16)
P Values (c)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (d)		0.980	0.980
Lower Limit		0.349	0.349
Upper Limit		2.757	2.757
Weeks to First Observed Tumor	71	21	94
Hematopoietic System: All			
Lymphomas (b)	0/49 (0)	3/50 (6)	1/50 (2)
P Values (c)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (d)		Infinite	Infinite
Lower Limit		0.590	0.053
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	5	19
Hematopoietic System: Leukemia			
or Lymphoma (b)	8/49 (16)	11/50 (22)	9/50 (18)
P Values (c)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (d)		1.348	1.103
Lower Limit		0.542	0.412
Upper Limit		3.529	3.016
Weeks to First Observed Tumor	71	5	19

Table 7. Analyses of the Incidence of Primary Tumors in Female Rats Administered Cytembena by Intraperitoneal Injection (a) (continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Liver: Neoplastic Nodule	0/49 (0)	1/50 (2)	4/50 (8)
P Values (c)	P=0.027	N.S.	N.S.
Relative Risk (Matched Control) (d)		Infinite	Infinite
Lower Limit		0.053	0.909
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	—	103	94
Pituitary: Adenoma, NOS (b)	14/47 (30)	13/46 (28)	16/47 (34)
P Values (c)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (d)		0.949	1.143
Lower Limit		0.464	0.594
Upper Limit		1.926	2.223
Weeks to First Observed Tumor	91	89	88
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant (b)	3/49 (6)	2/50 (4)	1/50 (2)
P Values (c)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (d)		0.653	0.327
Lower Limit		0.057	0.006
Upper Limit		5.457	3.903
Weeks to First Observed Tumor	75	104	104
Thyroid: C-cell Adenoma (b)	6/49 (12)	4/48 (8)	4/49 (8)
P Values (c)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (d)		0.681	0.667
Lower Limit		0.150	0.147
Upper Limit		2.683	2.631
Weeks to First Observed Tumor	100	101	89

Table 7. Analyses of the Incidence of Primary Tumors in Female Rats Administered Cytembena by Intraperitoneal Injection (a)
(continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Thyroid: C-cell Carcinoma (b)	2/49 (4)	2/48 (4)	4/49 (8)
P Values (c)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (d)		1.021	2.000
Lower Limit		0.077	0.302
Upper Limit		13.585	21.298
Weeks to First Observed Tumor	104	104	103
Thyroid: C-cell Adenoma or Carcinoma (b)	8/49 (16)	6/48 (13)	8/49 (16)
P Values (c)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (d)		0.766	1.000
Lower Limit		0.236	0.356
Upper Limit		2.322	2.810
Weeks to First Observed Tumor	100	101	89
Mammary Gland: Fibroadenoma (b)	13/49 (27)	22/50 (44)	36/50 (72)
P Values (c)	P 0.001	N.S.	P 0.001
Relative Risk (Matched Control) (d)		1.658	2.714
Lower Limit		0.910	1.656
Upper Limit		3.130	4.514
Weeks to First Observed Tumor	89	96	75
Uterus: Endometrial Stromal Polyp (b)	16/49 (33)	11/50 (22)	11/50 (22)
P Values (c)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (d)		0.674	0.674
Lower Limit		0.317	0.317
Upper Limit		1.382	1.382
Weeks to First Observed Tumor	43	80	88

Table 7. Analyses of the Incidence of Primary Tumors in Female Rats Administered Cytembena by Intraperitoneal Injection (a) (continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Mesentery: Lipoma (b)	0/49 (0)	0/50 (0)	3/50 (6)
P Values (c)	P=0.038	N.S.	N.S.
Relative Risk (Matched Control) (d)		—	Infinite
Lower Limit		—	0.590
Upper Limit		—	Infinite
Weeks to First Observed Tumor	—	—	94

(a) Dosed groups received doses of 7 or 14 mg/kg by intraperitoneal injection.
(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 vehicle-control group when P is less than 0.05; otherwise, not significant (N.S) is indicated.
(d) 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)

Mean body weights of dosed and vehicle-control male mice were comparable for the first 73 weeks of the study; thereafter, mean body weights of dosed groups were slightly lower (10% or less) than that of the vehicle controls. Mean body weights of dosed and control female mice were comparable for the first 87 weeks of the study; thereafter, weights in the high-dose group were slightly lower than that in the vehicle controls (Figure 4). No other compound-related clinical signs were observed.

B. Survival (Mice)

Estimates of the probabilities of survival for male and female mice administered cytembena by injection at the doses of this bioassay, and those of the controls, are shown by the Kaplan and Meier curves in Figure 5. The survival rates of the male and female dosed groups are comparable with those of their respective vehicle controls. The male group of untreated controls survived significantly longer than did any other male group.

In male mice, 36/50 (72%) of the untreated-control group, 20/50 (40%) of the vehicle-control group, 19/50 (38%) of the low-dose group, and 12/50 (24%) of the high-dose group lived to the end of the study at 104-105 weeks. At week 80, survival of the high- and low-dose males was 50% or greater. In females, 38/50 (76%) of the untreated-control group, 41/50 (82%) of the vehicle-control group, 33/50 (66%) of the low-dose group, and 34/50 (68%) of the high-dose group lived to the end of the study at 104-106 weeks. Thus, a sufficient number of animals were at risk for the development of late-appearing tumors in female mice, but some late tumor development may have been curtailed in the male mice groups due to shortened survival time.

C. Pathology (Mice)

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

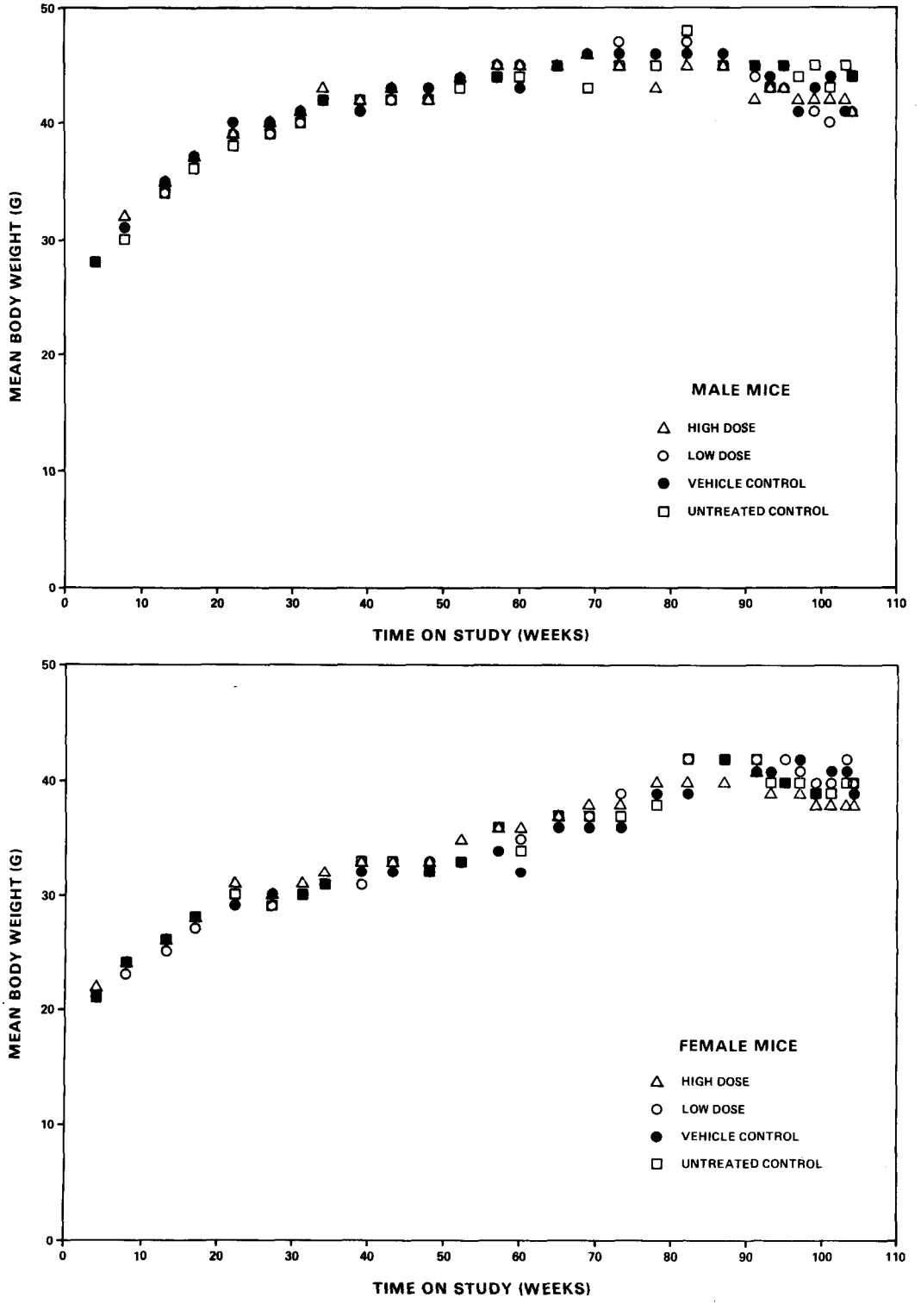

Figure 4. Growth Curves for Mice Administered Cytembena by Intraperitoneal Injection

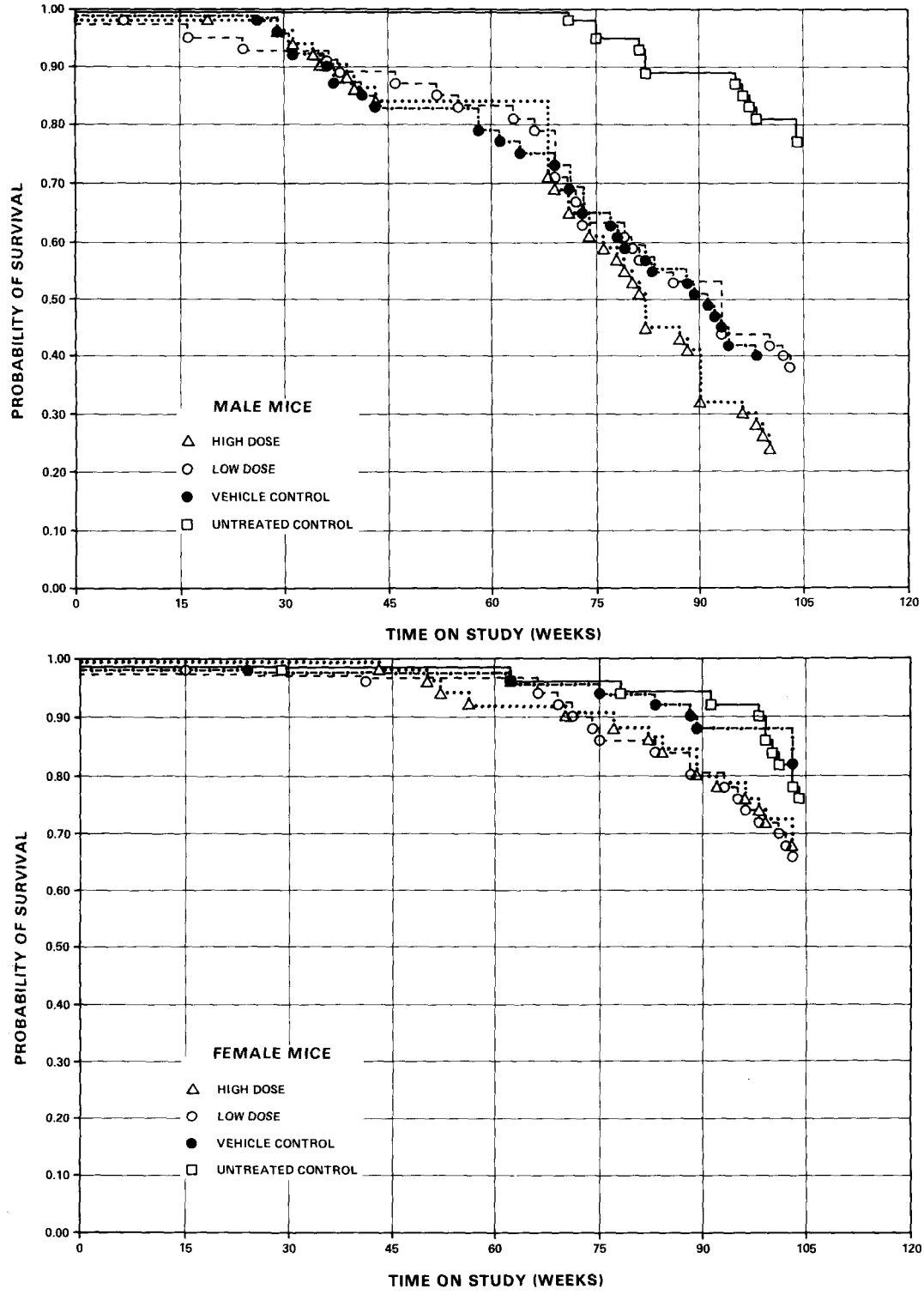

Figure 5. Survival Curves for Mice Administered Cytembena by Intraperitoneal Injection

A variety of tumors which were seen both in untreated-control and compound-treated groups represented the types of neoplasms encountered in the aging B6C3F1 mouse. Hepatocellular and lymphoreticular neoplasms were most often encountered. One mesothelioma was found in a low-dose male.

In addition to the neoplastic lesions, a number of degenerative, proliferative, and inflammatory changes were also encountered in animals of the dosed and control groups (Appendix D). These nonneoplastic lesions are commonly seen in aged B6C3F1 mice. Few peritoneal lesions were found.

The pathologists concluded that, under the conditions of this study, cytembena was not carcinogenic for B6C3F1 mice.

D. Statistical Analyses of Results (Mice)

Tables 8 and 9 contain the statistical analysis of the incidences of those primary tumors that occurred in at least two animals of one group and at an incidence of at least 5% in one or more than one group. Since the test conditions of the dosed groups are more comparable with conditions of the vehicle-control group than with those of the untreated control groups, the untreated control group has not been included in the tables. The incidences of the lesions in the untreated control groups are given in Appendixes B and D.

A dose-related trend in the incidence of female mice with malignant lymphomas of the histiocytic type is significant (P=0.049), but the results of the Fisher exact test are not significant. However, the incidences of dosed animals with any type of lymphoma are not significant when compared with the vehicle-control group under any of the tests, and no significant results were found in the male group incidences. The test comparing the time of observation of this lesion does not indicate significant differences between groups in either sex.

The Cochran-Armitage test indicates a significant (P=0.015) dose-related trend in the incidence of animals with hepatocellular adenomas of the liver in female mice, but the Fisher exact test indicates no significant difference in incidences between the dosed groups and the control group. A time-adjusted test eliminating those male mice dying before 34 weeks

(hepatocellular tumors) and 52 weeks (other tumor sites) indicated no statistically significant incidences at any site. An analysis of the time to observation of tumors was made of the hepatocellar tumors in male mice, since the first such tumor was observed in a male mouse at 34 weeks. The overall results indicated no significant difference between the dosed groups and the control. A negative trend in the incidence of alveolar/bronchiolar adenomas in the lung of females was also significant (P=0.040).

In each of the 95% confidence intervals for relative risk shown in the tables, the value of one or less than one is included. This 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 cytembena which could not be detected under the conditions of this test.

Table 8. Analyses of the Incidence of Primary Tumors in Male Mice Administered Cytembena by Intraperitoneal Injection (a)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma (b)	3/50 (6)	2/47 (4)	3/49 (6)
P Values (c)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (d)		0.709	1.020
Lower Limit		0.061	0.143
Upper Limit		5.913	7.273
Weeks to First Observed Tumor	58	63	81
Lung: Alveolar/Bronchiolar Carcinoma (b)	3/50 (6)	5/47 (11)	2/49 (4)
P Values (c)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (d)		1.773	0.680
Lower Limit		0.366	0.059
Upper Limit		10.850	5.680
Weeks to First Observed Tumor	105	80	79
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma (b)	6/50 (12)	7/47 (15)	5/49 (10)
P Values (c)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (d)		1.241	0.850
Lower Limit		0.385	0.219
Upper Limit		4.146	3.123
Weeks to First Observed Tumor	58	63	79
Hematopoietic System: All Lymphomas (b)	5/50 (10)	4/50 (8)	3/50 (6)
P Values (c)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (d)		0.800	0.600
Lower Limit		0.168	0.098
Upper Limit		3.499	2.910
Weeks to First Observed Tumor	93	79	71

Table 8. Analyses of the Incidence of Primary Tumors in Male Mice Administered Cytembena by Intraperitoneal Injection (a) (continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Hematopoietic System: Lymphoma or Leukemia (b)	5/50 (10)	4/50 (8)	4/50 (8)
P Values (c)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (d)		0.800	0.800
Lower Limit		0.168	0.168
Upper Limit		3.499	3.499
Weeks to First Observed Tumor	93	79	71
Circulatory System: Hemangiosarcoma (b)	1/50 (2)	3/50 (6)	1/50 (2)
P Values (c)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (d)		3.000	1.000
Lower Limit		0.251	0.013
Upper Limit		154.270	76.970
Weeks to First Observed Tumor	105	52	104
Liver: Hepatocellular Adenoma (b)	6/49 (12)	5/49 (10)	6/50 (12)
P Values (c)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (d)		0.833	0.980
Lower Limit		0.215	0.281
Upper Limit		3.059	3.418
Weeks to First Observed Tumor	96	66	34
Liver: Hepatocellular Carcinoma (b)	10/49 (20)	13/49 (27)	7/50 (14)
P Values (c)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (d)		1.300	0.686
Lower Limit		0.584	0.241
Upper Limit		2.987	1.830
Weeks to First Observed Tumor	82	63	76

Table 8. Analyses of the Incidence of Primary Tumors in Male Mice Administered Cytembena by Intraperitoneal Injection (a) (continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Liver: Hepatocellular Adenoma or Carcinoma (b)	16/49 (33)	18/49 (37)	13/50 (26)
P Values (c)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (d)		1.125	0.796
Lower Limit		0.618	0.397
Upper Limit		2.064	1.570
Weeks to First Observed Tumor	82	63	34
Harderian Gland: Adenoma, NOS (b)	2/50 (4)	3/50 (6)	1/50 (2)
P Values (c)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (d)		1.500	0.500
Lower Limit		0.180	0.009
Upper Limit		17.329	9.290
Weeks to First Observed Tumor	105	81	90

(a) Dosed groups received doses of 12 or 24 mg/kg by intraperitoneal injection.
(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 vehicle-control group when P is less than 0.05; otherwise, not significant (N.S) is indicated.
(d) The 95 percent confidence interval of the relative risk between each dosed group and the control group.

Table 9. Analyses of the Incidence of Primary Tumors in Female Mice Administered Cytembena by Intraperitoneal Injection (a)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma (b)	6/50 (12)	3/49 (6)	1/48 (2)
P Values (c,d)	P=0.040 (N)	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.510	0.174
Lower Limit		0.087	0.004
Upper Limit		2.243	1.355
Weeks to First Observed Tumor	105	101	104
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma (b)	7/50 (14)	4/49 (8)	2/48 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.583	0.298
Lower Limit		0.133	0.031
Upper Limit		2.139	1.468
Weeks to First Observed Tumor	105	101	104
Hematopoietic System: Malig. Lymphoma, Lymphocytic Type (b)	6/50 (12)	4/50 (8)	6/50 (12)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.667	1.000
Lower Limit		0.147	0.287
Upper Limit		2.635	3.489
Weeks to First Observed Tumor	103	88	77
Hematopoietic System: Malig. Lymphoma, Histiocytic Type (b)	0/50 (0)	3/50 (6)	4/50 (8)
P Values (c,d)	P=0.049	N.S.	N.S.
Relative Risk (Matched Control) (e)		Infinite	Infinite
Lower Limit		0.601	0.927
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor		95	99

Table 9. Analyses of the Incidence of Primary Tumors in Female Mice Administered Cytembena by Intraperitoneal Injection (a) (continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Hematopoietic System: All Lymphomas (b)	8/50 (16)	8/50 (16)	11/50 (22)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		1.000	1.375
Lower Limit		0.355	0.552
Upper Limit		2.815	3.603
Weeks to First Observed Tumor	103	88	77
Hematopoietic System: Lymphoma or Leukemia (b)	8/50 (16)	9/50 (18)	13/50 (26)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		1.125	1.625
Lower Limit		0.420	0.688
Upper Limit		3.079	4.120
Weeks to First Observed Tumor	103	83	77
Liver: Hepatocellular Adenoma (b)	0/50 (0)	0/48 (0)	4/49 (8)
P Values (c,d)	P=0.015	N.S.	N.S.
Relative Risk (Matched Control) (e)		—	Infinite
Lower Limit		—	0.946
Upper Limit		—	Infinite
Weeks to First Observed Tumor	—	—	104
Liver: Hepatocellular Carcinoma (b)	3/50 (6)	3/48 (6)	2/49 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		1.042	0.680
Lower Limit		0.146	0.059
Upper Limit		7.419	5.680
Weeks to First Observed Tumor	105	102	103

Table 9. Analyses of the Incidence of Primary Tumors in Female Mice Administered Cytembena by Intraperitoneal Injection (a) (continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Liver: Hepatocellular Adenoma or Carcinoma (b)	3/50 (6)	3/48 (6)	6/49 (12)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		1.042	2.041
Lower Limit		0.146	0.464
Upper Limit		7.419	11.991
Weeks to First Observed Tumor	105	102	103
Pituitary: Adenoma, NOS (b)	1/47 (2)	3/46 (7)	0/44 (0)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		3.065	0.000
Lower Limit		0.257	0.000
Upper Limit		157.288	19.878
Weeks to First Observed Tumor	105	105	--
Thyroid: Follicular-cell Adenoma (b)	3/49 (6)	2/48 (4)	2/49 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.681	0.667
Lower Limit		0.059	0.058
Upper Limit		5.677	5.565
Weeks to First Observed Tumor	105	105	103
Thyroid: Follicular-cell Adenoma or Carcinoma (b)	4/49 (8)	2/48 (4)	3/49 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		0.510	0.750
Lower Limit		0.048	0.115
Upper Limit		3.381	4.201
Weeks to First Observed Tumor	105	105	103

Table 9. Analyses of the Incidence of Primary Tumors in Female Mice Administered Cytembena by Intraperitoneal Injection (a) (continued)

Topography: Morphology	Vehicle Control	Low Dose	High Dose
Uterus: Endometrial Stromal Polyp or Sarcoma (b)	0/49 (0)	3/48 (6)	2/50 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (e)		Infinite	Infinite
Lower Limit		0.614	0.290
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	88	92

(a) Dosed groups received doses of 12 or 24 mg/kg by intraperitoneal injection.
(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 vehicle-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.

V. DISCUSSION

Mean body weights of dosed and vehicle-control rats were comparable throughout the bioassay. Mean body weights of dosed and vehicle-control mice were comparable for the first 73 weeks of the bioassay; mean body weights of the high-dose mice were slightly lower than those of the vehicle controls after week 73 (for males) and after week 87 (for females). The lack of an appreciable difference in mean body weight gain and lesions suggests that the mice may have been able to tolerate larger doses.

Survival in male mice at the end of the study was considered below average (vehicle control, 40%; low-dose, 38%; high-dose, 24%).

In male rats, mesotheliomas in the tunica vaginalis and malignant mesotheliomas in multiple organs occurred with dose-related trends ($P=0.003$ and $P=0.001$, respectively). The incidence of these tumors in each of the dosed groups was significantly higher ($P<0.001$) than that in the controls. The malignant mesotheliomas involved the serosal surfaces of most of the abdominal organs.

In female rats, fibroadenomas in the mammary gland occurred with a dose-related trend ($P<0.001$) and at a significantly higher incidence ($P<0.001$) in the high-dose group than in the controls. An increased incidence of cystic ducts, cystic hyperplasia, and epithelial and lobular hyperplasia in mammary tissue was also observed in female rats.

VI. CONCLUSIONS

Under the conditions of this bioassay, cytembena was carcinogenic for male and female F344 rats, causing increased incidences of mesotheliomas in the tunica vaginalis and in multiple organs of males, and fibroadenomas in the mammary gland of females. Cytembena was not carcinogenic for male or female B6C3F1 mice.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED CYTEMBENA BY INTRAPERITONEAL INJECTION

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED CYTEMBENA BY INTRAPERITONEAL INJECTION

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
PAPILLOMA, NOS		1 (2%)		
SQUAMOUS CELL PAPILLOMA	1 (2%)	1 (2%)		
SQUAMOUS CELL CARCINOMA		1 (2%)		1 (2%)
TRICHOEPITHELIOMA				1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)		
BASAL-CELL CARCINOMA	1 (2%)			
ADNEXAL CARCINOMA		1 (2%)		
SEBACEOUS ADENOCARCINOMA				1 (2%)
FIBROMA	3 (6%)	2 (4%)		2 (4%)
FIBROSARCOMA	2 (4%)	1 (2%)		
RESPIRATORY SYSTEM				
#LUNG	(50)	(49)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)	2 (4%)	1 (2%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)	
C-CELL CARCINOMA, METASTATIC		1 (2%)		
LIPOSARCOMA, METASTATIC			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)			
UNDIFFERENTIATED LEUKEMIA	20 (40%)	20 (40%)	11 (22%)	22 (44%)
#SPLEEN	(49)	(50)	(50)	(49)
UNDIFFERENTIATED LEUKEMIA			1 (2%)	
#PEYER'S PATCH	(47)	(50)	(49)	(47)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)			

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)			
#LARGE INTESTINE	(48)	(48)	(47)	(48)
HEMANGIOMA				1 (2%)
DIGESTIVE SYSTEM				
#LIVER	(50)	(49)	(50)	(50)
NEOPLASTIC NODULE		1 (2%)	1 (2%)	1 (2%)
HEPATOCELLULAR CARCINOMA	1 (2%)			1 (2%)
#STOMACH	(50)	(50)	(49)	(49)
CYSTADENOMA, NOS				1 (2%)
#JEJUNUM	(47)	(50)	(49)	(47)
MUCINOUS ADENOCARCINOMA			1 (2%)	
#COLON	(48)	(48)	(47)	(48)
ADENOCARCINOMA, NOS		1 (2%)		
ADENOMATOUS POLYP, NOS		1 (2%)		
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#PITUITARY	(50)	(50)	(50)	(50)
ADENOMA, NOS	3 (6%)	8 (16%)	3 (6%)	5 (10%)
#ADRENAL	(48)	(50)	(50)	(49)
CORTICAL ADENOMA	1 (2%)	1 (2%)		1 (2%)
PHEOCHROMOCYTOMA	11 (23%)	10 (20%)	6 (12%)	6 (12%)
PHEOCHROMOCYTOMA, MALIGNANT		2 (4%)	1 (2%)	1 (2%)
#THYROID	(48)	(50)	(49)	(50)
FOLLICULAR-CELL ADENOMA	1 (2%)	2 (4%)	1 (2%)	2 (4%)
FOLLICULAR-CELL CARCINOMA	1 (2%)	1 (2%)		1 (2%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
C-CELL ADENOMA	3 (6%)	2 (4%)	3 (6%)	3 (6%)
C-CELL CARCINOMA	2 (4%)	3 (6%)	1 (2%)	1 (2%)
#PARATHYROID	(41)	(48)	(40)	(46)
ADENOMA, NOS			1 (3%)	
#PANCREATIC ISLETS	(49)	(50)	(50)	(49)
ISLET-CELL ADENOMA	1 (2%)	2 (4%)	1 (2%)	3 (6%)
ISLET-CELL CARCINOMA	1 (2%)	1 (2%)	4 (8%)	1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(50)	(50)
ADENOCARCINOMA, NOS				1 (2%)
FIBROADENOMA	3 (6%)		2 (4%)	2 (4%)
*PREPUTIAL GLAND	(50)	(50)	(50)	(50)
CARCINOMA,NOS	1 (2%)	1 (2%)	1 (2%)	
ADENOMA, NOS	1 (2%)		1 (2%)	
#TESTIS	(50)	(50)	(50)	(50)
INTERSTITIAL-CELL TUMOR	47 (94%)	47 (94%)	41 (82%)	47 (94%)
*EPIDIDYMIS	(50)	(50)	(50)	(50)
MESOTHELIOMA, NOS				1 (2%)
NERVOUS SYSTEM				
#BRAIN	(50)	(50)	(50)	(50)
ASTROCYTOMA		2 (4%)		
GLIOBLASTOMA MULTIFORME				1 (2%)
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(50)	(50)	(50)	(50)
CARCINOMA,NOS	1 (2%)			
*EAR CANAL	(50)	(50)	(50)	(50)
SEBACEOUS ADENOCARCINOMA		1 (2%)		
MUSCULOSKELETAL SYSTEM				
NONE				

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES				
*ABDOMINAL WALL	(50)	(50)	(50)	(50)
SARCOMA, NOS				1 (2%)
*MESENTERY	(50)	(50)	(50)	(50)
LIPOMA	1 (2%)		2 (4%)	2 (4%)
MESOTHELIOMA, NOS			3 (6%)	
*TUNICA VAGINALIS	(50)	(50)	(50)	(50)
MESOTHELIOMA, NOS	1 (2%)		11 (22%)	10 (20%)
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
SARCOMA, NOS			1 (2%)	
LIPOSARCOMA			1 (2%)	
MESOTHELIOMA, MALIGNANT		3 (6%)	26 (52%)	26 (52%)
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	3	4	9	7
MORIBUND SACRIFICE	12	17	29	31
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	35	29	12	12
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	49	50	48	49
TOTAL PRIMARY TUMORS	112	119	126	146
TOTAL ANIMALS WITH BENIGN TUMORS	48	50	44	49
TOTAL BENIGN TUMORS	78	81	62	76
TOTAL ANIMALS WITH MALIGNANT TUMORS	29	32	41	41
TOTAL MALIGNANT TUMORS	33	38	49	58
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	1	
TOTAL SECONDARY TUMORS		1	1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1		12	12
TOTAL UNCERTAIN TUMORS	1		15	12
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

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

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS ADMINISTERED CYTEMBENA BY INTRAPERITONEAL INJECTION

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	49	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	49	50	50
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(49)	(49)	(50)	(50)
SARCOMA, NOS			1 (2%)	
FIBROMA	1 (2%)			2 (4%)
FIBROUS HISTIOCYTOMA, MALIGNANT			1 (2%)	
RESPIRATORY SYSTEM				
#LUNG	(49)	(49)	(50)	(49)
ALVEOLAR/BRONCHIOLAR ADENOMA			1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)			
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(49)	(49)	(50)	(50)
MALIG.LYMPHOMA, UNDIFFER-TYPE			1 (2%)	1 (2%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)	
UNDIFFERENTIATED LEUKEMIA	8 (16%)	8 (16%)	7 (14%)	8 (16%)
LYMPHOCYTIC LEUKEMIA	1 (2%)			
#SPLEEN	(49)	(49)	(50)	(50)
MALIGNANT LYMPHOMA, NOS			1 (2%)	
UNDIFFERENTIATED LEUKEMIA	1 (2%)			
#LIVER	(48)	(49)	(50)	(50)
UNDIFFERENTIATED LEUKEMIA			1 (2%)	
CIRCULATORY SYSTEM				
*ABDOMINAL MUSCLE	(49)	(49)	(50)	(50)
HEMANGIOSARCOMA			1 (2%)	

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM				
#LIVER	(48)	(49)	(50)	(50)
NEOPLASTIC NODULE			1 (2%)	4 (8%)
URINARY SYSTEM				
#KIDNEY	(49)	(49)	(50)	(50)
MIXED TUMOR, INVASIVE				1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY	(47)	(47)	(46)	(47)
CARCINOMA,NOS	2 (4%)	2 (4%)		
CARCINOMA, NOS, INVASIVE	1 (2%)			
ADENOMA, NOS	16 (34%)	14 (30%)	13 (28%)	16 (34%)
CHROMOPHOBE ADENOMA	2 (4%)	1 (2%)	1 (2%)	1 (2%)
CHROMOPHOBE CARCINOMA				1 (2%)
#ADRENAL	(49)	(49)	(50)	(50)
CORTICAL ADENOMA		2 (4%)	1 (2%)	
CORTICAL CARCINOMA		1 (2%)		
PHEOCHROMOCYTOMA		2 (4%)	2 (4%)	1 (2%)
PHEOCHROMOCYTOMA, MALIGNANT		1 (2%)		
#THYROID	(49)	(49)	(48)	(49)
FOLLICULAR-CELL ADENOMA			1 (2%)	2 (4%)
FOLLICULAR-CELL CARCINOMA		1 (2%)	1 (2%)	
C-CELL ADENOMA	5 (10%)	6 (12%)	4 (8%)	4 (8%)
C-CELL CARCINOMA	1 (2%)	2 (4%)	2 (4%)	4 (8%)
#PANCREATIC ISLETS	(49)	(49)	(48)	(49)
ISLET-CELL ADENOMA			1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(49)	(49)	(50)	(50)
ADENOMA, NOS				1 (2%)
ADENOCARCINOMA, NOS	1 (2%)	1 (2%)		2 (4%)
FIBROADENOMA	17 (35%)	13 (27%)	22 (44%)	36 (72%)
*MAMMARY DUCT	(49)	(49)	(50)	(50)
ADENOMA, NOS	1 (2%)			

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
*PREPUTIAL GLAND	(49)	(49)	(50)	(50)
CARCINOMA,NOS			2 (4%)	
*VAGINA	(49)	(49)	(50)	(50)
SQUAMOUS CELL PAPILLOMA			1 (2%)	
SARCOMA, NOS			1 (2%)	
#UTERUS	(48)	(49)	(50)	(50)
CARCINOMA,NOS			1 (2%)	
ENDOMETRIAL STROMAL POLYP	9 (19%)	16 (33%)	11 (22%)	11 (22%)
ENDOMETRIAL STROMAL SARCOMA	1 (2%)		1 (2%)	1 (2%)
#OVARY	(48)	(49)	(50)	(50)
GRANULOSA-CELL TUMOR	1 (2%)			
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EAR CANAL	(49)	(49)	(50)	(50)
SQUAMOUS CELL CARCINOMA			2 (4%)	
*ZYMBAL'S GLAND	(49)	(49)	(50)	(50)
CARCINOMA,NOS		2 (4%)		
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*ABDOMINAL CAVITY	(49)	(49)	(50)	(50)
SARCOMA, NOS				1 (2%)
*MESENTERY	(49)	(49)	(50)	(50)
SARCOMA, NOS				1 (2%)
LIPOMA				3 (6%)

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
LIPOMA				3 (6%)
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(49)	(49)	(50)	(50)
SARCOMA, NOS	1 (2%)			1 (2%)
MESOTHELIOMA, MALIGNANT				2 (4%)
PERIORBITAL REGION				
SQUAMOUS CELL CARCINOMA, INVASIV		1		
ADIPOSE TISSUE				
LIPOMA				1
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	7	9	9	3
MORIBUND SACRIFICE	9	11	8	19
SCHEDULED SACRIFICE	1			
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	33	30	33	28
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	43	38	44	47
TOTAL PRIMARY TUMORS	69	72	83	106
TOTAL ANIMALS WITH BENIGN TUMORS	38	33	36	44
TOTAL BENIGN TUMORS	51	54	58	81
TOTAL ANIMALS WITH MALIGNANT TUMORS	16	17	20	20
TOTAL MALIGNANT TUMORS	17	18	24	22
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1		1
TOTAL SECONDARY TUMORS	1	1		1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1		1	3
TOTAL UNCERTAIN TUMORS	1		1	3
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 B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE
ADMINISTERED CYTEMBENA BY INTRAPERITONEAL INJECTION

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED CYTEMBENA BY INTRAPERITONEAL INJECTION

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	49	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50	50
INTEGUMENTARY SYSTEM				
*MULTIPLE ORGANS	(49)	(50)	(50)	(50)
FIBROUS HISTIOCYTOMA, MALIGNANT				1 (2%)
*SKIN	(49)	(50)	(50)	(50)
FIBROMA		1 (2%)	1 (2%)	
*SUBCUT TISSUE	(49)	(50)	(50)	(50)
SEBACEOUS ADENOMA				1 (2%)
SARCOMA, NOS		1 (2%)		
RESPIRATORY SYSTEM				
#LUNG	(48)	(50)	(47)	(49)
HEPATOCELLULAR CARCINOMA, METAST			1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	6 (13%)	3 (6%)	2 (4%)	3 (6%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	8 (17%)	3 (6%)	5 (11%)	2 (4%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(49)	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS		1 (2%)		
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		2 (4%)	2 (4%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)	2 (4%)	2 (4%)
LYMPHOCYTIC LEUKEMIA				1 (2%)
#SMALL INTESTINE	(44)	(39)	(43)	(45)
MALIGNANT LYMPHOMA, MIXED TYPE				1 (2%)
#LARGE INTESTINE	(44)	(40)	(43)	(47)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)			

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM				
*MULTIPLE ORGANS	(49)	(50)	(50)	(50)
HEMANGIOSARCOMA			1 (2%)	
#SPLEEN	(47)	(46)	(47)	(49)
HEMANGIOSARCOMA		1 (2%)		
#LUNG	(48)	(50)	(47)	(49)
HEMANGIOSARCOMA	1 (2%)			
#LIVER	(47)	(49)	(49)	(50)
HEMANGIOSARCOMA	1 (2%)		2 (4%)	1 (2%)
*MESENTERY	(49)	(50)	(50)	(50)
HEMANGIOSARCOMA			1 (2%)	
DIGESTIVE SYSTEM				
#LIVER	(47)	(49)	(49)	(50)
HEPATOCELLULAR ADENOMA	4 (9%)	6 (12%)	5 (10%)	6 (12%)
HEPATOCELLULAR CARCINOMA	13 (28%)	10 (20%)	13 (27%)	7 (14%)
#GASTRIC SUBMUCOSA	(47)	(46)	(49)	(48)
SARCOMA, NOS			1 (2%)	
#SMALL INTESTINE	(44)	(39)	(43)	(45)
ADENOCARCINOMA, NOS			1 (2%)	
MUCINOUS ADENOCARCINOMA	1 (2%)			
#CECUM	(44)	(40)	(43)	(47)
SIGNET RING CARCINOMA			1 (2%)	
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#ADRENAL	(49)	(46)	(47)	(50)
PHEOCHROMOCYTOMA		1 (2%)		

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#THYROID	(44)	(44)	(44)	(46)
ADENOMA, NOS			1 (2%)	
FOLLICULAR-CELL ADENOMA	1 (2%)	1 (2%)		2 (4%)
C-CELL CARCINOMA				1 (2%)
REPRODUCTIVE SYSTEM				
#TESTIS	(49)	(50)	(49)	(50)
INTERSTITIAL-CELL TUMOR		1 (2%)		
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(49)	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)	2 (4%)	3 (6%)	1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*ABDOMINAL WALL	(49)	(50)	(50)	(50)
FIBROSARCOMA	1 (2%)			
*MESENTERY	(49)	(50)	(50)	(50)
LIPOMA			1 (2%)	1 (2%)
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(49)	(50)	(50)	(50)
HEPATOCELLULAR CARCINOMA, METAST		2 (4%)		
MESOTHELIOMA, MALIGNANT			1 (2%)	

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	9	23	23	27
MORIBUND SACRIFICE	2	6	7	10
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED	2	1	1	1
TERMINAL SACRIFICE	36	20	19	12
ANIMAL MISSING				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	30	28	30	24
TOTAL PRIMARY TUMORS	38	35	43	30
TOTAL ANIMALS WITH BENIGN TUMORS	12	14	12	12
TOTAL BENIGN TUMORS	12	15	13	14
TOTAL ANIMALS WITH MALIGNANT TUMORS	22	17	23	15
TOTAL MALIGNANT TUMORS	26	20	30	16
TOTAL ANIMALS WITH SECONDARY TUMORS#		2	1	1
TOTAL SECONDARY TUMORS		2	1	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

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE ADMINISTERED CYTEMBENA BY INTRAPERITONEAL INJECTION

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	48	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(48)	(50)	(50)	(50)
BASAL-CELL TUMOR				1 (2%)
RESPIRATORY SYSTEM				
#LUNG	(46)	(50)	(49)	(48)
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (7%)	6 (12%)	3 (6%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	1 (2%)	1 (2%)	1 (2%)
OSTEOSARCOMA, METASTATIC			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(48)	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS		2 (4%)		1 (2%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	2 (4%)	5 (10%)	3 (6%)	3 (6%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	6 (13%)			3 (6%)
LYMPHOCYTIC LEUKEMIA			1 (2%)	2 (4%)
*SUBCUT TISSUE	(48)	(50)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE				1 (2%)
#SPLEEN	(47)	(50)	(48)	(49)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)		1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		1 (2%)	1 (2%)
#LYMPH NODE	(48)	(50)	(48)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)			
#BRONCHIAL LYMPH NODE	(48)	(50)	(48)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)		
#PANCREATIC L.NODE	(48)	(50)	(48)	(50)
MALIGNANT LYMPHOMA, NOS			1 (2%)	

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#MESENTERIC L. NODE	(48)	(50)	(48)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE				2 (4%)
#LIVER	(48)	(50)	(48)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			2 (4%)	
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)			
CIRCULATORY SYSTEM				
*SUBCUT TISSUE	(48)	(50)	(50)	(50)
HEMANGIOSARCOMA				1 (2%)
#SPLEEN	(47)	(50)	(48)	(49)
HEMANGIOSARCOMA			1 (2%)	
#LIVER	(48)	(50)	(48)	(49)
HEMANGIOSARCOMA				1 (2%)
DIGESTIVE SYSTEM				
*TONGUE	(48)	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (2%)			
#LIVER	(48)	(50)	(48)	(49)
HEPATOCELLULAR ADENOMA				4 (8%)
HEPATOCELLULAR CARCINOMA	2 (4%)	3 (6%)	3 (6%)	2 (4%)
ENDOMETRIAL STROMAL SARCOMA, MET				1 (2%)
#DUODENUM	(44)	(49)	(46)	(43)
ADENOCARCINOMA, NOS	1 (2%)			
#JEJUNUM	(44)	(49)	(46)	(43)
SARCOMA, NOS, UNC PRIM OR META				1 (2%)
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#PITUITARY	(45)	(47)	(46)	(44)
CARCINOMA,NOS	1 (2%)	1 (2%)		1 (2%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ADENOMA, NOS		1 (2%)	3 (7%)	
#ADRENAL	(48)	(48)	(48)	(49)
CORTICAL ADENOMA		1 (2%)	1 (2%)	
PHEOCHROMOCYTOMA		1 (2%)		
#THYROID	(47)	(49)	(48)	(49)
ADENOMA, NOS				1 (2%)
FOLLICULAR-CELL ADENOMA	2 (4%)	3 (6%)	2 (4%)	2 (4%)
FOLLICULAR-CELL CARCINOMA		1 (2%)		1 (2%)
C-CELL ADENOMA			1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(48)	(50)	(50)	(50)
ADENOCARCINOMA, NOS		2 (4%)		
MIXED TUMOR, MALIGNANT				1 (2%)
#UTERUS	(47)	(49)	(48)	(50)
CARCINOMA,NOS	1 (2%)			
ENDOMETRIAL STROMAL POLYP	1 (2%)		1 (2%)	1 (2%)
ENDOMETRIAL STROMAL SARCOMA	2 (4%)		2 (4%)	1 (2%)
#OVARY	(48)	(49)	(48)	(49)
ADENOCARCINOMA, NOS		1 (2%)		
GRANULOSA-CELL TUMOR			1 (2%)	
NERVOUS SYSTEM				
#BRAIN/MENINGES	(47)	(49)	(49)	(50)
MYXOSARCOMA		1 (2%)		
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(48)	(50)	(50)	(50)
ADENOMA, NOS	3 (6%)	1 (2%)		1 (2%)
MUSCULOSKELETAL SYSTEM				
*CRANIAL AND FACIAL B	(48)	(50)	(50)	(50)
OSTEOMA		1 (2%)		

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
*SPHENOID AND ETHMOID	(48)	(50)	(50)	(50)
OSTEOSARCOMA				1 (2%)
*SACRUM	(48)	(50)	(50)	(50)
OSTEOSARCOMA			1 (2%)	
BODY CAVITIES				
*MESENTERY	(48)	(50)	(50)	(50)
SARCOMA, NOS, UNC PRIM OR META				1 (2%)
LIPOMA				1 (2%)
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(48)	(50)	(50)	(50)
OSTEOSARCOMA, METASTATIC			1 (2%)	
BASE OF TAIL				
FIBROSARCOMA	1			
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH@	8	3	12	8
MORIBUND SACRIFICE	4	6	5	8
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	38	41	33	34
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	25	26	22	29
TOTAL PRIMARY TUMORS	31	32	29	37
TOTAL ANIMALS WITH BENIGN TUMORS	9	13	10	11
TOTAL BENIGN TUMORS	9	14	11	12
TOTAL ANIMALS WITH MALIGNANT TUMORS	20	17	15	20
TOTAL MALIGNANT TUMORS	22	18	17	23
TOTAL ANIMALS WITH SECONDARY TUMORS#			2	1
TOTAL SECONDARY TUMORS			2	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			1	
TOTAL UNCERTAIN TUMORS			1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				1
TOTAL UNCERTAIN TUMORS				2

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

APPENDIX C

SUMMARY OF INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS ADMINISTERED CYTEMBENA BY INTRAPERITONEAL INJECTION

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED CYTEMBENA BY INTRAPERITONEAL INJECTION

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
ULCER, NOS	1 (2%)			
INFLAMMATION, NECROTIZING				1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
EDEMA, NOS				1 (2%)
HEMORRHAGE	1 (2%)			
STEATITIS			1 (2%)	
INFLAMMATION, SUPPURATIVE		1 (2%)		1 (2%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
ABSCESS, CHRONIC				1 (2%)
FIBROSIS, DIFFUSE	1 (2%)			
NECROSIS, FAT				1 (2%)
RESPIRATORY SYSTEM				
#LUNG	(50)	(49)	(50)	(50)
INFLAMMATION, INTERSTITIAL			1 (2%)	1 (2%)
INFLAMMATION, PYOGRANULOMATOUS				1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	2 (4%)			
METAPLASIA, SQUAMOUS			1 (2%)	
METAPLASIA, OSSEOUS				1 (2%)
#LUNG/ALVEOLI	(50)	(49)	(50)	(50)
MINERALIZATION				1 (2%)
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(47)	(49)	(49)	(50)
MYELOFIBROSIS			1 (2%)	
#SPLEEN	(49)	(50)	(50)	(49)
FIBROSIS, FOCAL	1 (2%)	1 (2%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFARCT, NOS				1 (2%)
INFARCT, ACUTE				1 (2%)
ATROPHY, NOS			1 (2%)	
HEMATOPOIESIS	1 (2%)	1 (2%)	7 (14%)	2 (4%)
#SPLENIC CAPSULE	(49)	(50)	(50)	(49)
INFLAMMATION, CHRONIC SUPPURATIV				1 (2%)
#MANDIBULAR L. NODE	(50)	(50)	(50)	(50)
INFLAMMATION, NECROTIZING			1 (2%)	
#LUNG	(50)	(49)	(50)	(50)
HYPERPLASIA, LYMPHOID			1 (2%)	
#PEYER'S PATCH	(47)	(50)	(49)	(47)
HYPERPLASIA, LYMPHOID	1 (2%)			
#THYMUS	(50)	(48)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)	
ATROPHY, NOS	1 (2%)			
CIRCULATORY SYSTEM				
#HEART/ATRIUM	(50)	(50)	(49)	(50)
THROMBUS, MURAL		1 (2%)	1 (2%)	
#AURICULAR APPENDAGE	(50)	(50)	(49)	(50)
THROMBUS, MURAL		1 (2%)	1 (2%)	1 (2%)
#MYOCARDIUM	(50)	(50)	(49)	(50)
MINERALIZATION				1 (2%)
INFLAMMATION, INTERSTITIAL	38 (76%)	42 (84%)	27 (55%)	36 (72%)
#LIVER	(50)	(49)	(50)	(50)
THROMBUS, ORGANIZED	1 (2%)			
*MESENTERY	(50)	(50)	(50)	(50)
PERIARTERITIS				1 (2%)
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(50)	(50)	(47)	(50)
EDEMA, NOS				1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#LIVER	(50)	(49)	(50)	(50)
CYST, NOS				1 (2%)
MULTILOCULAR CYST				1 (2%)
MULTIPLE CYSTS				1 (2%)
CONGESTION, PASSIVE		1 (2%)		1 (2%)
HEMORRHAGE	1 (2%)			
NECROSIS, COAGULATIVE	1 (2%)	2 (4%)		2 (4%)
LIPOIDOSIS	1 (2%)			
CYTOPLASMIC CHANGE, NOS	2 (4%)		2 (4%)	3 (6%)
CYTOPLASMIC VACUOLIZATION	7 (14%)	2 (4%)	4 (8%)	7 (14%)
BASOPHILIC CYTO CHANGE		1 (2%)		
FOCAL CELLULAR CHANGE			3 (6%)	
ANGIECTASIS		1 (2%)		1 (2%)
#LIVER/CENTRILOBULAR	(50)	(49)	(50)	(50)
CONGESTION, NOS			2 (4%)	
NECROSIS, NOS		1 (2%)		
NECROSIS, COAGULATIVE			1 (2%)	
#BILE DUCT	(50)	(49)	(50)	(50)
HYPERPLASIA, NOS	5 (10%)	2 (4%)		8 (16%)
HYPERPLASIA, FOCAL	1 (2%)			
#PANCREAS	(49)	(50)	(50)	(49)
INFLAMMATION, INTERSTITIAL		2 (4%)	4 (8%)	2 (4%)
#ESOPHAGUS	(50)	(50)	(50)	(50)
ULCER, NOS		1 (2%)		
#STOMACH	(50)	(50)	(49)	(49)
ULCER, NOS	1 (2%)			
INFLAMMATION, SUPPURATIVE	1 (2%)			
INFLAMMATION, ACUTE NECROTIZING	1 (2%)			
INFLAMMATION, CHRONIC		1 (2%)		
HYPERPLASIA, EPITHELIAL	1 (2%)			
HYPERKERATOSIS	1 (2%)			
#GASTRIC MUCOSA	(50)	(50)	(49)	(49)
MINERALIZATION				1 (2%)
#GASTRIC SUBMUCOSA	(50)	(50)	(49)	(49)
EDEMA, NOS		1 (2%)		
#SMALL INTESTINE	(47)	(50)	(49)	(47)
HEMORRHAGE			1 (2%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#COLON	(48)	(48)	(47)	(48)
INFLAMMATION, SUPPURATIVE		1 (2%)		
INFLAMMATION, NECROTIZING		1 (2%)		
INFLAMMATION, PYOGRANULOMATOUS		1 (2%)		
NEMATODIASIS		1 (2%)		1 (2%)
#COLONIC SUBSEROSA	(48)	(48)	(47)	(48)
HEMORRHAGE		1 (2%)		
#CECUM	(48)	(48)	(47)	(48)
HEMORRHAGE				1 (2%)
URINARY SYSTEM				
#KIDNEY	(49)	(50)	(50)	(49)
INFLAMMATION, INTERSTITIAL		1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC	39 (80%)	43 (86%)	31 (62%)	42 (86%)
INFLAMMATION, CHRONIC DIFFUSE				2 (4%)
FIBROSIS	1 (2%)			
HEMOSIDEROSIS	1 (2%)		2 (4%)	1 (2%)
#U.BLADDER/SUBMUCOSA	(44)	(49)	(48)	(46)
FIBROSIS, FOCAL		1 (2%)		
#U.BLADDER/SEROSA	(44)	(49)	(48)	(46)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
ENDOCRINE SYSTEM				
#PITUITARY	(50)	(50)	(50)	(50)
INFLAMMATION, NECROTIZING	1 (2%)			
#ADRENAL	(48)	(50)	(50)	(49)
CYTOPLASMIC VACUOLIZATION	1 (2%)			
#ADRENAL CORTEX	(48)	(50)	(50)	(49)
CYTOPLASMIC VACUOLIZATION		1 (2%)		1 (2%)
#ADRENAL MEDULLA	(48)	(50)	(50)	(49)
HYPERPLASIA, FOCAL			1 (2%)	1 (2%)
#THYROID	(48)	(50)	(49)	(50)
FOLLICULAR CYST, NOS				1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, C-CELL	1 (2%)	2 (4%)	2 (4%)	
#PARATHYROID	(41)	(48)	(40)	(46)
HYPERPLASIA, NOS				1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(50)	(50)
CYSTIC DUCTS	2 (4%)	3 (6%)	3 (6%)	3 (6%)
*MAMMARY LOBULE	(50)	(50)	(50)	(50)
HYPERPLASIA, NOS		1 (2%)		
*PREPUTIAL GLAND	(50)	(50)	(50)	(50)
DILATATION, NOS			1 (2%)	
ULCER, NOS		1 (2%)		
INFLAMMATION, SUPPURATIVE	1 (2%)	1 (2%)		1 (2%)
INFLAMMATION, CHRONIC	1 (2%)	1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC SUPPURATIV		1 (2%)		
INFLAMMATION, GRANULOMATOUS		1 (2%)		
HYPERPLASIA, NOS	1 (2%)	1 (2%)	1 (2%)	
HYPERPLASIA, EPITHELIAL		1 (2%)		
#PROSTATE	(46)	(48)	(49)	(47)
INFLAMMATION, SUPPURATIVE	3 (7%)	2 (4%)	1 (2%)	1 (2%)
INFLAMMATION, CHRONIC SUPPURATIV		1 (2%)		
HYPERPLASIA, EPITHELIAL	1 (2%)			
*SEMINAL VESICLE	(50)	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE				1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)			
#TESTIS	(50)	(50)	(50)	(50)
ATROPHY, NOS		1 (2%)		
SPERMATOGENIC ARREST				1 (2%)
HYPERPLASIA, INTERSTITIAL CELL			1 (2%)	
*EPIDIDYMIS	(50)	(50)	(50)	(50)
HYPERPLASIA, MESOTHELIAL			1 (2%)	
*SCROTUM	(50)	(50)	(50)	(50)
GRANULOMA, PYOGENIC			1 (2%)	
NERVOUS SYSTEM				
#BRAIN/MENINGES	(50)	(50)	(50)	(50)
INFLAMMATION, NOS				1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#CEREBRUM	(50)	(50)	(50)	(50)
HEMORRHAGE			1 (2%)	
#BRAIN	(50)	(50)	(50)	(50)
HEMORRHAGE	1 (2%)			
HYPERPLASIA, DIFFUSE		1 (2%)		
#BRAIN/THALAMUS	(50)	(50)	(50)	(50)
GLIOSIS	1 (2%)			
*SPINAL CORD	(50)	(50)	(50)	(50)
DEGENERATION, WALLERIAN			1 (2%)	
*TRIGEMINAL GANGLION	(50)	(50)	(50)	(50)
INFLAMMATION, NOS	1 (2%)			
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
SPECIAL SENSE ORGANS				
*EYE/CORNEA	(50)	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)			
*EYE/RETINA	(50)	(50)	(50)	(50)
DEGENERATION, NOS	1 (2%)		1 (2%)	2 (4%)
MUSCULOSKELETAL SYSTEM				
*FEMUR	(50)	(50)	(50)	(50)
FIBROUS OSTEODYSTROPHY				1 (2%)
BODY CAVITIES				
*ABDOMINAL CAVITY	(50)	(50)	(50)	(50)
INFLAMMATION, CHRONIC SUPPURATIV	1 (2%)			
*MESENTERY	(50)	(50)	(50)	(50)
HEMORRHAGE	1 (2%)			
STEATITIS	1 (2%)			
INFLAMMATION, SUPPURATIVE	1 (2%)			
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	1 (2%)		1 (2%)
INFLAMMATION, CHRONIC	3 (6%)	4 (8%)	3 (6%)	8 (16%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
INFLAMMATION, CHRONIC SUPPURATIV		1 (2%)		1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU				1 (2%)
NECROSIS, FAT		1 (2%)		
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
METAPLASIA, OSSEOUS			1 (2%)	
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 ADMINISTERED CYTEMBENA BY INTRAPERITONEAL INJECTION

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	49	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	49	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(49)	(49)	(50)	(50)
EPIDERMAL INCLUSION CYST	1 (2%)			
ULCER, NOS		1 (2%)		
FIBROSIS, FOCAL		1 (2%)		
*SUBCUT TISSUE	(49)	(49)	(50)	(50)
INFLAMMATION, CHRONIC SUPPURATIV		1 (2%)		
RESPIRATORY SYSTEM				
#LUNG	(49)	(49)	(50)	(49)
HYPERPLASIA, ADENOMATOUS				1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	2 (4%)		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(49)	(49)	(50)	(49)
MYELOFIBROSIS	1 (2%)			1 (2%)
APLASIA, HEMATOPOIETIC	1 (2%)			1 (2%)
#SPLEEN	(49)	(49)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
HEMATOPOIESIS	2 (4%)		2 (4%)	
#MANDIBULAR L. NODE	(49)	(49)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
#INGUINAL LYMPH NODE	(49)	(49)	(50)	(50)
HYPERPLASIA, NOS		1 (2%)		
#PEYER'S PATCH	(48)	(49)	(50)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)			

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM				
#HEART	(49)	(49)	(50)	(49)
ENDOCARDITIS, BACTERIAL	1 (2%)			
HYPERPLASIA, FOCAL			1 (2%)	
#MYOCARDIUM	(49)	(49)	(50)	(49)
INFLAMMATION, INTERSTITIAL	18 (37%)	12 (24%)	11 (22%)	6 (12%)
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(48)	(49)	(50)	(50)
EDEMA, NOS			1 (2%)	
#LIVER	(48)	(49)	(50)	(50)
CYTOPLASMIC CHANGE, NOS	5 (10%)	8 (16%)	4 (8%)	3 (6%)
CYTOPLASMIC VACUOLIZATION	3 (6%)	1 (2%)	2 (4%)	
BASOPHILIC CYTO CHANGE		4 (8%)	1 (2%)	2 (4%)
FOCAL CELLULAR CHANGE			1 (2%)	
ANGIECTASIS		1 (2%)	1 (2%)	
#LIVER/CENTRILOBULAR	(48)	(49)	(50)	(50)
CYTOPLASMIC VACUOLIZATION	1 (2%)			
#BILE DUCT	(48)	(49)	(50)	(50)
HYPERPLASIA, FOCAL			1 (2%)	
#PANCREAS	(49)	(49)	(48)	(49)
INFLAMMATION, INTERSTITIAL	3 (6%)	3 (6%)	2 (4%)	
#PANCREATIC ACINUS	(49)	(49)	(48)	(49)
ATROPHY, FOCAL				1 (2%)
#STOMACH	(49)	(49)	(50)	(50)
EDEMA, NOS		1 (2%)		
#GASTRIC SUBMUCOSA	(49)	(49)	(50)	(50)
EDEMA, NOS				1 (2%)
#SMALL INTESTINE	(48)	(49)	(50)	(50)
ULCER, CHRONIC			1 (2%)	
#JEJUNUM	(48)	(49)	(50)	(50)
HEMORRHAGE		1 (2%)		

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#ILEUM	(48)	(49)	(50)	(50)
HEMATOMA, NOS			1 (2%)	
#COLON	(48)	(49)	(50)	(50)
NEMATODIASIS	1 (2%)		3 (6%)	
#COLONIC MUSCULARIS P	(48)	(49)	(50)	(50)
ABSCESS, CHRONIC			1 (2%)	
URINARY SYSTEM				
#KIDNEY	(49)	(49)	(50)	(50)
INFLAMMATION, CHRONIC	6 (12%)	3 (6%)	2 (4%)	3 (6%)
#PERIRENAL TISSUE	(49)	(49)	(50)	(50)
HEMORRHAGE		1 (2%)		
NECROSIS, FAT				1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY	(47)	(47)	(46)	(47)
COLLOID CYST		1 (2%)		
#ADRENAL	(49)	(49)	(50)	(50)
ANGIECTASIS		1 (2%)		
#ADRENAL CORTEX	(49)	(49)	(50)	(50)
MINERALIZATION			1 (2%)	
NECROSIS, FOCAL		1 (2%)		
CYTOPLASMIC VACUOLIZATION		2 (4%)	2 (4%)	
HYPERPLASIA, FOCAL		1 (2%)		1 (2%)
#THYROID	(49)	(49)	(48)	(49)
HYPERPLASIA, C-CELL	1 (2%)	2 (4%)	5 (10%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(49)	(49)	(50)	(50)
CYSTIC DUCTS	25 (51%)	17 (35%)	25 (50%)	32 (64%)
INFLAMMATION, SUPPURATIVE			1 (2%)	
HYPERPLASIA, EPITHELIAL			1 (2%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, CYSTIC	8 (16%)	5 (10%)	14 (28%)	18 (36%)
*MAMMARY DUCT	(49)	(49)	(50)	(50)
HYPERPLASIA, EPITHELIAL			3 (6%)	1 (2%)
HYPERPLASIA, CYSTIC		1 (2%)		
*MAMMARY LOBULE	(49)	(49)	(50)	(50)
HYPERPLASIA, NOS			2 (4%)	3 (6%)
*PREPUTIAL GLAND	(49)	(49)	(50)	(50)
INFLAMMATION, SUPPURATIVE		1 (2%)	1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
INFLAMMATION, CHRONIC SUPPURATIV		1 (2%)		
HYPERPLASIA, NOS		1 (2%)		
*VESTIBULE OF VAGINA	(49)	(49)	(50)	(50)
EPIDERMAL INCLUSION CYST	1 (2%)			
*VAGINA	(49)	(49)	(50)	(50)
INFLAMMATION, NOS				1 (2%)
POLYP	1 (2%)			
#UTERUS/ENDOMETRIUM	(48)	(49)	(50)	(50)
INFLAMMATION, SUPPURATIVE				2 (4%)
HYPERPLASIA, NOS		1 (2%)		
HYPERPLASIA, EPITHELIAL			1 (2%)	
HYPERPLASIA, CYSTIC	7 (15%)	4 (8%)	2 (4%)	5 (10%)
#OVARY/OVIDUCT	(48)	(49)	(50)	(50)
INFLAMMATION, CHRONIC SUPPURATIV		1 (2%)		
METAPLASIA, SQUAMOUS		1 (2%)		
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EYE/RETINA	(49)	(49)	(50)	(50)
DEGENERATION, NOS	3 (6%)	2 (4%)		
*EYELID	(49)	(49)	(50)	(50)
ULCER, FOCAL			1 (2%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	1 (2%)	1 (2%)	
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*MEDIASTINUM	(49)	(49)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
*ABDOMINAL WALL	(49)	(49)	(50)	(50)
INFLAMMATION, NOS			1 (2%)	
*MESENTERY	(49)	(49)	(50)	(50)
MINERALIZATION			1 (2%)	2 (4%)
HEMORRHAGE				1 (2%)
INFLAMMATION, SUPPURATIVE			1 (2%)	
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
INFLAMMATION, CHRONIC	4 (8%)	7 (14%)	14 (28%)	14 (28%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)	1 (2%)		3 (6%)
ABSCESS, CHRONIC		1 (2%)		
NECROSIS, FAT			5 (10%)	8 (16%)
METAPLASIA, OSSEOUS				2 (4%)
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	2	5		
AUTOLYSIS/NO NECROPSY	1	1		

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS
IN MICE ADMINISTERED CYTEMBENA BY INTRAPERITONEAL INJECTION

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED CYTEMBENA BY INTRAPERITONEAL INJECTION

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	49	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(49)	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST	1 (2%)			
ULCER, FOCAL		1 (2%)		
INFLAMMATION, SUPPURATIVE		1 (2%)		
INFLAMMATION, PYOGRANULOMATOUS		2 (4%)		
FIBROSIS				1 (2%)
FIBROSIS, FOCAL				1 (2%)
*SUBCUT TISSUE	(49)	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE				1 (2%)
INFLAMMATION, PYOGRANULOMATOUS	1 (2%)			
RESPIRATORY SYSTEM				
#LUNG	(48)	(50)	(47)	(49)
EDEMA, NOS		1 (2%)		
BRONCHOPNEUMONIA SUPPURATIVE	1 (2%)			
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(46)	(47)	(49)	(49)
MYELOFIBROSIS		1 (2%)		
HYPERPLASIA, GRANULOCYTIC		2 (4%)		2 (4%)
HYPERPLASIA, NEUTROPHILIC			1 (2%)	
#SPLEEN	(47)	(46)	(47)	(49)
ATROPHY, NOS				1 (2%)
HYPERPLASIA, LYMPHOID			1 (2%)	1 (2%)
HEMATOPOIESIS		1 (2%)	1 (2%)	1 (2%)
#MESENTERIC L. NODE	(49)	(48)	(48)	(49)
METAPLASIA, OSSEOUS				1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, LYMPHOID				1 (2%)
#LIVER	(47)	(49)	(49)	(50)
HEMATOPOIESIS				1 (2%)
#PEYER'S PATCH	(44)	(39)	(43)	(45)
HYPERPLASIA, LYMPHOID				2 (4%)
CIRCULATORY SYSTEM				
#HEART	(47)	(50)	(47)	(49)
ENDOCARDITIS, BACTERIAL				2 (4%)
INFLAMMATION, INTERSTITIAL				1 (2%)
INFLAMMATION, SUPPURATIVE				1 (2%)
INFLAMMATION, NECROTIZING				1 (2%)
#MYOCARDIUM	(47)	(50)	(47)	(49)
INFLAMMATION, INTERSTITIAL			1 (2%)	2 (4%)
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(47)	(47)	(49)	(50)
GRANULOMA, NOS				1 (2%)
#LIVER	(47)	(49)	(49)	(50)
CYST, NOS			1 (2%)	
INFLAMMATION, NECROTIZING				1 (2%)
NECROSIS, COAGULATIVE	2 (4%)	1 (2%)	1 (2%)	4 (8%)
CYTOPLASMIC CHANGE, NOS		1 (2%)		
CYTOPLASMIC VACUOLIZATION			1 (2%)	2 (4%)
BASOPHILIC CYTO CHANGE				1 (2%)
FOCAL CELLULAR CHANGE	1 (2%)			
CYTOLOGIC ALTERATION, NOS			1 (2%)	
#LIVER/CENTRILOBULAR	(47)	(49)	(49)	(50)
NECROSIS, COAGULATIVE	1 (2%)			
CYTOPLASMIC VACUOLIZATION			3 (6%)	3 (6%)
#PANCREAS	(46)	(43)	(44)	(48)
INFLAMMATION, INTERSTITIAL	1 (2%)			
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
ABSCESS, CHRONIC				1 (2%)
#PANCREATIC ACINUS	(46)	(43)	(44)	(48)
ATROPHY, NOS	1 (2%)			

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#JEJUNUM	(44)	(39)	(43)	(45)
ABSCESS, CHRONIC			1 (2%)	
HYPERPLASIA, ADENOMATOUS			1 (2%)	
#COLONIC SUBMUCOSA	(44)	(40)	(43)	(47)
INFLAMMATION, CHRONIC FOCAL				1 (2%)
#CECUM	(44)	(40)	(43)	(47)
HEMORRHAGE				1 (2%)
URINARY SYSTEM				
#KIDNEY	(47)	(48)	(48)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)			
INFLAMMATION, CHRONIC	1 (2%)	2 (4%)	1 (2%)	
#KIDNEY/TUBULE	(47)	(48)	(48)	(50)
DILATATION, NOS				1 (2%)
#URINARY BLADDER	(46)	(44)	(45)	(48)
INFLAMMATION, SUPPURATIVE				1 (2%)
INFLAMMATION, CHRONIC				1 (2%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
*URETHRA	(49)	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL				1 (2%)
ENDOCRINE SYSTEM				
#THYROID	(44)	(44)	(44)	(46)
HYPERPLASIA, CYSTIC	1 (2%)			
#PANCREATIC ISLETS	(46)	(43)	(44)	(48)
HYPERPLASIA, NOS				1 (2%)
REPRODUCTIVE SYSTEM				
*PREPUTIAL GLAND	(49)	(50)	(50)	(50)
CYST, NOS		1 (2%)		
*SEMINAL VESICLE	(49)	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE		1 (2%)		

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, CHRONIC				1 (2%)
HYPERPLASIA, EPITHELIAL				1 (2%)
NERVOUS SYSTEM				
#BRAIN	(49)	(50)	(49)	(50)
EPIDERMAL INCLUSION CYST	1 (2%)			
SPECIAL SENSE ORGANS				
*EYE	(49)	(50)	(50)	(50)
PHTHISIS BULBI				1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*ABDOMINAL CAVITY	(49)	(50)	(50)	(50)
INFLAMMATION, CHRONIC				1 (2%)
*ABDOMINAL WALL	(49)	(50)	(50)	(50)
ABSCESS, CHRONIC				1 (2%)
*PERITONEUM	(49)	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE		2 (4%)		
INFLAMMATION, CHRONIC				1 (2%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
INFLAMMATION, CHRONIC SUPPURATIV			2 (4%)	
*PERITONEAL CAVITY	(49)	(50)	(50)	(50)
NECROSIS, FAT		1 (2%)		
*MESENTERY	(49)	(50)	(50)	(50)
HEMORRHAGE		1 (2%)		
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
INFLAMMATION, CHRONIC				1 (2%)
ABSCESS, CHRONIC			1 (2%)	
INFLAMMATION, PYOGRANULOMATOUS				1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(49)	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE		1 (2%)		
ABSCESS, CHRONIC		1 (2%)		
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	17	16	13	11

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

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED CYTEMBENA BY INTRAPERITONEAL INJECTION

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	48	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(48)	(50)	(50)	(50)
INFLAMMATION, PYOGRANULOMATOUS		1 (2%)		
RESPIRATORY SYSTEM				
#LUNG	(46)	(50)	(49)	(48)
INFLAMMATION, INTERSTITIAL				1 (2%)
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(48)	(50)	(48)	(49)
MYELOFIBROSIS		1 (2%)		
#SPLEEN	(47)	(50)	(48)	(49)
HEMATOPOIESIS		1 (2%)	2 (4%)	
#LUMBAR LYMPH NODE	(48)	(50)	(48)	(50)
INFLAMMATION, PYOGRANULOMATOUS	1 (2%)			
#MESENTERIC L. NODE	(48)	(50)	(48)	(50)
CONGESTION, NOS			1 (2%)	
CIRCULATORY SYSTEM				
#HEART	(48)	(50)	(50)	(49)
ENDOCARDITIS, BACTERIAL		1 (2%)	5 (10%)	4 (8%)
INFLAMMATION, NECROTIZING				1 (2%)
#MYOCARDIUM	(48)	(50)	(50)	(49)
INFLAMMATION, INTERSTITIAL				1 (2%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM				
#LIVER	(48)	(50)	(48)	(49)
INFLAMMATION, FOCAL GRANULOMATOU		1 (2%)		
NECROSIS, COAGULATIVE			2 (4%)	1 (2%)
CYTOPLASMIC VACUOLIZATION	1 (2%)		1 (2%)	1 (2%)
CYTOLOGIC ALTERATION, NOS	1 (2%)		1 (2%)	
ANGIECTASIS			1 (2%)	
#LIVER/CENTRILOBULAR	(48)	(50)	(48)	(49)
NECROSIS, COAGULATIVE		1 (2%)		
#PANCREAS	(44)	(47)	(47)	(47)
INFLAMMATION, INTERSTITIAL		1 (2%)		
ATROPHY, NOS				1 (2%)
#GASTRIC MUCOSA	(46)	(50)	(48)	(49)
ATROPHY, NOS				1 (2%)
URINARY SYSTEM				
#KIDNEY	(48)	(50)	(48)	(50)
HYDRONEPHROSIS				1 (2%)
INFLAMMATION, CHRONIC		1 (2%)		
GLOMERULOSCLEROSIS, NOS				1 (2%)
NECROSIS, COAGULATIVE			1 (2%)	
INFARCT, ACUTE			1 (2%)	
#U.BLADDER/SUBMUCOSA	(46)	(50)	(48)	(48)
HEMORRHAGE			1 (2%)	
ENDOCRINE SYSTEM				
#THYROID	(47)	(49)	(48)	(49)
EMBRYONAL REST		1 (2%)		
FOLLICULAR CYST, NOS		1 (2%)		
HYPERPLASIA, NOS		3 (6%)		
REPRODUCTIVE SYSTEM				
#UTERUS	(47)	(49)	(48)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)	1 (2%)		

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANGIECTASIS				1 (2%)
#UTERUS/ENDOMETRIUM	(47)	(49)	(48)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)			
HYPERPLASIA, CYSTIC	37 (79%)	41 (84%)	36 (75%)	39 (78%)
#OVARY	(48)	(49)	(48)	(49)
CYST, NOS		1 (2%)	1 (2%)	
HEMORRHAGE		1 (2%)		
INFLAMMATION, SUPPURATIVE	2 (4%)			
NERVOUS SYSTEM				
#BRAIN/EPENDYMA	(47)	(49)	(49)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)		
#BRAIN	(47)	(49)	(49)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)		
HEMORRHAGE			1 (2%)	1 (2%)
*SPINAL CORD	(48)	(50)	(50)	(50)
MALACIA			1 (2%)	
SPECIAL SENSE ORGANS				
*EYE/CORNEA	(48)	(50)	(50)	(50)
INFLAMMATION, CHRONIC				1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*PERITONEUM	(48)	(50)	(50)	(50)
STEATITIS		1 (2%)		
INFLAMMATION, CHRONIC		1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
INFLAMMATION, GRANULOMATOUS		1 (2%)		1 (2%)
INFLAMMATION, PYOGRANULOMATOUS		1 (2%)		
*MESENTERY	(48)	(50)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)		

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
NECROSIS, FAT		1 (2%)		
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	1	1	4	
AUTO/NECROPSY/HISTO PERF			1	
AUTOLYSIS/NO NECROPSY	2			

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

APPENDIX E

ANALYSIS OF CYTEMBENA LOT. NO. KL-110127
MIDWEST RESEARCH INSTITUTE

APPENDIX E

Analysis of Cytembena Lot No. KL-110127
Midwest Research Institute

Infrared Spectrum (Beckman IR12, KBr pellet)

The spectrum was consistent with a spectrum previously determined (Midwest Research Institute, 1977) (Figure 6).

TITRATION

Procedure: Potentiometric titration of the carboxylate anion with 0.1N HCl.

Results: Four titrations indicate a purity of 99.4%±1.0(δ)%.

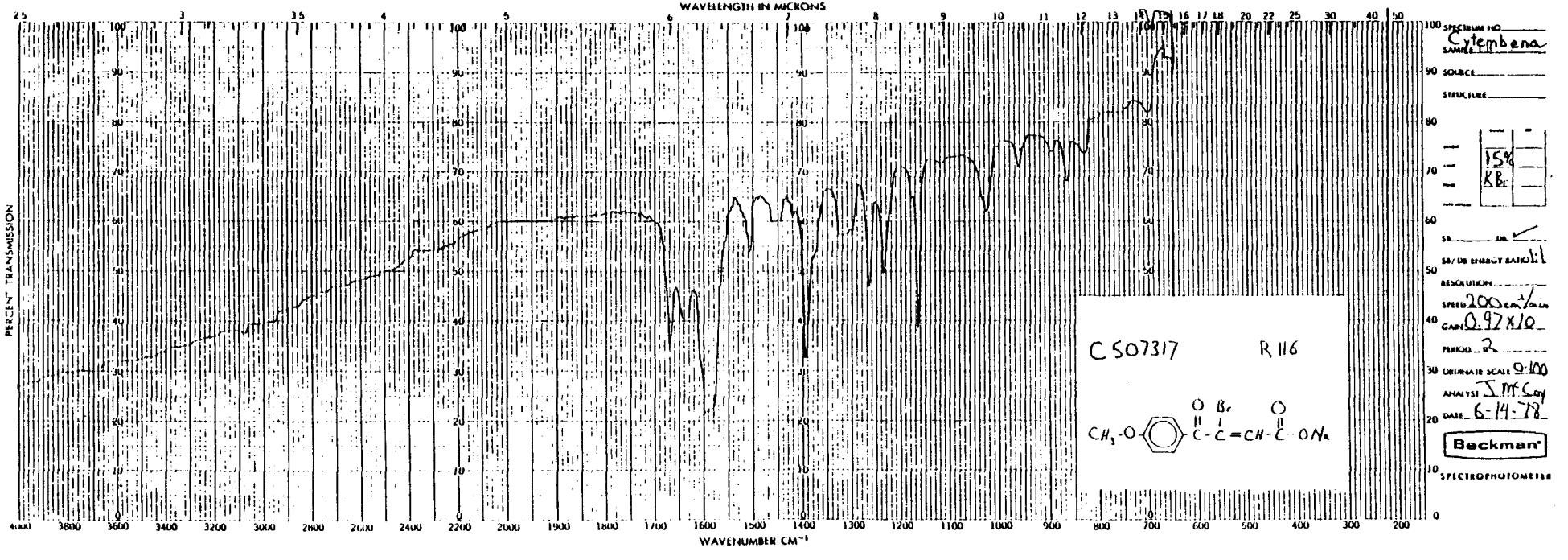

Figure 6. Infrared Absorption Spectrum of Cytembena Lot No. KL-110127

APPENDIX F

ANALYSIS OF CYTEMBENA
LOT NO. MF-II-250
Southern Research Institute

APPENDIX F

Analysis of Cytembena Lot No. MF II-250
Southern Research Institute

A. Elemental Analysis

Element	C	H
Theory:	43.03	2.63
Determined:		
Sample 1	43.15	2.61
Sample 2	43.42	2.64

B. Spectral Data

1. Infrared (Perkin-Elmer 621, 1.6 mg Cytembena/600 mg KBr) (Figure 7)

2. Ultraviolet (Cary 17, solvent Ethanol)

	λ max	ε X 104
Sample 1	290 nm	1.49
	214 nm	1.81
Sample 2	290 nm	1.49
	214 nm	1.80
	295 nm	1.53
	216 nm	1.61

Literature Value
(Stanford Research Institute Report, 1972.)

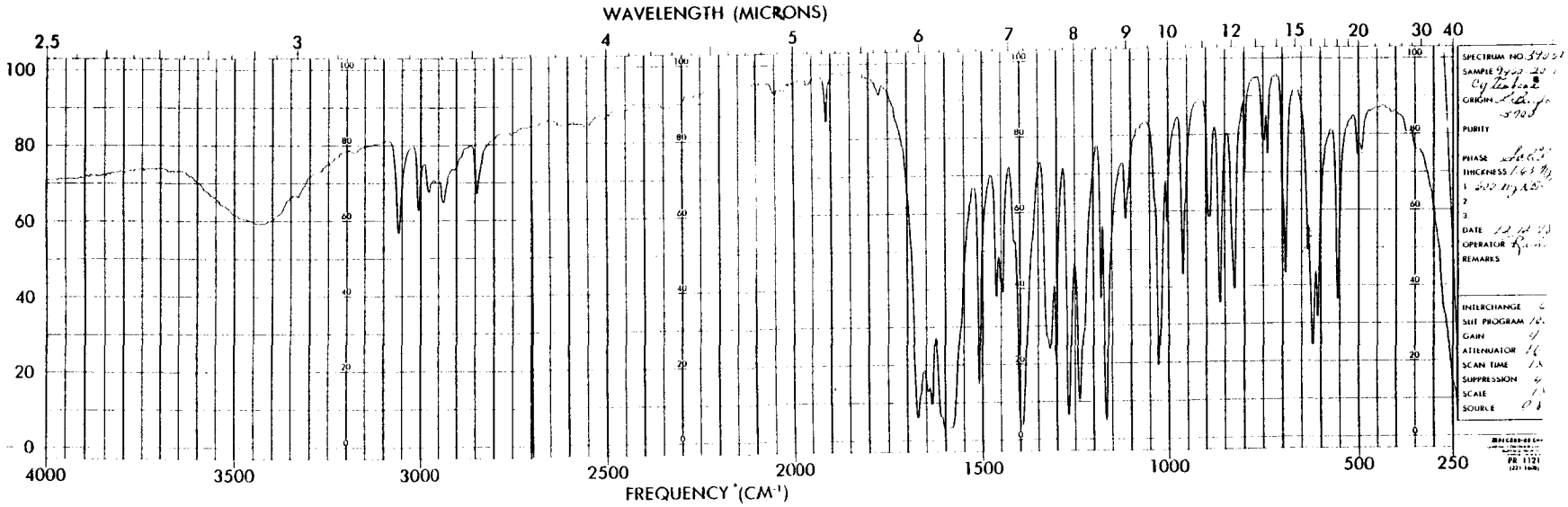

Figure 7. Infrared Absorption Spectrum of Cytembena Lot No. MF-250

APPENDIX G

ANALYTICAL PROCEDURE FOR CYTEMBENA INJECTION MIXTURES

APPENDIX G

Analytical Procedure for Cytembena Injection Mixtures

The concentration of cytembena in the injection solution was determined by ultraviolet absorption spectroscopy. Standards were prepared with the same weight of compound per unit volume of saline as that used in the injection solution. Aliquots of the standard solution and the injection solution were diluted with ethanol for analysis. The absorbance of the standard solution and the injection solution was determined at 293 nm. The concentration of cytembena in the injection solution was calculated from the standard ultraviolet absorption data.

Theoretical Concentration in Saline (ppm)	Number of Samples	Sample Analytical Mean (ppm)	Coefficient of Variation (%)	Range (ppm)
5,600	11	5,520	3.6	5,200-5,740
2,400	12	2,350	5.1	2,150-2,580

U.S. GOVERNMENT PRINTING OFFICE: 1981-341-132/3645

NIH Publication No. 81-1763
May 1981