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**CARCINOGENESIS BIOASSAY
OF
GUAR GUM
(CAS NO. 9000-30-0)
IN F344 RATS AND B6C3F₁ MICE
(FEED STUDY)**

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

NTP Technical Report
on the
CARCINOGENESIS BIOASSAY
of
GUAR GUM
(CAS No. 9000-30-0)
IN F344 RATS AND B6C3F₁ MICE
(FEED STUDY)



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NOTE TO THE READER

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

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

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ABSTRACT

A carcinogenesis bioassay of guar gum, a widely used food stabilizer, was conducted by feeding diets containing 25,000 or 50,000 ppm of the test substance from two batches having purities of 83.5% and 91.9% to 50 F344 rats and 50 B6C3F1 mice of either sex for 103 weeks. Groups of 50 untreated rats and mice of either sex served as controls. The rodents might have tolerated higher doses but 50,000 ppm (5% of diet) is the upper limit for chronic feeding studies in the Bioassay Program, and this level represented the maximum tolerated dose (MTD) for females of both species in the present study.

After week 20 in mice and week 40 in rats, mean body weights of high-dose females were lower than those of the untreated controls. No compound-related clinical signs or adverse effects on survival were observed. Feed consumption by dosed rats and dosed mice of either sex was lower than that of the controls. There were increased incidences of adenomas of the pituitary (8/45, 18% controls; 17/46, 37% low dose; 17/43, 40% high dose) in male rats and pheochromocytomas of the adrenal (0/50, 0%; 5/50, 10%; 6/50, 12%) in female rats, but these differences ($P < 0.035$) were considered to be unrelated to administration of guar gum. When pituitary adenomas or carcinomas and when pheochromocytomas or malignant pheochromocytomas are combined, the statistical differences disappear.

Hepatocellular carcinomas (15/44, 34%; 6/50, 12%; 6/49, 12%) occurred in treated male mice at incidences significantly ($P < 0.011$) lower than that in controls. The combined incidence of male mice with either hepatocellular adenomas or carcinomas (16/44, 36%; 12/50, 24%; 7/49, 14%) was also significantly ($P = 0.013$) lower in the high-dose group.

Under the conditions of this bioassay, guar gum was not carcinogenic for F344 rats or B6C3F1 mice of either sex.

CONTRIBUTORS

The bioassay of guar gum was conducted at EG&G Mason Research Institute, Worcester, Massachusetts, under a subcontract to Tracor Jitco, Inc., the prime contractor for the NCI/NTP Bioassay Program. The prechronic study was started on September 1976 and finished in February 1977; the chronic study was begun in May 1977 and completed in August 1979.

The bioassay was conducted under the direction of Drs. H. Lilja (1) and E. Massaro (1,2), principal investigators. Doses of the test chemical were selected by Drs. J. Robens (3,4), C. Cueto (6), and O. Fitzhugh (3,7). The program manager was Ms. R. Monson (1). Ms. A. Good (1) supervised the technicians in charge of animal care, and Ms. E. Zepp (1) supervised the preparation of the feed mixtures and collected samples of the diets for analysis. Ms. D. Bouthot (1) kept all daily records of the test. Dr. A. Russfield (1), pathologist, directed the necropsies and performed the histopathologic evaluations. The pathology report and selected slides were evaluated by the NCI Pathology Working Group as described in Ward et al. (1978). The diagnoses represent a consensus of contracting pathologists and the NCI Pathology Working Group, with final approval by the NCI Pathology Working Group.

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute, Rockville Maryland (8). The statistical analyses were performed by Dr. J. R. Joiner (3) and Mr. J. Warner (3) using methods selected for the bioassay program by Dr. J. J. Gart (9). Chemical analyses were conducted at Midwest Research Institute (10).

This report was prepared at Tracor Jitco (3). Those responsible for the report at Tracor Jitco were Dr. C. Cueto (6), Director of Bioassay Program; Dr. S. S. Olin, Associate Director; Dr. M. A. Stedham, pathologist; Dr. J. Tomaszewski, chemist; Dr. W. D. Theriault, reports manager; and Dr. A. C. Jacobs, bioscience writer.

The following scientists at NTP (5) were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. Michael P. Dieter (Chemical Manager), Dr. J. Fielding Douglas, Dr. Charles Grieshaber, Dr. James Huff, Dr. Joseph Haseman, Dr. Ernest E. McConnell, Dr. John A. Moore, Dr. Sherman F. Stinson, Dr. Raymond Tennant, and Dr. Jerrold M. Ward.

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SUMMARY OF PEER REVIEW COMMENTS

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

Dr. Schwetz, a principal reviewer for the technical report on the carcinogenesis bioassay of guar gum, agreed with the conclusion that guar gum was not carcinogenic for F344 rats or B6C3F1 mice of either sex. He commented that there were two batches of test material with differing purity, one of 83.5 percent and the other of 91.9 percent, and it was not identified as to whether either was food grade. Further, the stability of guar gum in the feed was not characterized, nor were the concentrations verified. He said the summary should state that 50,000 ppm, the upper dose level, is the upper limit recommended for feeding studies in the bioassay program. He indicated that more information should be given in the introduction about the earlier study by Krantz, especially on the strain of rat used. The duration over which food consumption was measured should be stated. Finally, Dr. Schwetz was critical of the poorly controlled environmental conditions under which the animals were maintained. The temperature range of 17 to 31 degrees C and the humidity range of 10 to 88 percent were intolerable.

As Dr. Whittemore, another principal reviewer, was not present, Dr. Hitchcock read her review. Dr. Whittemore, in her review, also agreed with the conclusion of the report. She reported that pituitary adenomas were significantly elevated in dosed male rats as compared with controls, but not in female rats or in mice. Non-malignant adrenal pheochromocytomas were significantly elevated in female rats, but this difference could be due to better survival in dosed rats. She said that an MTD was probably not reached but realized that this was because 50,000 ppm was the upper limit for feeding studies under program guidelines. Dr. Harper, as a third principal reviewer, noted that there were increased incidences of fibromas of subcutaneous tissues in male rats (0/50, 1/50, 4/50).

Dr. Schwetz moved that the report on the bioassay of guar gum be accepted and the summary be revised to state that 50,000 ppm is the upper limit recommended for chronic feeding studies. Dr. Harper seconded the motion and the report was approved unanimously by the Peer Review Panel.

I. INTRODUCTION

Guar gum (CAS No. 9000-30-0) is the milled endosperm of the leguminous plant Cyanopsis tetragonolobus. Structurally, it is a galactomannan consisting of a main chain of D-mannose with a side chain of D-galactose at approximately every second mannose unit. The mannose units are β -(1-4) linked, and the single D-galactose units are joined to the main chain by α -(1-6) linkages. The molecular weight is 220,000 (Chudzikowski, 1971).

Guar gum is approved for use as a food additive by the U.S. Food and Drug Administration and is on the list of substances "generally recognized as safe" (CFR 1974). The Food Chemicals Codex (1972) specifies that guar gum contain not less than 66.0% galactomannans and not more than 15% water, 10% protein, 7% acid-insoluble material, and 1.5% ash. It is widely used in the food industry as a stabilizer for ice cream, as a thickener or stabilizer for beverages, salad dressings, and pie fillings, and as a binder in processed meat (Furia, 1972). The following products may contain guar gum at the approximate concentrations listed: breakfast cereals, processed vegetables, sweet sauces, and cheeses (1,200-7,800 ppm); milk products and imitation dairy products (1,700-4,200 ppm); fruit ices, fats and oils, snack foods, and frozen dairy products (1,200-2,700 ppm); beverages, baked goods, processed fruits, and soups (1,200 ppm); condiments and relishes, meat products, and gelatin puddings (200 ppm) (Life Sciences Research Office, 1973).

Guar is used in cosmetics as an emulsifier and stabilizer and in pharmaceuticals as a tablet binder and disintegrant, an appetite depressant, a laxative, and a treatment for peptic ulcers (Kirk and Othmer, 1966; Merck, 1968).

Guar is used in industry as an additive to strengthen paper; a sizing and finishing agent for textiles; a thickener for dyestuffs, battery electrolytes, printing inks, agricultural sprays, and caulking materials; a stabilizer for foams and flotation materials (in mining); and as a binder,

thickener, a stabilizing agent for enamels and porcelain (Kirk and Othmer, 1966).

In 1970, 13 million kilograms of guar gum were imported into the United States (Life Sciences Research Office, 1973). More recent production figures are not available.

The oral LD₅₀ of guar gum is 8.1 g/kg for mice and 9.4 g/kg for rats (Bailey and Morgareidge, 1976).

When tested without metabolic activation, guar gum was mutagenic for Saccharomyces cerevisiae D-3, but not for Salmonella typhimurium TA 1530 or G-46 (Green, 1977). Guar gum caused chromosome aberrations in human embryonic lung cells (WI-38) (Green, 1977).

No compound-related histopathologic effects were observed in the liver, kidney, spleen, gut, or bone marrow when groups of 7 or 8 rats (strain unknown) of either sex were fed diets containing 50,000 ppm guar gum for 24 months (Krantz, 1948).

Guar gum was tested by the Bioassay Program because of its widespread use in food. The only previous test for carcinogenicity was considered inadequate because only one species was used and because the number of animals was considered small by current standards (Krantz, 1948).

II. MATERIALS AND METHODS

A. Chemical

Guar gum was obtained in two batches from Stein Hall Company (Louisville, KY), a division of the Celanese Polymer Specialties Company. Lot No. A-40-F was used for the subchronic studies and the first 3 months of the chronic studies. Lot F10-77-966-1 was used for the remainder of the chronic studies.

Purity and identity analyses were performed at Midwest Research Institute (Appendix E). Results from the titration of hydrolysis products by periodate oxidation indicated that Lot No. A-40-F was 83.5% pure and that Lot No. F10-77-966-1 was 91.9% pure relative to glucose. Results of Karl Fischer titrations indicated 7.3% water in Lot No. A-40-F and 4.9% water in Lot No. F10-77-966-1. Mannose and galactose were identified by thin-layer chromatography as the major and minor components, respectively, in the hydrolysates of both batches. A trace impurity was detected in the hydrolysate of Lot No. F10-77-966-1. The infrared spectra of both batches were consistent with the literature spectra. The bulk compound was stored in the dark at 4°C.

Throughout the course of the studies, the bioassay laboratory monitored the chemical by infrared spectroscopy and saw no change in the spectra.

B. Dietary Preparation

Test diets were prepared by first mixing the chemical with an aliquot of Wayne Lab Blox[®] meal (Table 1) in a mortar and pestle and then layering this mixture in a Patterson-Kelly[®] twin-shell V-blender (without an intensifier bar) with the remainder of the feed and mixing for 10 minutes. Test diets were sealed in labelled plastic bags and stored at 4°C for no longer than 7 days.

Due to similar components in guar gum and the feed, the quantitative method available could not measure chronic dose levels of guar gum in feed

Table 1. Source and Description of Materials Used for Animal Maintenance

Item	Description	Source
Animal Feed	Wayne Lab Blox [®] Meal	Allied Mills (Chicago, IL)
Feed Hoppers	Stainless steel, gang style	Scientific Cages, Inc. (Bryan, TX)
Cages	Polycarbonate	Lab Products, Inc. (Rochelle Park, NJ)
Filter Sheets	Disposable, nonwoven fiber	Lab Products, Inc. (Rochelle Park, NJ)
Bedding	Hardwood chips:	
	Aspen bed [®]	American Excelsior (Baltimore, MD)
	Beta [®] Chips	Agway Corp. (Syracuse, NY)

reproducibility within +10%. Thus, formulated diets were not analyzed for concentrations of guar gum during the study.

C. Animals

Subchronic

Three-week-old F344 rats and 4-week-old B6C3F1 mice were obtained from the NCI Frederick Cancer Research (Frederick, Maryland). The animals were observed for 7 days and then assigned to control or dosed groups in such a manner that average cage weights were approximately equal.

Chronic

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 animals were observed for 2 weeks, randomly assigned to individual cages, and the cages were randomly assigned to dosed and control groups.

D. Animal Maintenance

Rats and mice were housed five per cage in suspended polycarbonate cages equipped with disposable nonwoven filter sheets (Table 1). Hardwood chip bedding and cages were changed twice weekly, and cage racks were changed every 2 weeks. Water and Wayne Lab Blox[®] meal were available ad libitum, the former supplied through an Edstrom automatic watering system and the latter in stainless steel, gang-style hoppers that were changed once per week.

The temperature of animal rooms was 17^o-31^oC (average 23^oC) and relative humidity was controlled (10%-88%). Incoming air was filtered through Tri-Dek 15/40 denier Dacron filters, with 10 room air changes per hour. Fluorescent lighting was provided 12 hours per day.

Rats and mice were housed by species in separate rooms in which chronic feeding studies were being conducted on di(2-ethylhexyl)phthalate (CAS 117-81-7), butyl benzyl phthalate (CAS 85-68-7), and di(2-ethylhexyl)adipate (CAS 103-23-1).

E. Acute Oral Toxicity and Repeated Dose Studies

Acute oral and repeated dose feed studies were conducted using F344 rats and B6C3F1 mice to determine the toxicity of guar gum and the concentrations to be used in the subchronic studies.

In the acute study, five males and five females of each species were administered a single dose (0.42 g/kg) of the test substance in water by gavage. No mortality or compound-related effects were observed. All animals were killed on day 15.

In the repeated dose study, groups of five males and five females of each species were fed diets containing 0, 6,300, 12,500, 25,000, 50,000, or 100,000 ppm guar gum for 2 weeks. No mortality or compound-related effects were observed. All animals were killed on day 15.

F. Subchronic Studies

Subchronic studies were conducted to determine the concentrations to be used in the chronic studies. Diets containing 0, 6,300, 12,500, 25,000, 50,000, or 100,000 ppm guar gum were fed for 13 weeks to groups of 10 males and 10 females of each species (Tables 2 and 3).

Mortality and morbidity checks were made twice daily; individual animals were weighed and feed consumption by cage was determined weekly. At the end of the 91-day study, survivors were killed, necropsies were performed on all animals, and tissues (see section H) were taken for histopathologic examinations.

Table 2. Dosage, Survival, and Mean Body Weights of Rats Fed Diets Containing Guar Gum for 91 Days

Dose (ppm)	Survival (a)	Mean Body Weights (grams)			Weight Change Relative to Controls (b) (Percent)
		Initial	Final	Change	
<u>MALE</u>					
0	10/10	112	339	+227	
6,300	10/10	110	332	+222	-2
12,500	10/10	111	332	+221	-3
25,000	10/10	112	327	+215	-5
50,000	10/10	111	322	+211	-7
100,000	10/10	111	302	+191	-16
<u>FEMALE</u>					
0	10/10	95	195	+100	
6,300	10/10	97	202	+105	+5
12,500	10/10	95	195	+100	0
25,000	10/10	94	198	+104	+4
50,000	9/10	95	197	+102	+2
100,000	9/10	95	192	+97	-3

(a) Number surviving/number per group

(b) Weight Change Relative to Controls =

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

Table 3. Dosage, Survival, and Mean Body Weights of Mice Fed Diets Containing Guar Gum for 91 Days

Dose (ppm)	Survival (a)	Mean Body Weights (grams)			Weight Change Relative to Controls (b) (Percent)
		Initial	Final	Change	
<u>MALE</u>					
0	10/10	20.2	32.5	+12.3	
6,300	10/10	20.4	32.8	+12.4	+1
12,500	10/10	20.4	32.0	+11.6	-6
25,000	10/10	20.2	31.8	+11.6	-6
50,000	10/10	20.7	32.3	+11.6	-6
100,000	10/10	20.7	31.9	+11.2	-9
<u>FEMALE</u>					
0	10/10	16.9	27.6	+10.7	
6,300	10/10	16.7	26.8	+10.1	-6
12,500	10/10	17.1	27.3	+10.2	-5
25,000	10/10	16.7	26.4	+9.7	-9
50,000	10/10	17.0	26.1	+9.1	-15
100,000	9/10	16.5	25.5	+9.0	-16

(a) Number surviving/number per group

(b) Weight Change Relative to Controls =

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

Rats: Two female rats died; one receiving 50,000 ppm and one receiving 100,000 ppm. Weight gain as compared with controls was depressed 16% in male rats receiving 100,000 ppm. A dose-related decrease in feed consumption was observed for rats of either sex. Feed consumption by rats fed 100,000 ppm was 80% that of the controls. No compound related clinical signs or histopathologic effects were detected.

Doses selected for rats for the chronic study were 25,000 ppm and 50,000 ppm, since the upper limit recommended for chronic feeding studies in the Bioassay Program is 50,000 ppm (NCI, 1976).

Mice: One female mouse receiving 100,000 ppm died. Weight gain as compared with controls was depressed by 15% or 16% in female mice receiving 50,000 or 100,000 ppm. Feed consumption by dosed mice of either sex was comparable with or higher than that of the corresponding controls. No compound related clinical signs or histopathologic effects were observed.

Doses selected for mice for the chronic study were 25,000 or 50,000 ppm guar gum in feed.

G. Chronic Studies

The number of animals per group, the concentrations of guar gum administered in the feed, and the duration of the chronic studies are shown in Table 4. Dosed groups were given diets containing guar gum for 103 consecutive weeks, followed by 1 to 3 weeks on basal diet.

H. Clinical Examinations and Pathology

Animals were observed twice daily for morbidity and mortality; individual clinical signs, individual body weights and feed consumption by cage were recorded every 4 weeks. The mean animals in the group by the number of (surviving) animals in the group. The average feed consumption per animal was calculated by dividing the total feed consumption measured for all cages by the number of surviving animals in the group. Animals that were moribund

Table 4. Experimental Design of Chronic Feeding Studies with Guar Gum in Rats and Mice

Test Group	Initial No. of Animals	Guar Gum (ppm)	Weeks on Study	
			Dosed (a)	Not Dosed
<u>Male Rats</u>				
Untreated-Control (b)	50	0	0	105
Low-Dose	50	25,000	103	1
High-Dose	50	50,000	103	1
<u>Female Rats</u>				
Untreated-Control (b)	50	0	0	104-105
Low-Dose	50	25,000	103	1
High-Dose	50	50,000	103	1
<u>Male Mice</u>				
Untreated-Control (b)	50	0	0	106
Low-Dose	50	25,000	103	3
High-Dose	50	50,000	103	2
<u>Female Mice</u>				
Untreated-Control (b)	50	0	0	106
Low-Dose	50	25,000	103	3
High-Dose	50	50,000	103	3

(a) The start dates were August 8, 1977 for rats and May 12, 1977 for mice. The kill dates were August 8, 1979 for rats and May 18, 1979 for mice.

(b) Control and dosed groups were of the same strain, sex, and age range and from the same source and shipment. All animals of the same strain shared the same room, and all aspects of animal care and maintenance were similar. Animals were randomized to dosed and control groups as described in Section II.C.

and those that survived to the end of the study were killed using carbon dioxide inhalation and necropsied.

Gross and microscopic examinations were performed on major tissues, organs, and all gross lesions from killed animals and from animals found dead unless precluded in whole or in part by autolysis or cannibalization. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and does not necessarily represent the number of animals that were placed on study in each group.

The tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following were examined microscopically: skin (abdominal), lungs and bronchi, trachea, bone, bone marrow (femur) and thigh muscle, spleen, lymph nodes, thymus, heart, salivary glands, liver pancreas, esophagus, stomach, duodenum, jejunum, ileum,, cecum, colon, kidney, urinary bladder, pituitary, adrenal, thyroid parathyroid, testis, prostate, mammary gland uterus, ovary, brain epididymus, and all tissue masses.

I. 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 have been

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

The incidence of neoplastic or noneoplastic 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 include 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) before histological sampling or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the number of animals necropsied.

The purpose of the statistical analyses for 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 the results from two dosed groups are compared simultaneously with that for a control, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality criterion (Miller, 1966) requires that the P values for any comparison be less than or equal to 0.025. When this correction was used, it is discussed in the narrative section. It is not presented in the tables, where the Fischer 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.

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 test, etc.) were followed.

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

The approximate 95 percent confidence interval for the relative risk of each dose 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 less than 0.025 one-tailed test when the control incidence is not zero, P less than 0.05 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)

After 40 weeks, mean body weights of high-dose female rats were consistently lower than those of the controls (Figure 1 and Table 5). A dose-related decrease in feed consumption was observed for rats of either sex. For male rats feed consumption in the low- and high-dose groups averaged 92% and 86% of the control values, respectively (Appendix F, Tables F1 and F2). For female rats the corresponding figures were 85% and 79%. Clinical signs observed for dosed and control animals were comparable.

B. Survival (Rats)

Estimates of the probabilities of survival of male and female rats fed diets containing guar gum at the concentrations of this bioassay, together with those of the control group, are shown by the Kaplan and Meier curves in Figure 2. The female control group had a statistically significant lower survival than either of the dosed groups. No significant differences in survival were observed between the female dosed groups or between any of the groups of male rats.

In male rats, 31/50 (62%) of the controls, 31/50 (62%) of the low-dose, and 33/50 (66%) of the high-dose group lived to the end of the study at 104-105 weeks. In female rats, 25/50 (50%) of the controls, 41/50 (82%) of the low-dose, and 37/50 (74%) of the high-dose group lived to the end of the study at 104-105 weeks.

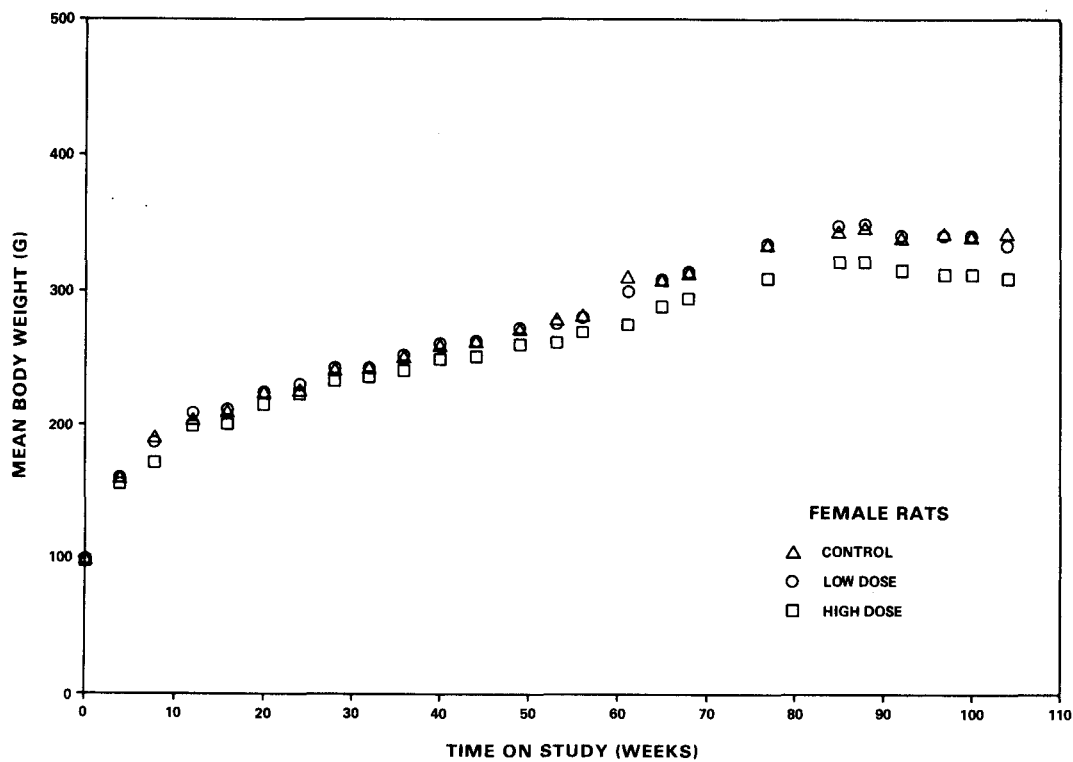
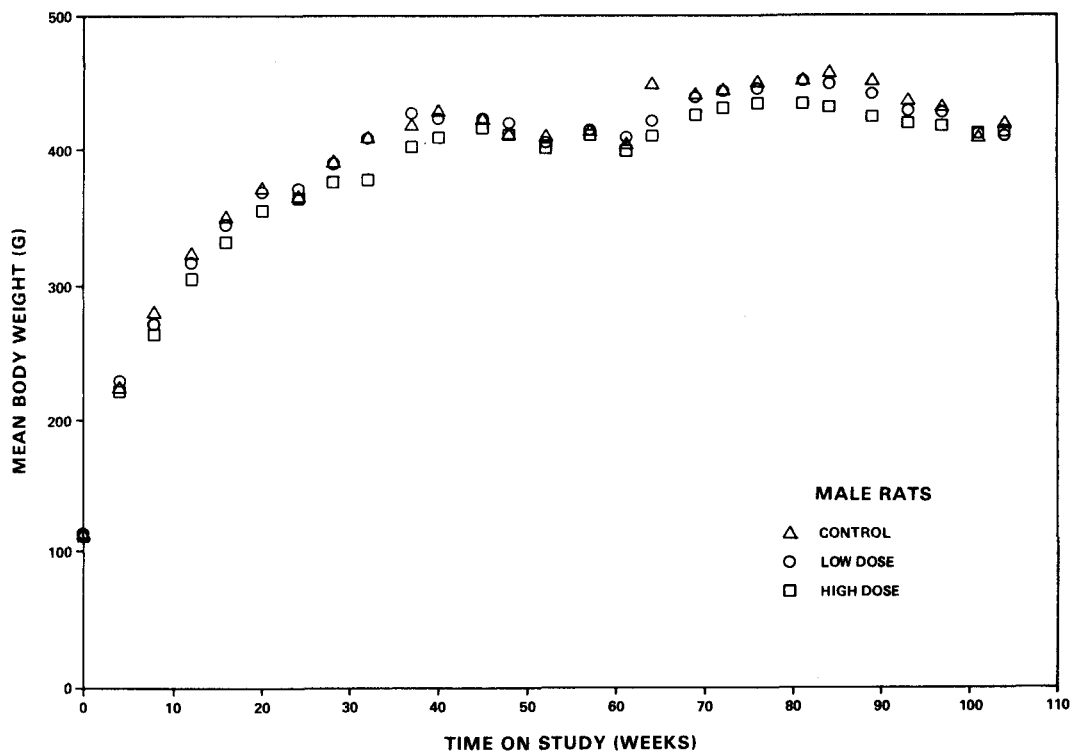


Figure 1. Growth Curves for Rats Fed Diets Containing Guar Gum

Table 5. Mean Body Weight Change (Relative to Controls) of Rats Fed Diets Containing Guar Gum

Week No.	Control	Mean Body Weight change (grams)		Weight Change Relative to Controls percent (a)	
		Low-Dose	High-Dose	Low-Dose	High-Dose
Males					
0	113 (b)	112 (b)	104 (b)		
4	112	115	111	+3	-1
24	352	357	353	+1	0
45	311	311	315	0	+1
64	337	309	301	-8	-11
84	345	330	322	-4	-7
104	306	295	301	-4	-2
Females					
0	97 (b)	97 (b)	96 (b)		
4	62	62	59	0	-5
24	129	134	128	+4	-1
44	166	166	156	0	-6
65	210	210	192	0	-9
85	247	250	227	+1	-8
104	246	237	215	-4	-13

(a) $\text{Weight Change Relative to Controls} = \frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$

(b) Initial weight

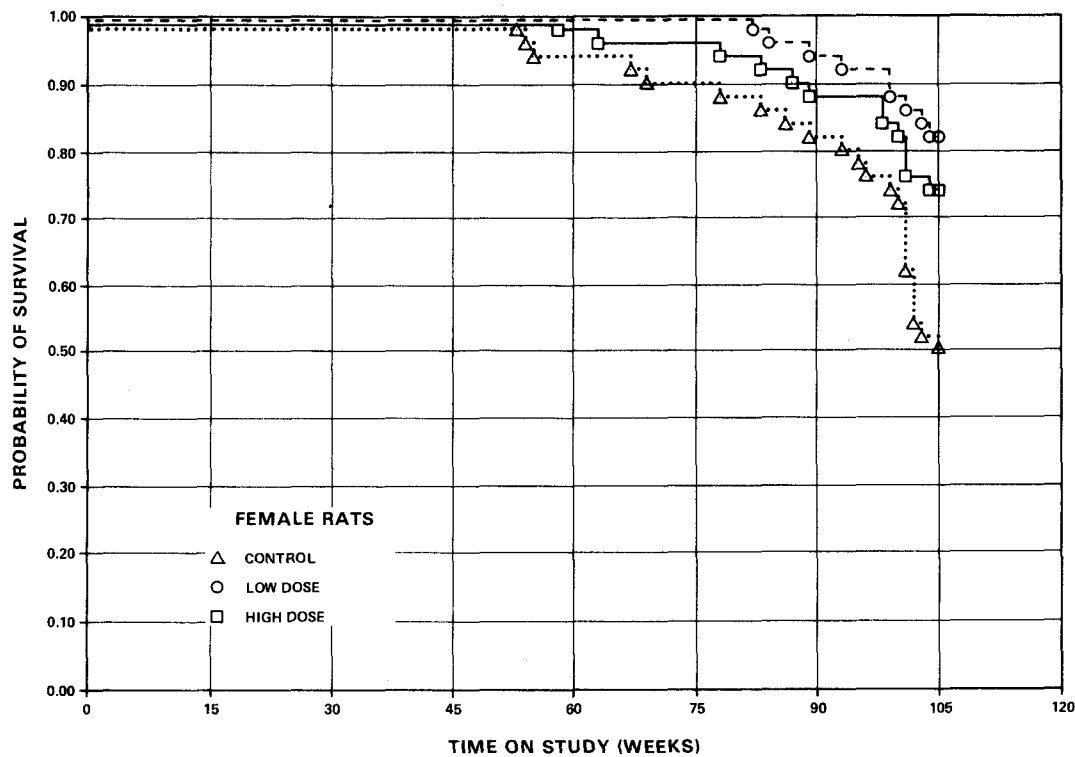
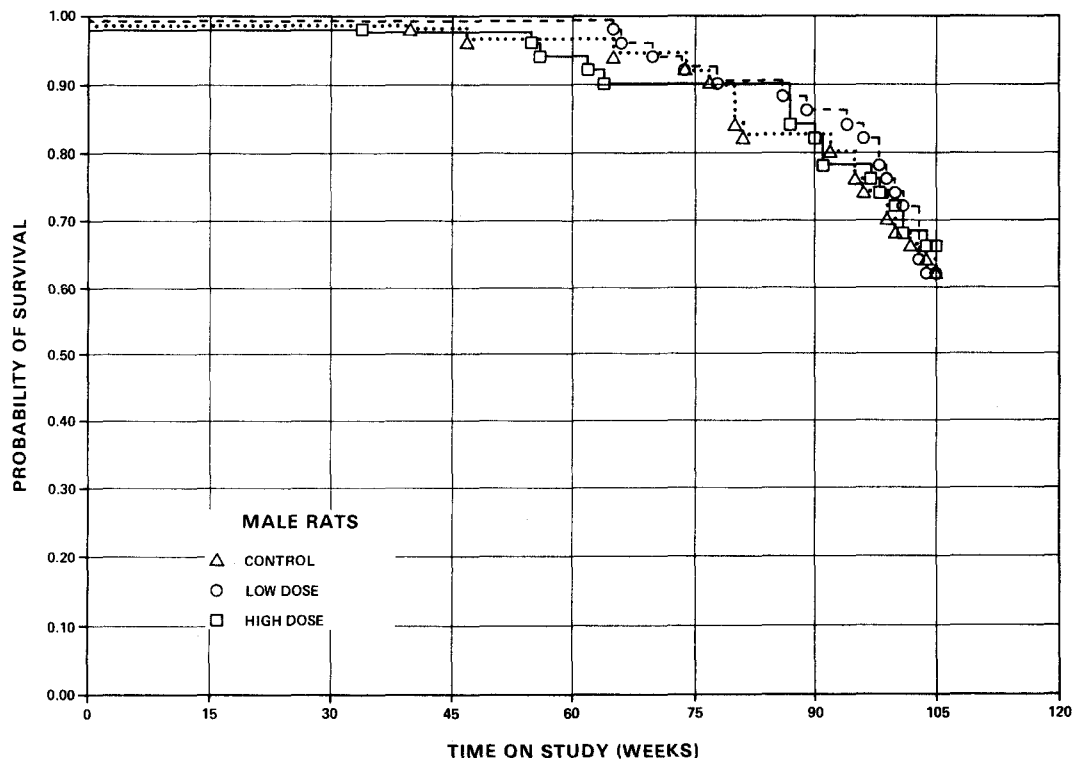


Figure 2. Survival Curves for Rats Fed Diets Containing Guar Gum

C. Pathology (Rats)

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

A variety of neoplasms was observed in this study. Except for those mentioned below, the neoplasms were of a type, incidence, and distribution commonly seen in aging F344 rats. Among rats receiving the high dose of guar gum as compared with the controls, there was an increased incidence of subcutaneous fibromas in males and in subcutaneous fibrosarcomas and pheochromocytomas in females. As the numbers of these tumors were very small, these findings are not considered to be related to administration of the test compound. Pituitary tumors were more frequent in dosed male rats than in the controls, but the numbers observed were within the range of historical variation. The incidence of mammary tumors, most of which were fibroadenomas, was lower in dosed female rats than in the controls.

Rats in all groups exhibited a variety of nonneoplastic degenerative and inflammatory lesions. None was associated with administration of the compound.

The results of histopathologic examination indicated that guar gum was not carcinogenic for F344 rats under the condition of this bioassay.

D. Statistical Analyses of Results (Rats)

Tables 6 and 7 contain the statistical analysis of those primary tumors that met both of the following criteria: 1) At least two animals in one group had the tumor, and 2) The incidence in one or more groups was at least 5%.

Fibromas of the subcutaneous tissue in male rats were observed in increasing incidence (0/50, 0% in the controls; 1/50, 2% in the low-dose; and 4/50, 8% in the high-dose). The Cochran-Armitage test for linear trend

was statistically significant ($P=0.026$), but the Fisher exact tests were not significant. The historical incidence of untreated male rats with fibroma of the skin or subcutaneous tissue observed at this laboratory is 33/916 (3.6%). This tumor did not appear in statistically significant incidence in female rats.

Adenomas of the pituitary in male rats were observed in a statistically significant positive relation in the dosed groups compared with the untreated control group (8/45, 18% in the controls; 17/46, 37% in the low-dose; and 17/43, 40% in the high-dose). The Cochran-Armitage test for linear trend was statistically significant ($P=0.018$), and the Fisher exact test between the dosed groups and the untreated control group was significant for the high-dose group ($P=0.021$); the value for the low-dose group ($P=0.034$) is above the value of $P=0.025$ required by the Bonferroni inequality criterion for an overall significance of $P=0.05$ when two dosed groups are compared with a common control group. The incidence of male rats with either adenomas or carcinomas of the pituitary was not statistically significant (13/45, 29% in the controls; 17/46, 37% in the low-dose; 19/43, 44% in the high-dose). The historical incidence of untreated male F344 rats with adenomas or carcinomas of the pituitary at this laboratory is 140/819 (17.1%). When a life table analysis was performed, using death as the time point of examination for pituitary adenomas or carcinomas, there was no statistically significant result. In female rats, these tumors were not observed in statistically significant proportions.

Pheochromocytomas of the adrenal in female rats were observed in a statistically significant positive relation in the dosed groups compared with the control group (0/50, 0% in the controls; 5/50, 10% in the low-dose; and 6/50, 12% in the high-dose). The Cochran-Armitage test for linear trend was statistically significant ($P=0.018$), and the Fisher exact test between the dosed groups and the untreated control group was significant for the high-dose group ($P=0.013$); the value for the low-dose group ($P=0.028$) is above the value of $P=0.025$ required by the Bonferroni inequality criterion for an overall significance of $P=0.05$ when two dosed groups are compared with a common control group. The combined incidence of female rats with

either pheochromocytoma or malignant pheochromocytoma of the adrenals was not statistically significant (1/50, 2% in the controls; 6/50, 12% in the low-dose; 6/50, 12% in the high-dose). The historical incidence of untreated female F344 rats with pheochromocytomas or malignant pheochromocytomas at this laboratory is 42/958 (4.4%). Pheochromocytomas of the adrenal in male rats were observed in decreasing incidence (18/50, 36% in the controls; 14/50, 28% in the low-dose; and 13/49, 27% in the high-dose). The combined incidence of male rats with either pheochromocytomas or malignant pheochromocytomas of the adrenals was not statistically significant (19/50, 38% in the controls; 19/50, 38% in the low-dose; 15/49, 31% in the high-dose).

Time adjusted analysis, eliminating those animals dying before 52 weeks, and life table analysis, using death as the time point of examination for tumors, did not materially alter the conclusions presented above.

Table 6. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing Guar Gum (a)

Topography: Morphology	Untreated Control	Low Dose	High Dose
Subcutaneous Tissues:			
Fibroma (b)	0/50(0)	1/50(2)	4/50(8)
P Values (c),(d)	P=0.026	N.S.	N.S.
Relative Risk (Control) (e)		Infinite	Infinite
Lower Limit		0.054	0.927
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	104	100
Hematopoietic System:			
Lymphoma, All Malignant (b)	2/50(4)	4/50(8)	3/50(6)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		2.000	1.500
Lower Limit		0.301	0.180
Upper Limit		21.316	17.329
Weeks to First Observed Tumor	74	100	87
Hematopoietic System:			
Leukemia, NOS (b)	13/50(26)	12/50(24)	12/50(24)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.923	0.923
Lower Limit		0.428	0.428
Upper Limit		1.971	1.971
Weeks to First Observed Tumor	80	78	87

Table 6. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing Guar Gum (a)

(Continued)

Topography: Morphology	Untreated Control	Low Dose	High Dose
Hematopoietic System: Lymphoma Malignant or Leukemia (b)	15/50(30)	16/50(32)	15/50(30)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.067	1.000
Lower Limit		0.558	0.513
Upper Limit		2.050	1.948
Weeks to First Observed Tumor	74	78	87
Liver: Neoplastic Nodule or Hepatocellular Carcinoma (b)	3/50(6)	0/50(0)	1/49(2)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.000	0.340
Lower Limit		0.000	0.007
Upper Limit		1.663	4.062
Weeks to First Observed Tumor	96	--	90
Pituitary: Adenoma (b)	8/45(18)	17/46(37)	17/43(40)
P Values (c),(d)	P=0.018	P=0.034	P=0.021
Relative Risk (Control) (e)		2.079	2.224
Lower Limit		0.995	1.025
Upper Limit		4.962	5.263
Weeks to First Observed Tumor	95	89	55

Table 6. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing Guar Gum (a)

(Continued)

Topography: Morphology	Untreated Control	Low Dose	High Dose
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Pituitary:			
Carcinoma, NOS (b)	5/45(11)	0/46(0)	2/43(5)
P Values (c),(d)	N.S.	P=0.026(N)	N.S.
Relative Risk (Control) (e)		0.000	0.419
Lower Limit		0.000	0.042
Upper Limit		0.773	2.401
Weeks to First Observed Tumor	105	--	104
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Pituitary: Adenoma, or			
Carcinoma, NOS (b)	13/45(29)	17/46(37)	19/43(44)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.279	1.530
Lower Limit		0.668	0.825
Upper Limit		2.506	2.899
Weeks to First Observed Tumor	95	89	55
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Adrenal:			
Pheochromocytoma (b)	18/50(36)	14/50(28)	13/49(27)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.778	0.737
Lower Limit		0.406	0.376
Upper Limit		1.463	1.408
Weeks to First Observed Tumor	102	66	97
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Table 6. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing Guar Gum (a)

(Continued)

Topography: Morphology	Untreated Control	Low Dose	High Dose
Adrenal: Pheochromocytoma, Malignant (b)	1/50(2)	5/50(10)	2/49(4)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		5.000	2.041
Lower Limit		0.588	0.110
Upper Limit		231.346	117.931
Weeks to First Observed Tumor	105	98	104
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant (b)	19/50(38)	19/50(38)	15/49(31)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.000	0.806
Lower Limit		0.576	0.434
Upper Limit		1.737	1.469
Weeks to First Observed Tumor	102	66	97
Thyroid: C-Cell Adenoma or Carcinoma (b)	1/50(2)	1/49(2)	3/47(6)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.020	3.191
Lower Limit		0.013	0.267
Upper Limit		78.488	163.836
Weeks to First Observed Tumor	105	104	90

Table 6. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing Guar Gum (a)

(Continued)

Topography: Morphology	Untreated Control	Low Dose	High Dose
Pancreatic Islets: Islet-Cell Adenoma or Carcinoma (b)	3/46(7)	0/48(0)	2/44(5)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.000	0.697
Lower Limit		0.000	0.061
Upper Limit		1.591	5.790
Weeks to First Observed Tumor	80	--	104
Preputial Gland: Carcinoma, NOS (b)	5/50(10)	4/50(8)	3/50(6)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.800	0.600
Lower Limit		0.168	0.098
Upper Limit		3.499	2.910
Weeks to First Observed Tumor	77	103	97
Preputial Gland: Adenoma, NOS or Carcinoma, NOS (b)	7/50(14)	5/50(10)	4/50(8)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.714	0.571
Lower Limit		0.191	0.130
Upper Limit		2.434	2.099
Weeks to First Observed Tumor	77	103	97

Table 6. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing Guar Gum (a)

(Continued)

Topography: Morphology	Untreated Control	Low Dose	High Dose
Testis: Interstitial-Cell Tumor (b)	36/48(75)	38/50(76)	38/46(83)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.013	1.101
Lower Limit		0.795	0.872
Upper Limit		1.293	1.360
Weeks to First Observed Tumor	92	78	87

- (a) Dosed groups received doses of 25,000 or 50,000 ppm in the diet.
- (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 untreated control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.
- (d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.
- (e) The 95 percent confidence interval of the relative risk between each dosed group and the control group.

Table 7. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing Guar Gum (a)

Topography: Morphology	Untreated Control	Low Dose	High Dose
Subcutaneous Tissue: Fibrosarcoma (b)	0/50(0)	1/50(2)	3/50(6)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		Infinite	Infinite
Lower Limit		0.054	0.601
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	89	104
Hematopoietic System: Leukemia (b) (b)	12/50(24)	6/50(12)	9/50(18)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.500	0.750
Lower Limit		0.167	0.307
Upper Limit		1.318	1.760
Weeks to First Observed Tumor	54	104	78
Hematopoietic System: Lymphoma, Malignant or Leukemia (b)	14/50(28)	8/50(16)	11/50(22)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.571	0.786
Lower Limit		0.228	0.359
Upper Limit		1.322	1.674
Weeks to First Observed Tumor	53	99	78

Table 7. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing Guar Gum (a)

(Continued)

Topography: Morphology	Untreated Control	Low Dose	High Dose
Pituitary: Adenoma (b)	21/47(45)	19/50(38)	17/50(34)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.850	0.761
Lower Limit		0.504	0.438
Upper Limit		1.436	1.315
Weeks to First Observed Tumor	67	99	58
Pituitary: Carcinoma, NOS (b)	1/47(2)	4/50(8)	3/50(6)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		3.760	2.820
Lower Limit		0.391	0.236
Upper Limit		181.270	145.009
Weeks to First Observed Tumor	105	104	104
Pituitary: Adenoma, or Carcinoma (b)	22/47(47)	23/50(46)	20/50(40)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.983	0.855
Lower Limit		0.616	0.518
Upper Limit		1.576	1.411
Weeks to First Observed Tumor	67	99	58

Table 7. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing Guar Gum (a)

(Continued)

Topography: Morphology	Untreated Control	Low Dose	High Dose
Adrenal: Pheochromocytoma (b)	0/50(0)	5/50(10)	6/50(12)
P Values (c),(d)	P=0.018	P=0.028	P=0.013
Relative Risk (Control) (e)		Infinite	Infinite
Lower Limit		1.261	1.600
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	104	100
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant (b)	1/50(2)	6/50(12)	6/50(12)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		6.000	6.000
Lower Limit		0.768	0.768
Upper Limit		269.891	269.891
Weeks to First Observed Tumor	101	104	100
Thyroid: C-Cell Adenoma or Carcinoma (b)	3/48(6)	1/47(2)	7/48(15)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.340	2.333
Lower Limit		0.007	0.570
Upper Limit		4.058	13.259
Weeks to First Observed Tumor	105	105	104

Table 7. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing Guar Gum (a)

(Continued)

Topography: Morphology	Untreated Control	Low Dose	High Dose
Mammary Gland:			
Fibroadenoma (b)	20/50(40)	19/50(38)	12/50(24)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.950	0.600
Lower Limit		0.553	0.303
Upper Limit		1.629	1.141
Weeks to First Observed Tumor	67	82	101
Clitoral Gland:			
All Carcinomas (b)	3/50(6)	6/50(12)	1/50(2)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		2.000	0.333
Lower Limit		0.454	0.006
Upper Limit		11.761	3.983
Weeks to First Observed Tumor	95	105	104
Clitoral Gland: Adenoma or Carcinoma (b)	4/50(8)	7/50(14)	2/50(4)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.750	0.500
Lower Limit		0.476	0.047
Upper Limit		7.682	3.318
Weeks to First Observed Tumor	95	105	104

Table 7. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing Guar Gum (a)

(Continued)

Topography: Morphology	Untreated Control	Low Dose	High Dose
Uterus: Endometrial Stromal Polyp (b)	17/49(35)	17/50(34)	21/49(43)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.980	1.235
Lower Limit		0.536	0.714
Upper Limit		1.793	2.158
Weeks to First Observed Tumor	67	99	98

- (a) Dosed groups received doses of 25,000 or 50,000 ppm in the diet.
 (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 untreated 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.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

After 20 weeks the mean body weight of high-dose female mice was consistently lower than that of the corresponding controls (Figure 3 and Table 8). No compound-related clinical signs were observed. A decrease in feed consumption was observed for mice of either sex (Appendix F). For male mice feed consumption in the low- and high-dose groups averaged 82% and 84% of the control values, respectively. For female mice the corresponding figures were 88% and 92%.

B. Survival (Mice)

Estimates of the probabilities of survival of male and female mice fed diets containing guar gum at the concentrations of this bioassay, together with those of the control group, are shown by the Kaplan and Meier curves in Figure 4. The survival of the untreated control group of male mice was significantly lower than the survival of the high-dose group. No significant differences in survival were observed between the two dosed groups. No significant differences were observed between any of the groups of female mice.

In male mice, 33/50 (66%) of the untreated controls, 41/50 (82%) of the low-dose, and 43/50 (86%) of the high-dose group lived to the end of the study at 105-106 weeks. In female mice, 38/50 (76%) of the untreated controls, 35/50 (70%) of the low-dose, and 36/50 (72%) of the high-dose group lived to the end of the study at 106 weeks.

C. Pathology (Mice)

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

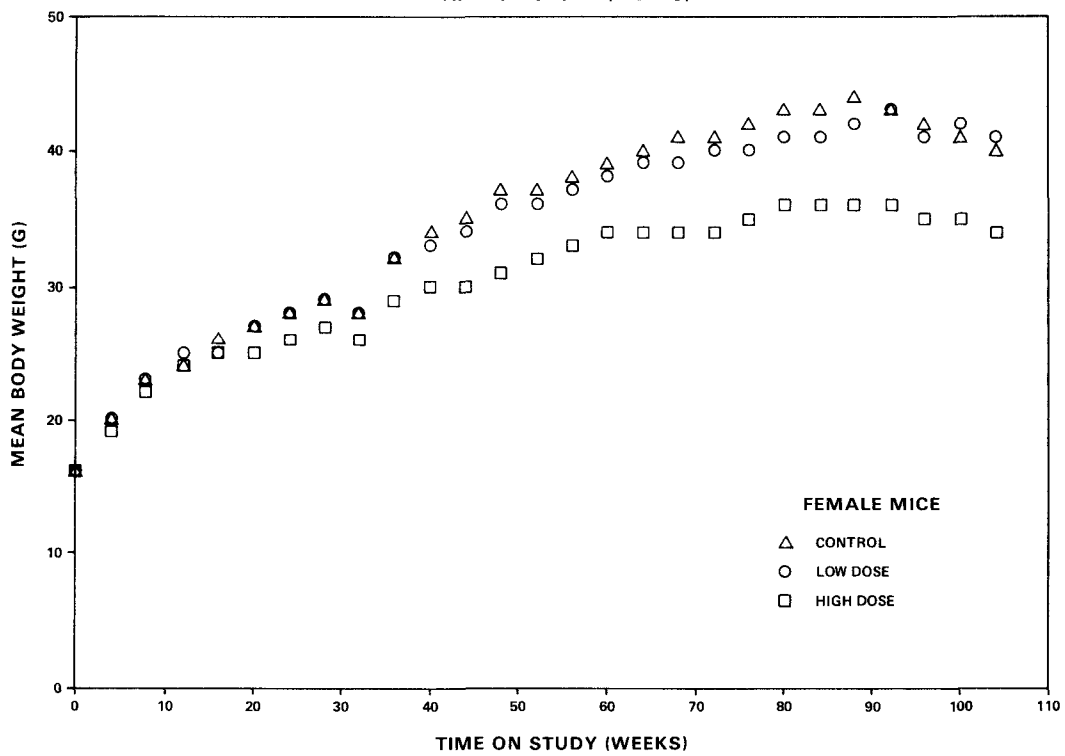
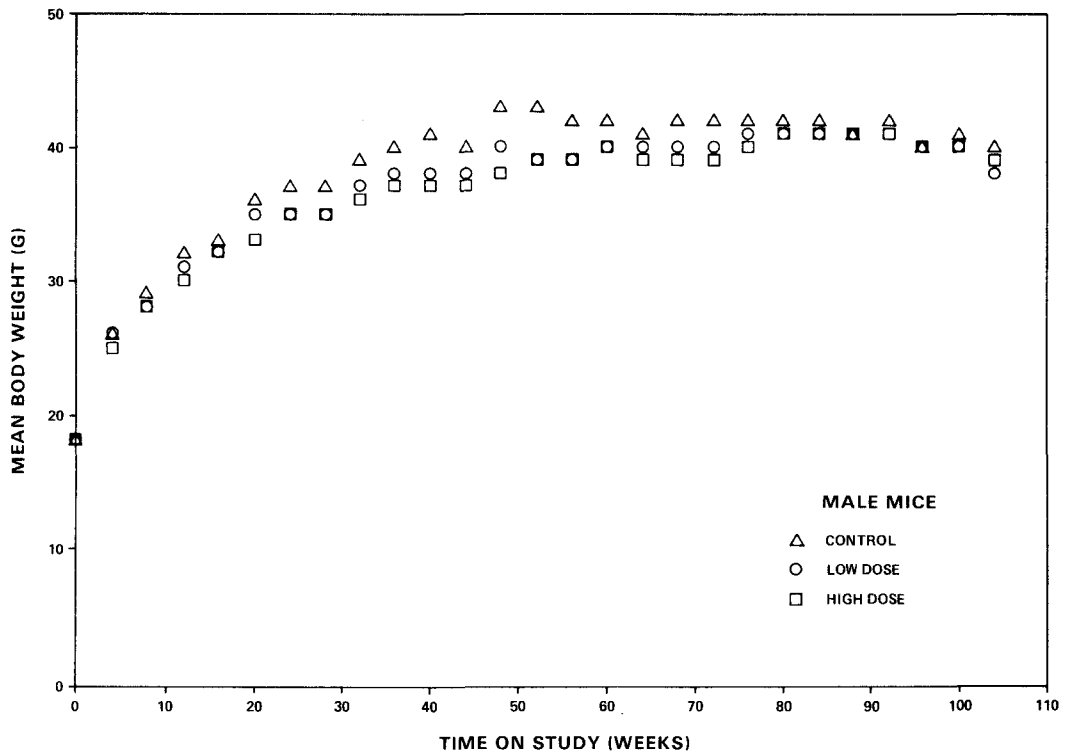


Figure 3. Growth Curves for Mice Fed Diets Containing Guar Gum

Table 8. Mean Body Weight Change (Relative to Controls) of Mice Fed Diets Containing Guar Gum

Week No.	Control	Mean Body Weight Change (grams)		Weight Change Relative to Controls (Percent)(a)	
		Low-Dose	High-Dose	Low-Dose	High-Dose
Males					
0	18 (b)	18 (b)	18 (b)		
4	8	8	7	0	-13
24	19	17	17	-11	-11
44	22	20	19	-10	-14
64	23	22	21	-4	-9
84	24	23	23	-4	-4
104	22	20	21	-10	-5
Females					
0	16 (b)	16 (b)	16 (b)		
4	4	4	3	0	-25
24	12	12	10	0	-17
44	19	18	14	-5	-26
64	24	23	18	-4	-25
84	27	25	20	-7	-26
104	25	26	19	+4	-24

(a) Weight Change Relative to Controls =
$$\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$$

(b) Initial weight

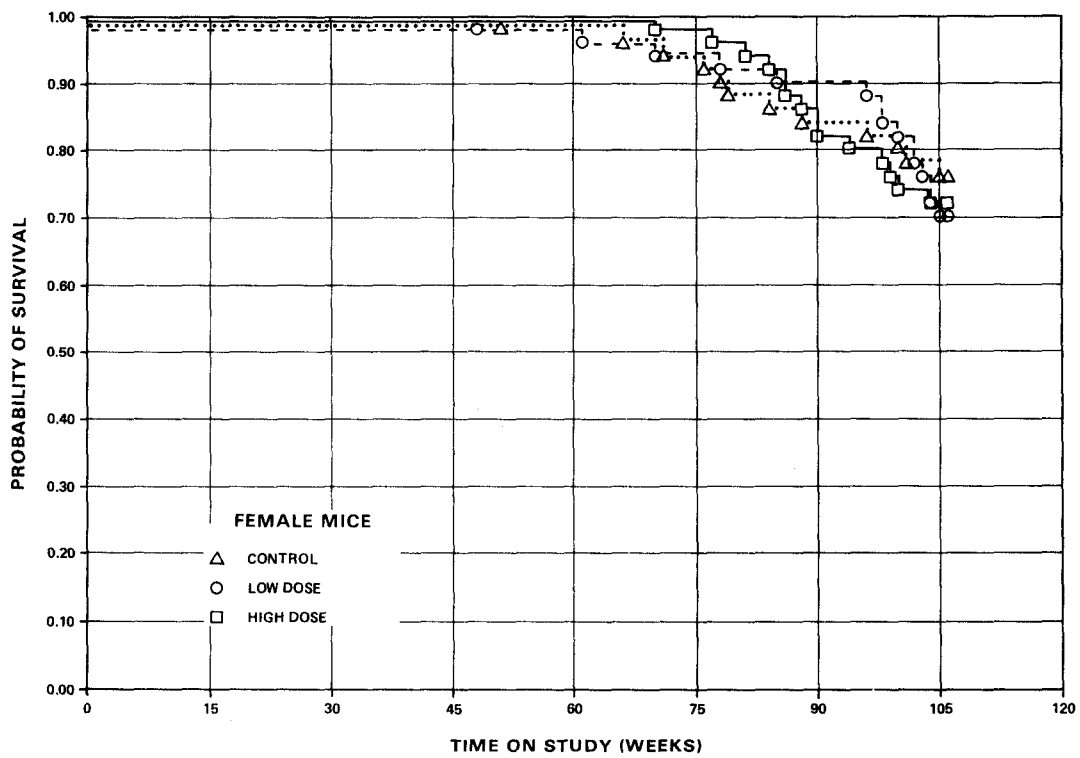
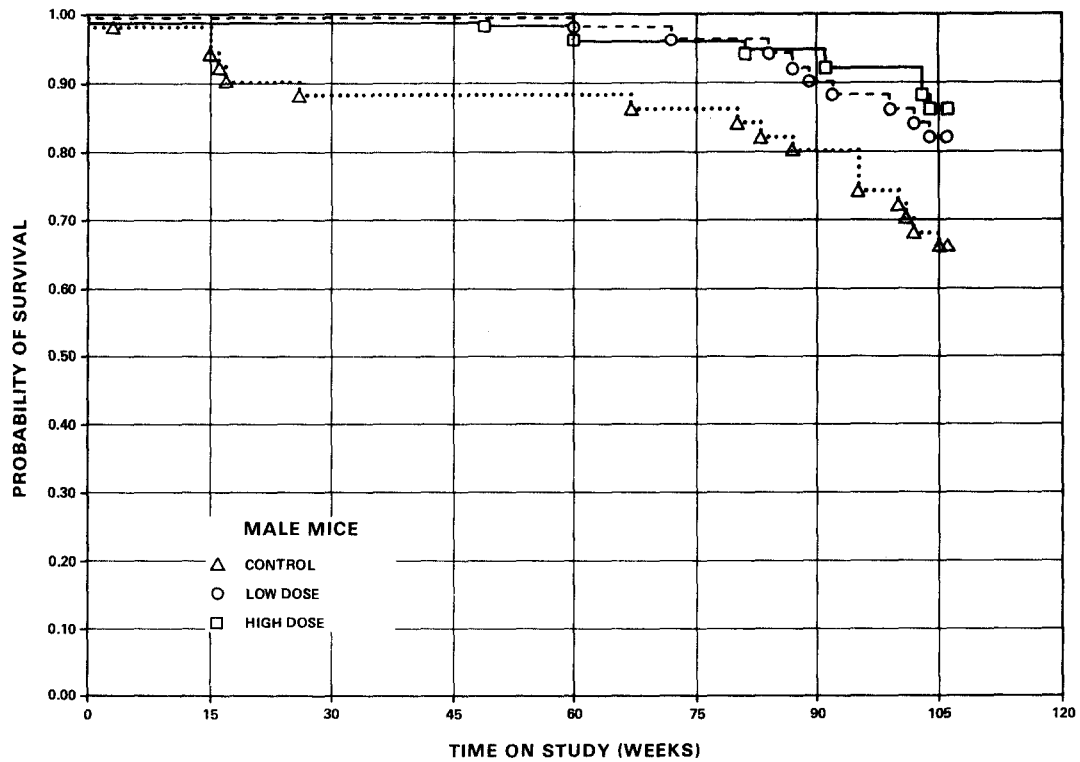


Figure 4. Survival Curves for Mice Fed Diets Containing Guar Gum

The neoplasms found following chronic administration of guar gum were of a type, incidence, and distribution commonly seen in aging B6C3F1 mice. The most frequent neoplasms found in all groups were those of the hematopoietic system in both sexes and tumors of the lung and liver in males. Incidences of tumors of the liver, most of which were hepatocellular carcinomas, decreased in dosed males. Pituitary tumors showed a slightly decreased incidence in dosed females.

A variety of nonneoplastic inflammatory and degenerative changes occurred in all groups of mice. None were considered to be related to administration of guar gum.

No carcinogenic or toxic effect of guar gum on B6C3F1 mice has been demonstrated under the conditions of this bioassay.

D. Statistical Analyses of Results (Mice)

Tables 9 and 10 contain the statistical analyses of those primary tumors which met both of the following criteria: 1) At least two animals of one group had the tumor, and 2) The incidence in one or more groups was at least 5%. Time adjusted analyses, eliminating animals that died before 52 weeks on study (except for 49 weeks in the case of malignant lymphoma), were used for statistical tests between the groups of male mice because six of the male controls and one high-dose male died during the first year.

Male mice with tumors in the circulatory system were observed in decreased incidence in the dosed groups compared with the control group. The Cochran-Armitage test for linear trend was significant in the negative direction ($P=0.036$), but the Fisher exact tests were not significant. In female mice, these tumors were not observed in statistically significant proportions.

Hepatocellular carcinomas in male mice were observed in statistically significant negative incidence in the dosed groups compared with the untreated control groups. The Cochran-Armitage test for linear trend was

statistically significant in the negative direction ($P=0.006$), and the Fisher exact tests between the untreated control group and either of the dosed groups was significant ($P=0.011$ in the high-dose and $P=0.010$ in the low-dose). The combined incidence of male mice with either adenomas or carcinomas of the liver was also statistically significant in the negative direction (16/44, 36% in the controls; 12/50, 24% in the low-dose; 7/49, 14% in the high-dose). The Cochran-Armitage test for linear trend was significant ($P=0.010$), and the Fisher exact test between the control and high-dose group was significant ($P=0.013$). No significant incidence was observed in the low-dose group. In female mice, these tumors were not observed in statistically significant proportions.

Table 9. Analyses of the Time Adjusted Incidence of Primary Tumors in Male Mice Fed Diets Containing Guar Gum (a)

Topography: Morphology	Untreated Control	Low Dose	High Dose
<hr/>			
Subcutaneous Tissue:			
Fibrosarcoma (b)	4/44(9)	7/50(14)	1/49(2)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.540	0.224
Lower Limit		0.422	0.005
Upper Limit		6.744	2.160
Weeks to First Observed Tumor	83	84	105
<hr/>			
Lung: Alveolar/Bronchiolar			
Adenoma (b)	9/44(20)	5/50(10)	6/49(12)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.489	0.599
Lower Limit		0.139	0.191
Upper Limit		1.497	1.728
Weeks to First Observed Tumor	87	106	105
<hr/>			
Lung: Alveolar/Bronchiolar			
Carcinoma (b)	3/44(7)	4/50(8)	2/49(4)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.173	0.599
Lower Limit		0.210	0.052
Upper Limit		7.629	4.991
Weeks to First Observed Tumor	106	106	103
<hr/>			

Table 9. Analyses of the Time Adjusted Incidence of Primary Tumors in Male Mice Fed Diets Containing Guar Gum (a)

(Continued)

Topography: Morphology	Untreated Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma (b)	12/44(27)	9/50(18)	8/49(16)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.660	0.599
Lower Limit		0.273	0.235
Upper Limit		1.541	1.440
Weeks to First Observed Tumor	87	106	103
Hematopoietic System: Lymphoma, All Malignant (b)	7/44(16)	9/50(18)	12/50(24)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.131	1.509
Lower Limit		0.411	0.605
Upper Limit		3.287	4.133
Weeks to First Observed Tumor	80	99	49
Circulatory System: Hemangiosarcoma (b)	4/44(9)	0/50(0)	1/49(2)
P Values (c),(d)	N.S.	P=0.045(N)	N.S.
Relative Risk (Control) (e)		0.000	0.224
Lower Limit		0.000	0.005
Upper Limit		0.948	2.160
Weeks to First Observed Tumor	67	--	105

Table 9. Analyses of the Time Adjusted Incidence of Primary Tumors in Male Mice Fed Diets Containing Guar Gum (a)

(Continued)

Topography: Morphology	Untreated Control	Low Dose	High Dose
<hr/>			
Circulatory System:			
All Tumors (b)	5/44(11)	1/50(2)	1/49(2)
P Values (c),(d)	P=0.036(N)	N.S.	N.S.
Relative Risk (Control) (e)		0.176	0.180
Lower Limit		0.004	0.004
Upper Limit		1.492	1.522
Weeks to First Observed Tumor	67	106	105
<hr/>			
Liver: Hepatocellular Adenoma (b)			
	1/44(2)	6/50(12)	1/49(2)
P Values (c),(d)	N.S.	N.S.	N.S.
Departure from Linear Trend (f)	P=0.015		
Relative Risk (Control) (e)		5.280	0.898
Lower Limit		0.697	0.012
Upper Limit		237.529	69.071
Weeks to First Observed Tumor	106	106	105
<hr/>			
Liver: Hepatocellular Carcinoma (b)			
	15/44(34)	6/50(12)	6/49(12)
P Values (c),(d)	P=0.006(N)	P=0.010(N)	P=0.011(N)
Relative Risk (Control) (e)		0.352	0.359
Lower Limit		0.124	0.126
Upper Limit		0.868	0.885
Weeks to First Observed Tumor	95	92	103
<hr/>			

Table 9. Analyses of the Time Adjusted Incidence of Primary Tumors in Male Mice Fed Diets Containing Guar Gum (a)

(Continued)

Topography: Morphology	Untreated Control	Low Dose	High Dose
Liver: Hepatocellular Adenoma or Carcinoma (b)	16/44(36)	12/50(24)	7/49(14)
P Values (c),(d)	P=0.010(N)	N.S.	P=0.013(N)
Relative Risk (Control) (e)		0.660	0.393
Lower Limit		0.324	0.152
Upper Limit		1.318	0.907
Weeks to First Observed Tumor	95	92	103

- (a) Dosed groups received doses of 25,000 or 50,000 ppm in the diet.
- (b) Number of tumor-bearing animals/number of animals examined at site (percent). Only those animals living beyond 52 weeks are included in the denominators except for the occurrence of malignant lymphoma where all animals living 49 weeks and beyond are included, because of the observation of one animal in the high-dose group with such a tumor at 49 weeks.
- (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 untreated-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 10. Analyses of the Incidence of Primary Tumors in Female Mice Fed Diets Containing Guar Gum (a)

Topography: Morphology	Untreated Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma (b)	3/50(6)	0/49(0)	1/50(2)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.000	0.333
Lower Limit		0.000	0.006
Upper Limit		1.696	3.983
Weeks to First Observed Tumor	105	--	106
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma (b)	5/50(10)	1/49(2)	3/50(6)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.204	0.600
Lower Limit		0.004	0.098
Upper Limit		1.733	2.910
Weeks to First Observed Tumor	105	106	70
Hematopoietic System: Lymphoma, All Malignant (b)	19/50(38)	17/49(35)	15/50(30)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.913	0.789
Lower Limit		0.511	0.425
Upper Limit		1.620	1.443
Weeks to First Observed Tumor	71	100	81

Table 10. Analyses of the Incidence of Primary Tumors in Female Mice Fed Diets Containing Guar Gum (a)

(Continued)

Topography: Morphology	Untreated Control	Low Dose	High Dose
Hematopoietic System: Lymphoma, Malignant or Leukemia (b)	19/50(38)	17/49(35)	17/50(34)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.913	0.895
Lower Limit		0.511	0.500
Upper Limit		1.620	1.591
Weeks to First Observed Tumor	71	100	77
Circulatory System: All Tumors (b)	3/50(6)	3/49(6)	1/50(2)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.020	0.333
Lower Limit		0.143	0.006
Upper Limit		7.273	3.983
Weeks to First Observed Tumor	106	106	106
Liver: Hepatocellular Carcinoma (b)	4/50(8)	2/49(4)	3/49(6)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.510	0.765
Lower Limit		0.048	0.118
Upper Limit		3.383	4.288
Weeks to First Observed Tumor	96	104	86

Table 10. Analyses of the Incidence of Primary Tumors in Female Mice Fed Diets Containing Guar Gum (a)

(Continued)

Topography: Morphology	Untreated Control	Low Dose	High Dose
Liver: Hepatocellular Adenoma or Carcinoma (b) (*)	5/50(10)	2/49(4)	4/49(8)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.408	0.816
Lower Limit		0.040	0.171
Upper Limit		2.358	3.567
Weeks to First Observed Tumor	96	104	86
Pituitary: All Adenomas (b)	4/43(9)	1/43(2)	1/43(2)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.250	0.250
Lower Limit		0.005	0.005
Upper Limit		2.392	2.392
Weeks to First Observed Tumor	106	106	106
Pituitary: Adenoma, or Carcinoma (b)	4/43(9)	2/43(5)	1/43(2)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.500	0.250
Lower Limit		0.047	0.005
Upper Limit		3.290	2.392
Weeks to First Observed Tumor	106	106	106

(*) One animal was reported with both adenoma and carcinoma.

Table 10. Analyses of the Incidence of Primary Tumors in Female Mice Fed Diets Containing Guar Gum (a)

(Continued)

Topography: Morphology	Untreated Control	Low Dose	High Dose
Uterus: Endometrial Stromal Polyp (b)	0/49(0)	4/48(8)	0/48(0)
P Values (c),(d)	N.S.	N.S.	N.S.
Departure from Linear Trend (f)	P=0.004		
Relative Risk (Control) (e)		Infinite	--
Lower Limit		0.947	--
Upper Limit		Infinite	--
Weeks to First Observed Tumor	--	106	--

(a) Dosed groups received doses of 25,000 or 50,000 ppm in the diet.

(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 untreated-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.

(d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.

(e) The 95 percent confidence interval of the relative risk between each dosed group and the control group.

(f) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

V. DISCUSSION

After week 20 in mice and week 40 in rats, the mean body weights of high-dose females were lower than those of the untreated controls. No compound-related clinical signs or adverse effects on survival were observed. Average feed consumption was reduced in all dosed groups of rats and mice when compared with the controls.

A variety of tumors was seen in control and dosed animals; none are clearly associated with administration of guar gum. The incidence of adenomas observed in the pituitary was significantly greater in the dosed groups of male rats than in the controls but more male rats with carcinomas were observed in the control group than in the dosed groups with the overall result that there was no statistically significant difference in the combined incidence of animals with these tumors. Similarly, pheochromocytomas of the adrenal of female rats were observed in the dosed groups at incidences significantly higher than that in the controls, but there was no significant increase in the combined incidence of female rats with pheochromocytomas or malignant pheochromocytomas.

Hepatocellular carcinomas occurred in dosed male mice at incidences significantly lower than those in the controls. The combined incidence of male mice with either hepatocellular adenomas or carcinomas was also significantly lower in the high-dose group than in the controls.

In the only other available study, no compound-related histopathologic effects were observed when 7-8 rats (strain unknown) of either sex were fed diets containing 50,000 ppm guar gum for 24 months (Krantz, 1948).

Two other galactomannan, legume-derived gums (locust bean gum, NTP 1982a and tara gum, NTP 1982b) were tested at the same laboratory as the present study. Besides these, two additional "gums" have been tested recently by the NTP bioassay program (agar, NTP 1982c and gum arabic, 1982d). Each of the four gums was added to the diet (2.5% and 5%) and fed for 104 weeks to F344 rats and B6C3F1 mice of each sex. Under these test conditions all were considered not carcinogenic.

VI. CONCLUSION

Under the conditions of this bioassay, guar gum was not carcinogenic for F344 rats or B6C3F1 mice of either sex.

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Appendix A

Summary of the Incidence of Neoplasms in Rats
Fed Diets Containing Guar Gum

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS FED
DIETS CONTAINING GUAR GUM

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
BASAL-CELL CARCINOMA		1 (2%)	
KERATOACANTHOMA		1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
BASAL-CELL CARCINOMA			1 (2%)
SARCOMA, NOS	1 (2%)		
FIBROMA		1 (2%)	4 (8%)
FIBROSARCOMA	1 (2%)		1 (2%)
LIPOMA	1 (2%)		1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA			1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)		1 (2%)
PHEOCHROMOCYTOMA, METASTATIC			1 (2%)
FIBROSARCOMA, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	2 (4%)	4 (8%)	1 (2%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			2 (4%)
LEUKEMIA,NOS	13 (26%)	12 (24%)	12 (24%)
CIRCULATORY SYSTEM			
#SPLEEN	(50)	(50)	(49)
HEMANGIOMA		2 (4%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HEMANGIOSARCOMA	1 (2%)		
#HEART	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CA, INVASIV	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(49)
BILE DUCT CARCINOMA	1 (2%)		
NEOPLASTIC NODULE	2 (4%)		1 (2%)
HEPATOCELLULAR CARCINOMA	1 (2%)		
#STOMACH	(49)	(50)	(48)
SQUAMOUS CELL PAPILOMA		1 (2%)	
#COLON	(45)	(49)	(43)
ADENOCARCINOMA, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CA, METASTA	1 (2%)		
TUBULAR-CELL ADENOMA		1 (2%)	
#URINARY BLADDER	(48)	(50)	(46)
TRANSITIONAL-CELL PAPILOMA	1 (2%)	1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(45)	(46)	(43)
CARCINOMA, NOS	5 (11%)		2 (5%)
ADENOMA, NOS	6 (13%)	15 (33%)	16 (37%)
CHROMOPHOBE ADENOMA	2 (4%)	2 (4%)	1 (2%)
#ADRENAL	(50)	(50)	(49)
CORTICAL ADENOMA	1 (2%)		
PHEOCHROMOCYTOMA	18 (36%)	14 (28%)	13 (27%)
PHEOCHROMOCYTOMA, MALIGNANT	1 (2%)	5 (10%)	2 (4%)
#THYROID	(50)	(49)	(47)
C-CELL ADENOMA		1 (2%)	2 (4%)
C-CELL CARCINOMA	1 (2%)		1 (2%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#PANCREATIC ISLETS	(46)	(48)	(44)
ISLET-CELL ADENOMA	1 (2%)		1 (2%)
ISLET-CELL CARCINOMA	2 (4%)		1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
FIBROADENOMA	2 (4%)	2 (4%)	
*MAMMARY DUCT	(50)	(50)	(50)
PAPILLOMA, NOS		1 (2%)	
*PREPUTIAL GLAND	(50)	(50)	(50)
CARCINOMA, NOS	5 (10%)	4 (8%)	3 (6%)
ADENOMA, NOS	2 (4%)	1 (2%)	1 (2%)
#TESTIS	(48)	(50)	(46)
INTERSTITIAL-CELL TUMOR	36 (75%)	38 (76%)	38 (83%)
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(48)
GLIOMA, NOS	1 (2%)		
ASTROCYTOMA			2 (4%)
SPECIAL SENSE ORGANS			
*ZYMBAL'S GLAND	(50)	(50)	(50)
CERUMINOUS CARCINOMA	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)		
*MESENTERY	(50)	(50)	(50)
LIPOMA			1 (2%)
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*TUNICA VAGINALIS MESOTHELIOMA, NOS	(50)	(50)	(50) 1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS MESOTHELIOMA, NOS	(50)	(50)	(50) 1 (2%)
DIAPHRAGM ALVEOLAR/BRONCHIOLAR CA, INVASIV	1		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH ^a	10	13	12
MORIBUND SACRIFICE	9	6	5
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	31	31	33
ANIMAL MISSING			
^a INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	47	49	48
TOTAL PRIMARY TUMORS	110	109	112
TOTAL ANIMALS WITH BENIGN TUMORS	41	47	46
TOTAL BENIGN TUMORS	70	82	79
TOTAL ANIMALS WITH MALIGNANT TUMORS	27	23	30
TOTAL MALIGNANT TUMORS	38	27	30
TOTAL ANIMALS WITH SECONDARY TUMORS#	2		1
TOTAL SECONDARY TUMORS	4		1
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT	2		3
TOTAL UNCERTAIN TUMORS	2		3
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			
* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS			
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN			

TABLE A2.

**SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS FED
DIETS CONTAINING GUAR GUM**

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
FIBROMA		2 (4%)	
FIBROSARCOMA		1 (2%)	3 (6%)
NEUROFIBROSARCOMA		1 (2%)	1 (2%)
NEURILEMOMA, MALIGNANT	2 (4%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)
SARCOMA, NOS, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	2 (4%)	2 (4%)	2 (4%)
LEUKEMIA, NOS	12 (24%)	6 (12%)	7 (14%)
LYMPHOCYTIC LEUKEMIA			2 (4%)
CIRCULATORY SYSTEM			
#LIVER	(49)	(50)	(50)
HEMANGIOMA			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(49)	(50)	(50)
NEOPLASTIC NODULE	2 (4%)	1 (2%)	1 (2%)
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#STOMACH	(49)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)		1 (2%)
LEIOMYOMA		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
TUBULAR-CELL ADENOMA		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(47)	(50)	(50)
CARCINOMA, NOS	1 (2%)	4 (8%)	3 (6%)
ADENOMA, NOS	18 (38%)	19 (38%)	16 (32%)
CHROMOPHOBE ADENOMA	3 (6%)		1 (2%)
#ADRENAL	(50)	(50)	(50)
CORTICAL ADENOMA	2 (4%)	2 (4%)	
CORTICAL CARCINOMA		1 (2%)	
PHEOCHROMOCYTOMA		5 (10%)	6 (12%)
PHEOCHROMOCYTOMA, MALIGNANT	1 (2%)	1 (2%)	
GANGLIONEUROMA		1 (2%)	
#THYROID	(48)	(47)	(48)
C-CELL ADENOMA	2 (4%)		6 (13%)
C-CELL CARCINOMA	1 (2%)	1 (2%)	1 (2%)
#PANCREATIC ISLETS	(47)	(50)	(49)
ISLET-CELL ADENOMA	1 (2%)		1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOMA, NOS			1 (2%)
ADENOCARCINOMA, NOS	2 (4%)	1 (2%)	
SARCOMA, NOS			1 (2%)
FIBROMA		1 (2%)	
FIBROADENOMA	20 (40%)	19 (38%)	12 (24%)
*CLITORAL GLAND	(50)	(50)	(50)
CARCINOMA, NOS	3 (6%)	4 (8%)	1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
SQUAMOUS CELL CARCINOMA		2 (4%)	
ADENOMA, NOS	1 (2%)	1 (2%)	1 (2%)
#UTERUS	(49)	(50)	(49)
ADENOCARCINOMA, NOS		1 (2%)	1 (2%)
LEIOMYOMA			1 (2%)
ENDOMETRIAL STROMAL POLYP	17 (35%)	17 (34%)	21 (43%)
ENDOMETRIAL STROMAL SARCOMA			2 (4%)
#UTERUS/ENDOMETRIUM	(49)	(50)	(49)
ADENOCARCINOMA, NOS		2 (4%)	1 (2%)
#OVARY	(49)	(50)	(49)
GRANULOSA-CELL TUMOR		2 (4%)	1 (2%)
GRANULOSA-CELL CARCINOMA		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
NEOPLASM, NOS	1 (2%)		
CARCINOMA, NOS	1 (2%)		
GLIOMA, NOS		1 (2%)	
ASTROCYTOMA		2 (4%)	
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
ADENOMA, NOS		1 (2%)	
*ZYMBAL'S GLAND	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA			1 (2%)
CERUMINOUS CARCINOMA			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH ^a	18	4	7
MORIBUND SACRIFICE	7	5	6
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	25	41	37
ANIMAL MISSING			
^a INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	46	47	46
TOTAL PRIMARY TUMORS	93	105	100
TOTAL ANIMALS WITH BENIGN TUMORS	37	42	37
TOTAL BENIGN TUMORS	65	71	71
TOTAL ANIMALS WITH MALIGNANT TUMORS	24	24	22
TOTAL MALIGNANT TUMORS	25	31	27
TOTAL ANIMALS WITH SECONDARY TUMORS#			1
TOTAL SECONDARY TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT	3	3	2
TOTAL UNCERTAIN TUMORS	3	3	2
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
Fed Diets Containing Guar Gum**

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE FED
DIETS CONTAINING GUAR GUM

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*EAR	(50)	(50)	(50)
FIBROUS HISTIOCYTOMA	1 (2%)		
*SKIN	(50)	(50)	(50)
EPITHELIAL TUMOR, NOS, BENIGN		1 (2%)	1 (2%)
BASAL-CELL CARCINOMA			1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)		
FIBROMA		1 (2%)	
FIBROSARCOMA	4 (8%)	7 (14%)	1 (2%)
LEIOMYOSARCOMA		1 (2%)	
NEUROFIBROSARCOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
HEPATOCELLULAR CARCINOMA, METAST	6 (12%)		1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	9 (18%)	5 (10%)	7 (14%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	3 (6%)	4 (8%)	2 (4%)
FIBROSARCOMA, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	1 (2%)	1 (2%)	3 (6%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	2 (4%)	2 (4%)	1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)	1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)	3 (6%)	1 (2%)
#SPLEEN	(49)	(50)	(47)
MALIGNANT LYMPHOMA, MIXED TYPE			1 (2%)

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#LYMPH NODE MALIG.LYMPHOMA, HISTIOCYTIC TYPE	(42)	(47) 1 (2%)	(46)
#ABDOMINAL LYMPH NODE MALIG.LYMPHOMA, HISTIOCYTIC TYPE	(42)	(47)	(46) 1 (2%)
#MESENTERIC L. NODE MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	(42)	(47)	(46) 2 (4%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
MALIGNANT LYMPHOMA, MIXED TYPE			1 (2%)
#LIVER MALIG.LYMPHOMA, HISTIOCYTIC TYPE	(50) 1 (2%)	(50)	(50)
#JEJUNUM MALIG.LYMPHOMA, HISTIOCYTIC TYPE	(46)	(49)	(48) 1 (2%)
CIRCULATORY SYSTEM			
*SUBCUT TISSUE ANGIOSARCOMA	(50)	(50) 1 (2%)	(50)
#LIVER HEMANGIOMA	(50) 1 (2%)	(50)	(50)
HEMANGIOSARCOMA	2 (4%)		
#KIDNEY HEMANGIOSARCOMA	(50) 1 (2%)	(50)	(50)
#URINARY BLADDER HEMANGIOSARCOMA	(49)	(49)	(48) 1 (2%)
#TESTIS HEMANGIOSARCOMA	(50) 1 (2%)	(49)	(50)
DIGESTIVE SYSTEM			
#LIVER HEPATOCELLULAR ADENOMA	(50) 1 (2%)	(50) 6 (12%)	(50) 1 (2%)
HEPATOCELLULAR CARCINOMA	15 (30%)	6 (12%)	6 (12%)
#FORESTOMACH SQUAMOUS CELL PAPILLOMA	(49)	(49) 1 (2%)	(49) 1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*RECTUM MUCINOUS ADENOCARCINOMA	(50)	(50) 1 (2%)	(50)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY ADENOMA, NOS	(46)	(44) 1 (2%)	(44)
#ADRENAL PHEOCHROMOCYTOMA	(46) 1 (2%)	(47)	(48) 1 (2%)
#THYROID FOLLICULAR-CELL ADENOMA FOLLICULAR-CELL CARCINOMA	(49) 1 (2%)	(49) 1 (2%)	(47) 1 (2%)
#PANCREATIC ISLETS ISLET-CELL ADENOMA	(47)	(48)	(43) 1 (2%)
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND ADENOMA, NOS	(50)	(50) 1 (2%)	(50)
#TESTIS INTERSTITIAL-CELL TUMOR	(50) 1 (2%)	(49)	(50)
*EPIDIDYMIS HEPATOCELLULAR CARCINOMA, METAST	(50) 1 (2%)	(50)	(50)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND ADENOMA, NOS	(50) 1 (2%)	(50) 1 (2%)	(50) 1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
*EAR	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(50)	(50)	(50)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH ^a	13	5	6
MORIBUND SACRIFICE	4	4	1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	33	41	43
ANIMAL MISSING			
^a INCLUDES AUTOLYZED ANIMALS			
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	32	33	32
TOTAL PRIMARY TUMORS	51	48	37
TOTAL ANIMALS WITH BENIGN TUMORS	14	15	14
TOTAL BENIGN TUMORS	15	18	14
TOTAL ANIMALS WITH MALIGNANT TUMORS	27	25	22
TOTAL MALIGNANT TUMORS	36	30	23
TOTAL ANIMALS WITH SECONDARY TUMORS#	8	1	1
TOTAL SECONDARY TUMORS	8	1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			
* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS			
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN			

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE FED
DIETS CONTAINING GUAR GUM

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(50)
SQUAMOUS CELL CARCINOMA	1 (2%)		
*SUBCUT TISSUE	(50)	(49)	(50)
FIBROSARCOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(49)	(50)
SQUAMOUS CELL CARCINOMA, METASTA	1 (2%)		
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)		3 (6%)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)	1 (2%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	3 (6%)		1 (2%)
OSTEOSARCOMA, METASTATIC	1 (2%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(49)	(50)
MALIGNANT LYMPHOMA, NOS	3 (6%)	1 (2%)	1 (2%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	6 (12%)	4 (8%)	3 (6%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)	5 (10%)	5 (10%)
MALIGNANT LYMPHOMA, MIXED TYPE	5 (10%)	3 (6%)	3 (6%)
LYMPHOCYTIC LEUKEMIA			1 (2%)
GRANULOCYTIC LEUKEMIA			1 (2%)
*MEDIASTINUM	(50)	(49)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
#SPLEEN	(50)	(49)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		2 (4%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	2 (4%)		
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
MALIGNANT LYMPHOMA, MIXED TYPE			2 (4%)
#LYMPH NODE	(42)	(41)	(45)
MALIGNANT LYMPHOMA, NOS			1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)		
#MESENTERIC L. NODE	(42)	(41)	(45)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)		
#ILEUM	(46)	(49)	(47)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	
CIRCULATORY SYSTEM			
#SPLEEN	(50)	(49)	(50)
HEMANGIOMA	1 (2%)		
HEMANGIOSARCOMA		2 (4%)	
#LIVER	(50)	(49)	(49)
HEMANGIOMA	1 (2%)		
#UTERUS	(49)	(48)	(48)
HEMANGIOMA	1 (2%)		
HEMANGIOSARCOMA		1 (2%)	1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(49)
HEPATOCELLULAR ADENOMA	2 (4%)		1 (2%)
HEPATOCELLULAR CARCINOMA	4 (8%)	2 (4%)	3 (6%)
#STOMACH	(47)	(48)	(47)
SQUAMOUS CELL PAPILLOMA	1 (2%)	1 (2%)	
#FORESTOMACH	(47)	(48)	(47)
SQUAMOUS CELL PAPILLOMA			2 (4%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(43)	(43)	(43)
CARCINOMA, NOS		1 (2%)	

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ADENOMA, NOS	4 (9%)	1 (2%)	
CHROMOPHOBE ADENOMA			1 (2%)
#ADRENAL	(47)	(46)	(46)
PHEOCHROMOCYTOMA	1 (2%)		
#THYROID	(49)	(44)	(45)
FOLLICULAR-CELL ADENOMA		1 (2%)	
PAPILLARY CYSTADENOMA, NOS	1 (2%)		
#THYROID FOLLICLE	(49)	(44)	(45)
CYSTADENOMA, NOS	1 (2%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(49)	(50)
ADENOCARCINOMA, NOS			1 (2%)
ACINAR-CELL CARCINOMA		1 (2%)	
*VAGINA	(50)	(49)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
#UTERUS	(49)	(48)	(48)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	
ENDOMETRIAL STROMAL POLYP		4 (8%)	
#OVARY	(40)	(42)	(41)
CYSTADENOMA, NOS		1 (2%)	
PAPILLARY CYSTADENOMA, NOS	1 (3%)		
PAPILLARY CYSTADENOCARCINOMA, NOS	1 (3%)		
MUCINOUS CYSTADENOMA			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(50)	(47)	(50)
CARCINOMA, NOS, INVASIVE		1 (2%)	
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(49)	(50)
ADENOMA, NOS	1 (2%)		1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
*FEMUR OSTEOSARCOMA	(50)	(49) 1 (2%)	(50)
BODY CAVITIES			
*ABDOMINAL CAVITY MESOTHELIOMA, NOS OSTEOSARCOMA	(50) 1 (2%)	(49) 1 (2%)	(50)
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH ^a	11	12	11
MORIBUND SACRIFICE	1	3	3
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	38	35	36
ANIMAL MISSING			

^a INCLUDES AUTOLYZED ANIMALS

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	32	26	27
TOTAL PRIMARY TUMORS	47	36	31
TOTAL ANIMALS WITH BENIGN TUMORS	13	10	8
TOTAL BENIGN TUMORS	17	10	8
TOTAL ANIMALS WITH MALIGNANT TUMORS	27	22	23
TOTAL MALIGNANT TUMORS	30	25	23
TOTAL ANIMALS WITH SECONDARY TUMORS#	3	3	3
TOTAL SECONDARY TUMORS	3	3	3
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT		1	
TOTAL UNCERTAIN TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			
* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS			
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN			

Appendix C

Summary of the Incidence of Nonneoplastic Lesions
in Rats Fed Diets Containing Guar Gum

TABLE C1.

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

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	
ABSCESS, NOS			1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
CYST, NOS		1 (2%)	
NECROSIS, FAT	1 (2%)		
RESPIRATORY SYSTEM			
*NASAL TURBINATE	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
#LUNG/BRONCHIOLE	(50)	(50)	(50)
METAPLASIA, NOS		2 (4%)	
#LUNG	(50)	(50)	(50)
CONGESTION, NOS		1 (2%)	1 (2%)
INFLAMMATION, NOS			1 (2%)
PNEUMONIA, CHRONIC MURINE		1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(47)	(49)	(49)
FIBROSIS	2 (4%)		
FIBROSIS, FOCAL		2 (4%)	
HYPERPLASIA, NOS	1 (2%)		
*SPLEEN	(50)	(50)	(49)
ACCESSORY SPLEEN	1 (2%)	1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CONGESTION, NOS	1 (2%)		
FIBROSIS	1 (2%)		
FIBROSIS, FOCAL	1 (2%)	2 (4%)	2 (4%)
NECROSIS, FOCAL		1 (2%)	
INFARCT, NOS			1 (2%)
HEMATOPOIESIS	2 (4%)	3 (6%)	1 (2%)
#MESENTERIC L. NODE	(48)	(47)	(44)
CONGESTION, NOS		1 (2%)	1 (2%)
#RENAL LYMPH NODE	(48)	(47)	(44)
INFLAMMATION, CHRONIC		1 (2%)	
#THYMUS	(36)	(36)	(33)
ATROPHY, NOS			1 (3%)
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
PERIARTERITIS			1 (2%)
#MANDIBULAR L. NODE	(48)	(47)	(44)
LYMPHANGIECTASIS	1 (2%)		1 (2%)
#MESENTERIC L. NODE	(48)	(47)	(44)
LYMPHANGIECTASIS	3 (6%)	3 (6%)	2 (5%)
#HEART	(50)	(50)	(50)
THROMBUS, MURAL	1 (2%)	1 (2%)	
#HEART/ATRIUM	(50)	(50)	(50)
DILATATION, NOS	1 (2%)		
THROMBUS, MURAL			2 (4%)
#MYOCARDIUM	(50)	(50)	(50)
THROMBUS, MURAL	2 (4%)	2 (4%)	1 (2%)
DEGENERATION, NOS	31 (62%)	35 (70%)	24 (48%)
*MESENTERY	(50)	(50)	(50)
PERIARTERITIS		1 (2%)	
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(49)	(46)
INFLAMMATION, NOS	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION ACUTE AND CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)
FIBROSIS	1 (2%)		
FIBROSIS, FOCAL	1 (2%)		
NECROSIS, FOCAL	1 (2%)		
ATROPHY, NOS	1 (2%)		
#LIVER	(50)	(50)	(49)
CONGESTION, NOS			1 (2%)
CONGESTION, CHRONIC PASSIVE	3 (6%)	1 (2%)	
NECROSIS, FOCAL	1 (2%)		
METAMORPHOSIS FATTY	9 (18%)	5 (10%)	5 (10%)
BASOPHILIC CYTO CHANGE			1 (2%)
FOCAL CELLULAR CHANGE	1 (2%)		
CLEAR-CELL CHANGE	1 (2%)		
#LIVER/CENTRIOLOBULAR	(50)	(50)	(49)
NECROSIS, NOS	1 (2%)	1 (2%)	
#BILE DUCT	(50)	(50)	(49)
HYPERPLASIA, NOS	32 (64%)	27 (54%)	33 (67%)
#PANCREAS	(46)	(48)	(44)
FIBROSIS, FOCAL	2 (4%)		2 (5%)
#PANCREATIC ACINUS	(46)	(48)	(44)
ATROPHY, NOS	1 (2%)		
#STOMACH	(49)	(50)	(48)
ULCER, NOS	4 (8%)	2 (4%)	2 (4%)
INFLAMMATION, CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC FOCAL			3 (6%)
CALCIFICATION, FOCAL			1 (2%)
HYPERPLASIA, BASAL CELL	5 (10%)	2 (4%)	3 (6%)
ACANTHOSIS	1 (2%)	1 (2%)	2 (4%)
#GASTRIC SUBMUCOSA	(49)	(50)	(48)
FIBROSIS			1 (2%)
#COLON	(45)	(49)	(43)
EDEMA, NOS			1 (2%)
PARASITISM	5 (11%)	7 (14%)	6 (14%)
#COLONIC SUBMUCOSA	(45)	(49)	(43)
FIBROSIS			1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#CECUM ULCER, NOS	(45) 1 (2%)	(49)	(43)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
CYST, NOS		1 (2%)	
CONGESTION, NOS	1 (2%)		
NEPHROPATHY	1 (2%)		
NEPHROSIS, NOS	40 (80%)	41 (82%)	39 (78%)
NEPHROSIS, CHOLEMIC	2 (4%)		2 (4%)
NECROSIS, MEDULLARY			1 (2%)
CALCIFICATION, FOCAL	3 (6%)		1 (2%)
#KIDNEY/CORTEX	(50)	(50)	(50)
CYST, NOS	1 (2%)		
#KIDNEY/TUBULE	(50)	(50)	(50)
REGENERATION, NOS		1 (2%)	
#KIDNEY/PELVIS	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL	2 (4%)		1 (2%)
#URINARY BLADDER	(48)	(50)	(46)
CALCULUS, NOS		1 (2%)	1 (2%)
OBSTRUCTION, NOS			1 (2%)
INFLAMMATION, ACUTE	1 (2%)		1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(45)	(46)	(43)
CYST, NOS	4 (9%)		2 (5%)
HEMORRHAGIC CYST	2 (4%)		
INFARCT, NOS			1 (2%)
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, FOCAL	3 (7%)	4 (9%)	1 (2%)
VASCULARIZATION	1 (2%)	1 (2%)	
#ADRENAL	(50)	(50)	(49)
NECROSIS, FOCAL			1 (2%)
INFARCT HEMORRHAGIC	1 (2%)		
#ADRENAL CORTEX	(50)	(50)	(49)
HYPERPLASIA, NODULAR			2 (4%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#ADRENAL MEDULLA HYPERPLASIA, FOCAL	(50) 10 (20%)	(50) 4 (8%)	(49) 4 (8%)
#THYROID HYPERPLASIA, C-CELL	(50) 2 (4%)	(49)	(47) 3 (6%)
#PANCREATIC ISLETS HYPERPLASIA, NOS	(46)	(48) 1 (2%)	(44) 1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND DILATATION/DUCTS GALACTOCELE	(50)	(50) 1 (2%) 3 (6%)	(50)
*MAMMARY DUCT HEMORRHAGIC CYST	(50)	(50) 1 (2%)	(50)
#PROSTATE INFLAMMATION, NOS INFLAMMATION, ACUTE INFLAMMATION ACUTE AND CHRONIC INFLAMMATION, CHRONIC ATROPHY, NOS	(45) 1 (2%) 1 (2%) 6 (13%) 7 (16%)	(50) 1 (2%)	(47) 1 (2%) 1 (2%) 1 (2%) 1 (2%)
*SEMINAL VESICLE CALCULUS, NOS HEMORRHAGE INFLAMMATION, CHRONIC ATROPHY, NOS	(50) 1 (2%) 1 (2%) 3 (6%)	(50) 1 (2%)	(50) 1 (2%) 1 (2%) 1 (2%)
#TESTIS CALCIFICATION, NOS ATROPHY, NOS HYPERPLASIA, INTERSTITIAL CELL	(48) 1 (2%) 1 (2%)	(50) 1 (2%) 2 (4%)	(46)
NERVOUS SYSTEM			
#BRAIN HYDROCEPHALUS, NOS HEMORRHAGE CALCIFICATION, FOCAL	(50) 1 (2%) 1 (2%)	(50) 1 (2%) 1 (2%)	(48) 1 (2%)
SPECIAL SENSE ORGANS			
NONE			

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
*SKULL HYPEROSTOSIS	(50) 1 (2%)	(50) 1 (2%)	(50)
BODY CAVITIES			
*MESENTERY NECROSIS, FAT	(50) 3 (6%)	(50) 2 (4%)	(50) 1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS CONGESTION, NOS FIBROSIS, FOCAL HYPERPLASIA, EPITHELIAL	(50) 1 (2%)	(50) 1 (2%)	(50) 1 (2%)
SPECIAL MORPHOLOGY SUMMARY			
AUTO/NECROPSY/HISTO PERF			1
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

TABLE C2.

**SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS
FED DIETS CONTAINING GUAR GUM**

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE EDEMA, NOS	(50)	(50) 1 (2%)	(50)
RESPIRATORY SYSTEM			
*NASAL TURBINATE INFLAMMATION, CHRONIC INFLAMMATION, CHRONIC FOCAL	(50)	(50) 2 (4%) 1 (2%)	(50)
#LUNG/BRONCHIOLE METAPLASIA, NOS	(50)	(50)	(50) 3 (6%)
#LUNG CONGESTION, NOS PNEUMONIA, CHRONIC MURINE INFARCT, NOS CALCIFICATION, FOCAL	(50) 1 (2%)	(50) 2 (4%)	(50) 1 (2%) 1 (2%) 1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS HEMATOPOIESIS	(50)	(50) 1 (2%)	(50)
#SPLEEN HEMATOMA, ORGANIZED FIBROSIS, FOCAL INFARCT, FOCAL HEMATOPOIESIS	(50) 1 (2%) 1 (2%)	(50) 1 (2%) 2 (4%)	(50) 1 (2%) 2 (4%)
#LYMPH NODE CONGESTION, NOS	(45)	(48) 1 (2%)	(48)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#MEDIASTINAL L.NODE HEMOSIDEROSIS	(45) 1 (2%)	(48) 1 (2%)	(48)
#MESENTERIC L. NODE CONGESTION, NOS	(45) 1 (2%)	(48) 2 (4%)	(48) 2 (4%)
#THYMUS CYST, NOS ATROPHY, NOS	(38) 1 (3%)	(37)	(34) 1 (3%)
CIRCULATORY SYSTEM			
#HEART THROMBUS, MURAL PERIARTERITIS	(49) 1 (2%)	(50) 1 (2%)	(50)
#MYOCARDIUM DEGENERATION, NOS	(49) 13 (27%)	(50) 20 (40%)	(50) 17 (34%)
#UTERUS THROMBOSIS, NOS	(49)	(50) 2 (4%)	(49) 1 (2%)
#THYMUS LYMPHANGIECTASIS	(38)	(37) 1 (3%)	(34)
DIGESTIVE SYSTEM			
#LIVER CONGESTION, CHRONIC PASSIVE NECROSIS, NOS METAMORPHOSIS FATTY BASOPHILIC CYTO CHANGE FOCAL CELLULAR CHANGE	(49) 1 (2%) 9 (18%) 2 (4%) 3 (6%)	(50) 1 (2%) 4 (8%) 1 (2%)	(50) 5 (10%) 5 (10%) 4 (8%)
#BILE DUCT HYPERPLASIA, NOS	(49) 12 (24%)	(50) 9 (18%)	(50) 11 (22%)
#STOMACH EPIDERMAL INCLUSION CYST ULCER, NOS INFLAMMATION, CHRONIC FOCAL HYPERPLASIA, BASAL CELL	(49) 2 (4%) 1 (2%) 4 (8%)	(50) 1 (2%) 2 (4%)	(50) 1 (2%) 1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ACANTHOSIS	2 (4%)		
#GASTRIC MUCOSA CALCIFICATION, NOS	(49) 1 (2%)	(50)	(50)
#DUODENUM HYPERTROPHY, NOS	(48) 1 (2%)	(50)	(49)
#ILEAL SUBMUCOSA ABSCESS, NOS	(48) 1 (2%)	(50)	(49)
#COLON PARASITISM	(47) 4 (9%)	(48) 8 (17%)	(47) 3 (6%)
#CECUM PARASITISM	(47)	(48)	(47) 1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
HAMARTOMA		1 (2%)	
SCAR			1 (2%)
NEPHROSIS, NOS	12 (24%)	17 (34%)	11 (22%)
NEPHROSIS, CHOLEMIC	1 (2%)	1 (2%)	
CALCIFICATION, FOCAL	17 (34%)	11 (22%)	12 (24%)
#KIDNEY/PELVIS HYPERPLASIA, EPITHELIAL	(50) 1 (2%)	(50)	(50)
ENDOCRINE SYSTEM			
#PITUITARY	(47)	(50)	(50)
CYST, NOS	11 (23%)	10 (20%)	9 (18%)
MULTIPLE CYSTS		1 (2%)	1 (2%)
HEMORRHAGIC CYST	1 (2%)	1 (2%)	1 (2%)
HEMOSIDEROSIS			1 (2%)
HYPERPLASIA, FOCAL	2 (4%)	1 (2%)	4 (8%)
ANGIECTASIS		1 (2%)	
VASCULARIZATION	3 (6%)	2 (4%)	2 (4%)
#ADRENAL HYPERPLASIA, FOCAL	(50)	(50) 1 (2%)	(50)
#ADRENAL CORTEX HYPERPLASIA, NODULAR	(50) 8 (16%)	(50) 2 (4%)	(50) 7 (14%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, FOCAL			1 (2%)
#ADRENAL MEDULLA HYPERPLASIA, FOCAL	(50) 3 (6%)	(50) 1 (2%)	(50) 1 (2%)
#THYROID HYPERPLASIA, C-CELL	(48) 4 (8%)	(47)	(48) 3 (6%)
#PANCREATIC ISLETS HYPERPLASIA, ATYPICAL	(47) 1 (2%)	(50)	(49)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND GALACTOCELE LACTATION	(50) 18 (36%)	(50) 7 (14%)	(50) 10 (20%) 1 (2%)
*MAMMARY LOBULE HYPERPLASIA, NOS	(50) 1 (2%)	(50)	(50)
*CLITORAL GLAND INFLAMMATION, CHRONIC	(50)	(50) 1 (2%)	(50)
#UTERUS HYDROMETRA	(49) 2 (4%)	(50) 1 (2%)	(49) 2 (4%)
#CERVIX UTERI ULCER, NOS	(49) 1 (2%)	(50)	(49)
#UTERUS/ENDOMETRIUM HYPERPLASIA, CYSTIC	(49)	(50)	(49) 2 (4%)
#OVARY CYST, NOS	(49) 2 (4%)	(50) 2 (4%)	(49) 1 (2%)
NERVOUS SYSTEM			
#BRAIN HYDROCEPHALUS, NOS HEMORRHAGE	(50) 2 (4%)	(50)	(50) 1 (2%)
SPECIAL SENSE ORGANS			
NONE			

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY NECROSIS, FAT	(50) 2 (4%)	(50) 3 (6%)	(50) 1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS CONGESTION, NOS	(50) 1 (2%)	(50)	(50)
HEMORRHAGE	1 (2%)		
ABSCESS, NOS	1 (2%)		
NECROSIS, FOCAL			1 (2%)
TAIL			
EPIDERMAL INCLUSION CYST		1	
SPECIAL MORPHOLOGY SUMMARY			
AUTO/NECROPSY/HISTO PERF			1
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

Appendix D

Summary of the Incidence of Nonneoplastic Lesions
in Mice Fed Diets Containing Guar Gum

TABLE D1.

**SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE
FED DIETS CONTAINING GUAR GUM**

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN ULCER, NOS	(50)	(50) 1 (2%)	(50)
*SUBCUT TISSUE ABSCESS, NOS NECROSIS, NOS	(50) 1 (2%)	(50)	(50) 1 (2%)
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS INFLAMMATION, NOS	(50)	(50) 1 (2%)	(50) 2 (4%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW HYPERPLASIA, HEMATOPOIETIC	(47) 1 (2%)	(50)	(47)
#SPLEEN HEMATOPOIESIS	(49) 3 (6%)	(50) 5 (10%)	(47) 2 (4%)
#LYMPH NODE NECROSIS, NOS	(42)	(47) 1 (2%)	(46)
#LUMBAR LYMPH NODE HYPERPLASIA, NOS	(42) 1 (2%)	(47)	(46)
#MESENTERIC L. NODE CONGESTION, NOS INFLAMMATION ACUTE AND CHRONIC INFLAMMATION, CHRONIC HYPERPLASIA, NOS	(42) 22 (52%) 1 (2%)	(47) 20 (43%) 1 (2%) 2 (4%) 1 (2%)	(46) 15 (33%)
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HEMATOPOIESIS		1 (2%)	
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS PERIVASCULITIS	(50) 1 (2%)	(50)	(50)
#LUNG PERIVASCULITIS	(50) 1 (2%)	(50) 3 (6%)	(50) 3 (6%)
#HEART PERIVASCULITIS CALCIFICATION, FOCAL	(50) 1 (2%)	(50) 1 (2%)	(50)
#SALIVARY GLAND PERIVASCULITIS	(49) 3 (6%)	(50)	(49)
#STOMACH PERIVASCULITIS	(49) 1 (2%)	(49)	(49)
#KIDNEY PERIVASCULITIS	(50) 6 (12%)	(50)	(50)
#URINARY BLADDER PERIVASCULITIS	(49) 2 (4%)	(49)	(48)
DIGESTIVE SYSTEM			
#SALIVARY GLAND INFLAMMATION, CHRONIC FOCAL	(49)	(50)	(49) 1 (2%)
#LIVER CYST, NOS INFLAMMATION ACUTE AND CHRONIC NECROSIS, NOS NECROSIS, FOCAL METAMORPHOSIS FATTY CLEAR-CELL CHANGE	(50) 1 (2%) 2 (4%) 1 (2%)	(50) 1 (2%) 1 (2%) 3 (6%) 1 (2%) 1 (2%)	(50)
*GALLBLADDER INFLAMMATION, CHRONIC	(50)	(50) 1 (2%)	(50)
#BILE DUCT DILATATION, NOS	(50)	(50) 2 (4%)	(50)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CYST, NOS		1 (2%)	
#PANCREATIC ACINUS ATROPHY, NOS	(47)	(48) 1 (2%)	(43)
#STOMACH	(49)	(49)	(49)
EPIDERMAL INCLUSION CYST		2 (4%)	
INFLAMMATION, ACUTE FOCAL	1 (2%)		
PARASITISM	2 (4%)		
HYPERPLASIA, BASAL CELL			1 (2%)
HYPERKERATOSIS		1 (2%)	1 (2%)
ACANTHOSIS		1 (2%)	
#GASTRIC MUCOSA	(49)	(49)	(49)
ECTOPIA		1 (2%)	
ATYPIA, NOS			3 (6%)
METAPLASIA, SQUAMOUS	2 (4%)	2 (4%)	1 (2%)
#FORESTOMACH	(49)	(49)	(49)
HYPERPLASIA, BASAL CELL			1 (2%)
HYPERKERATOSIS			1 (2%)
ACANTHOSIS		1 (2%)	
#COLON	(45)	(48)	(42)
PARASITISM		1 (2%)	1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
PYELONEPHRITIS, FOCAL		2 (4%)	
INFLAMMATION, CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
AMYLOIDOSIS			1 (2%)
CALCIFICATION, FOCAL	1 (2%)	1 (2%)	
#KIDNEY/TUBULE	(50)	(50)	(50)
REGENERATION, NOS		1 (2%)	
#URINARY BLADDER	(49)	(49)	(48)
CALCULUS, NOS	1 (2%)	2 (4%)	
OBSTRUCTION, NOS	1 (2%)		
INFLAMMATION, CHRONIC		1 (2%)	
*PROSTATIC URETHRA	(50)	(50)	(50)
CALCULUS, NOS		1 (2%)	1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#ADRENAL CYST, NOS	(46)	(47) 1 (2%)	(48)
#ADRENAL MEDULLA HYPERPLASIA, NOS	(46)	(47) 2 (4%)	(48)
#PANCREATIC ISLETS HYPERPLASIA, NOS	(47) 1 (2%)	(48) 1 (2%)	(43) 1 (2%)
REPRODUCTIVE SYSTEM			
*PENIS INFLAMMATION, ACUTE INFLAMMATION, CHRONIC	(50) 1 (2%)	(50) 1 (2%)	(50)
*PREPUTIAL GLAND INFLAMMATION, NOS ABSCESS, NOS	(50) 1 (2%)	(50) 1 (2%)	(50)
#PROSTATE INFLAMMATION, CHRONIC	(42) 1 (2%)	(45)	(48)
*SEMINAL VESICLE FIBROSIS ATROPHY, NOS	(50)	(50) 2 (4%) 1 (2%)	(50)
#TESTIS AMYLOIDOSIS CALCIFICATION, FOCAL ATROPHY, NOS ATROPHY, FOCAL	(50) 1 (2%) 1 (2%)	(49) 1 (2%)	(50) 1 (2%) 1 (2%)
NERVOUS SYSTEM			
#BRAIN CALCIFICATION, FOCAL	(50) 20 (40%)	(50) 31 (62%)	(50) 34 (68%)
SPECIAL SENSE ORGANS			
NONE			

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
*SKULL	(50)	(50)	(50)
FIBROSIS	1 (2%)		
HYPEROSTOSIS	2 (4%)		
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
NECROSIS, FAT			1 (2%)
ALL OTHER SYSTEMS			
OMENTUM			
NECROSIS, FAT	1		
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	5	1	4
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

TABLE D2.

**SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE
FED DIETS CONTAINING GUAR GUM**

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS INFLAMMATION, NOS	(50)	(49) 1 (2%)	(50) 1 (2%)
#LUNG/BRONCHIOLE METAPLASIA, NOS	(50) 1 (2%)	(49)	(50)
#LUNG METAPLASIA, NOS	(50)	(49) 1 (2%)	(50)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS HEMATOPOIESIS	(50) 1 (2%)	(49)	(50)
#BONE MARROW FIBROSIS, FOCAL HYPERPLASIA, HEMATOPOIETIC	(48) 32 (67%) 1 (2%)	(47) 26 (55%)	(49) 26 (53%) 2 (4%)
#SPLEEN CONGESTION, NOS INFARCT, FOCAL HEMATOPOIESIS	(50) 2 (4%)	(49) 2 (4%) 1 (2%) 1 (2%)	(50) 1 (2%) 8 (16%)
#MEDIASTINAL L. NODE HYPERPLASIA, NOS	(42)	(41) 1 (2%)	(45)
#MESENTERIC L. NODE CONGESTION, NOS	(42) 3 (7%)	(41) 2 (5%)	(45) 2 (4%)
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, NOS			1 (2%)
#RENAL LYMPH NODE INFLAMMATION ACUTE AND CHRONIC HYPERPLASIA, NOS	(42)	(41)	(45) 1 (2%) 1 (2%)
#LUNG HEMATOPOIESIS	(50)	(49)	(50) 1 (2%)
#LIVER HEMATOPOIESIS	(50)	(49)	(49) 2 (4%)
#THYMUS CYST, NOS	(23)	(25)	(27) 1 (4%)
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS PERIARTERITIS PERIVASCULITIS	(50) 1 (2%)	(49) 1 (2%)	(50) 1 (2%)
#LUNG PERIVASCULITIS	(50) 2 (4%)	(49)	(50) 1 (2%)
#MYOCARDIUM DEGENERATION, NOS	(50) 1 (2%)	(49)	(50)
#STOMACH PERIARTERITIS	(47)	(48)	(47) 1 (2%)
#KIDNEY PERIVASCULITIS	(49)	(49) 4 (8%)	(49)
#URINARY BLADDER PERIARTERITIS PERIVASCULITIS	(47) 7 (15%)	(48) 6 (13%)	(48) 1 (2%) 1 (2%)
DIGESTIVE SYSTEM			
#LIVER ABSCESS, NOS NECROSIS, FOCAL INFARCT, NOS	(50) 1 (2%)	(49) 1 (2%) 1 (2%)	(49) 2 (4%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
METAMORPHOSIS FATTY	2 (4%)	4 (8%)	1 (2%)
FOCAL CELLULAR CHANGE		1 (2%)	
CLEAR-CELL CHANGE	1 (2%)	1 (2%)	
*GALLBLADDER	(50)	(49)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
#BILE DUCT	(50)	(49)	(49)
CYST, NOS		1 (2%)	
#PANCREAS	(44)	(48)	(47)
DILATATION/DUCTS	1 (2%)	1 (2%)	
CYSTIC DUCTS	1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	
FIBROSIS	1 (2%)		
ATROPHY, NOS		1 (2%)	
ATROPHY, FOCAL	1 (2%)		
#PANCREATIC ACINUS	(44)	(48)	(47)
ATROPHY, NOS		2 (4%)	1 (2%)
#STOMACH	(47)	(48)	(47)
ULCER, NOS	1 (2%)		
INFLAMMATION, FOCAL	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)	2 (4%)	
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, EPITHELIAL	2 (4%)		
HYPERPLASIA, PAPILLARY	1 (2%)		
HYPERPLASIA, BASAL CELL			1 (2%)
HYPERKERATOSIS		1 (2%)	1 (2%)
ACANTHOSIS		4 (8%)	
#GASTRIC MUCOSA	(47)	(48)	(47)
ATYPIA, NOS			3 (6%)
METAPLASIA, SQUAMOUS	2 (4%)		1 (2%)
#FORESTOMACH	(47)	(48)	(47)
INFLAMMATION ACUTE AND CHRONIC			1 (2%)
HYPERPLASIA, BASAL CELL			1 (2%)
ACANTHOSIS	1 (2%)		2 (4%)
#COLON	(44)	(45)	(45)
PARASITISM		3 (7%)	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#KIDNEY	(49)	(49)	(49)
NEPHROPATHY		1 (2%)	
AMYLOIDOSIS			1 (2%)
CALCIFICATION, FOCAL			1 (2%)
#URINARY BLADDER	(47)	(48)	(48)
INFLAMMATION, CHRONIC		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(43)	(43)	(43)
HEMORRHAGE			1 (2%)
HYPERPLASIA, FOCAL	3 (7%)	1 (2%)	
HYPERPLASIA, CHROMOPHOBE-CELL			2 (5%)
#ADRENAL	(47)	(46)	(46)
AMYLOIDOSIS			1 (2%)
#THYROID	(49)	(44)	(45)
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)	1 (2%)	
#PARATHYROID	(34)	(26)	(24)
HYPERPLASIA, NOS	1 (3%)		
#PANCREATIC ISLETS	(44)	(48)	(47)
HYPERPLASIA, NOS			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(49)	(50)
LACTATION		1 (2%)	
#UTERUS	(49)	(48)	(48)
HYDROMETRA	8 (16%)	3 (6%)	1 (2%)
CYST, NOS	1 (2%)		
INFLAMMATION, NOS	1 (2%)		1 (2%)
PYOMETRA	2 (4%)	2 (4%)	
#UTERUS/ENDOMETRIUM	(49)	(48)	(48)
INFLAMMATION, ACUTE		1 (2%)	2 (4%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, CHRONIC HYPERPLASIA, CYSTIC	23 (47%)	18 (38%)	1 (2%) 20 (42%)
#OVARY/OVIDUCT INFLAMMATION, CHRONIC	(49)	(48)	(48) 1 (2%)
#TUBO OVARIAN COMBINE ABSCESS, NOS	(49) 1 (2%)	(48)	(48) 4 (8%)
#OVARY CYST, NOS HEMORRHAGIC CYST ABSCESS, NOS	(40) 4 (10%) 2 (5%)	(42) 5 (12%)	(41) 7 (17%) 3 (7%)
NERVOUS SYSTEM			
#BRAIN CALCIFICATION, FOCAL CHOLESTEATOMA	(50) 16 (32%) 1 (2%)	(47) 15 (32%)	(50) 12 (24%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM NECROSIS, FAT	(50)	(49) 1 (2%)	(50)
*ABDOMINAL CAVITY NECROSIS, FAT	(50)	(49) 1 (2%)	(50)
*PERITONEUM CYST, NOS INFLAMMATION, NOS	(50) 1 (2%) 1 (2%)	(49)	(50)
ALL OTHER SYSTEMS			
OMENTUM NECROSIS, FAT		1	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	2	1	
AUTOLYSIS/NO NECROPSY		1	

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

Appendix E

Analysis of Guar Gum
(Lot No. A-40-F and Lot No. F10-77-966-1)
Midwest Research Institute

Appendix E

(Batch 01, Lot No. A-40 and Batch 02, Lot No. F10-77-966-1)
Midwest Research Institute

A. MELTING POINT

	<u>Determined</u>	<u>Literature Values</u>
Batch 01	m.p.: 215°-300°, decomp. (visual, capillary) Endotherm 202°-266° C Exotherm beginning at 300°C, decomp. (Dupont 900 DTA)	No literature value found

B. THIN-LAYER CHROMATOGRAPHY OF HYDROLYSIS PRODUCTS AFTER REACTION WITH H₂SO₄, NEUTRALIZATION WITH BaCO₃, AND FILTRATION (Varma et al., 1973)

Batch 01	Plates: Silica Gel 60 F-254	Ref. Standard: D-galactose D-mannose
	Amount Spotted: 20 μg	Visualization: 0.5% potassium permanganate in 1 N sodium hydroxide
	System 1: n-Butanol:acetic acid:water (63:12:25)	System 2: n-Butanol:pyridine:water (46:31:23)
	R _f : 0.18 (minor) (D-galactose) 0.28 (major) (D-mannose)	R _f : 0.51 (minor) 0.62 (major)
	R _{st} : 0.67, 1.04 relative to D-mannose 0.95, 1.47 relative to D-galactose	R _{st} : 0.82, 1.00 relative to D-mannose 0.98, 1.19 relative to D-galactose
Batch 02	Plates: Silica Gel 60 F-254	Ref. Standard: D-galactose D-mannose
	Amount Spotted: 42.3 μg, 2.1 μg/μl in H ₂ O:methanol, (25:75)	Visualization: 0.5% potassium permanganate in 1 N sodium hydroxide
	System 1: n-Butanol:acetic acid:water (63:12:25)	System 2: n-Butanol:pyridine: water (46:31:23)
	R _f : 0.19 (minor) (D-galactose) 0.27 (major) (D-mannose)	R _f : 0.01 (trace), 0.48 (minor) (D-galactose), 0.57 (major) (D-mannose)
	R _{st} : 0.75, 1.05 relative to D-mannose 0.98, 1.38 relative to D-galactose	R _{st} : 0.01, 0.86, 1.02 relative to D-mannose 0.02, 1.01, 1.19 relative to D-galactose

C. WATER ANALYSIS

Batch 01 (Karl Fisher) 7.3 ± 0.1 (δ)%

Batch 02 (Karl Fisher) 4.94 ± 0.02 (δ)%

D. TITRATION BY PERIODATE OXIDATION

Modification of U. S. P. Assay for Mannitol (USP, 1970).

Samples were dissolved in 25 ml of concentrated sulfuric acid and 150 ml water in 250-ml volumetric flasks and left at room temperature for 65 hours. The solutions were then boiled for 55 minutes on a hot plate. The flasks were cooled and diluted to volume with water. Aliquouts (5 ml) were transferred to 125-ml Erlenmeyer flasks with 50.0 ml potassium periodate/sulfuric acid solution added. One sample and the blank were heated on a steam bath for 25 hours.

Batch 01 Results: 83.5 ± 0.9 (δ)% compared with glucose.

Batch 02 Results: 91.9 ± 1.9 (δ)%

E. SPECTRAL DATA

(1) Infrared

	<u>Methods</u>	<u>Results</u>
Batch 01	Instrument: Beckman IR-12	(See Figures 5 and 6) Consistent with literature spectrum of guar gum (McNulty, 1960).
and	Cell: 1.5% in KBr	
Batch 02		

(2) Ultraviolet/Visible

Batch 01	Instrument: Cary 118	No absorbance between 220 and 350 nm (ultraviolet range) or between 350 and 800 nm (visible range).
	Concentration: 0.1 mg/ml	No literature reference found.
	Solvent: water	

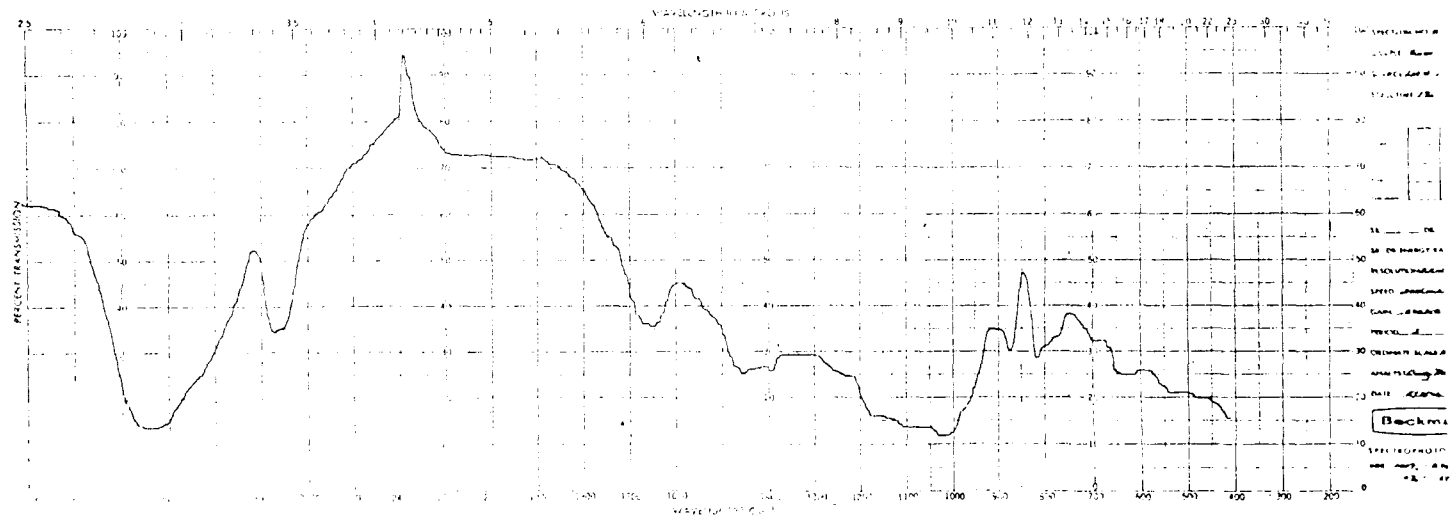


Figure 5. Infrared Absorption Spectrum of Guar Gum (Lot No. A-40-F)

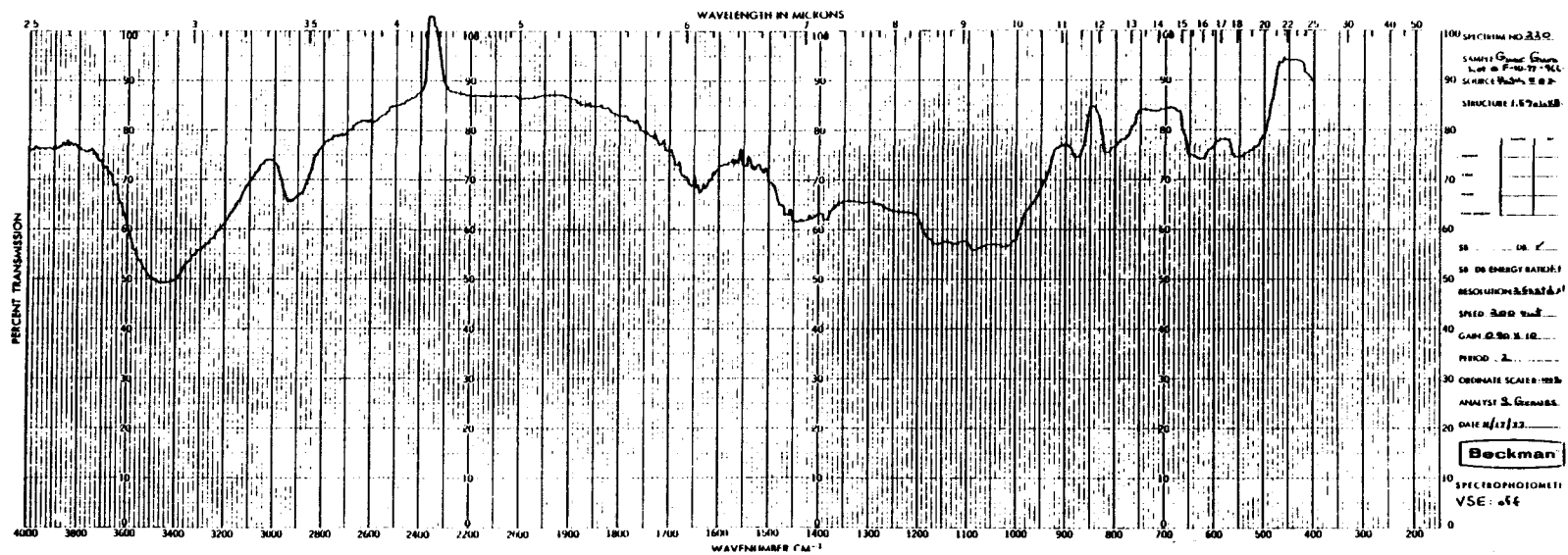


Figure 6. Infrared Absorption Spectrum of Guar Gum (Lot No. F10-77-966-1)

Appendix F

**Feed Consumption by Rats
and Mice Receiving Guar Gum**

Appendix F

Feed Consumption by Rats and Mice
Receiving Guar Gum

Table F-1. Feed Consumption by Male Rats Receiving Guar Gum

Week	Control	Low		High	
	Grams Feed/ Day (a)	Grams Feed/ Day (a)	Low/ Control (b)	Grams Feed/ Day (a)	High/ Control (b)
4	18.6	20.6	1.1	22.4	1.2
8	18.7	16.1	0.9	13.9	0.7
12	19.9	17.1	0.9	17.7	0.9
16	20.0	18.7	0.9	17.9	0.9
20	15.0	12.3	0.8	11.6	0.8
24	26.4	19.9	0.8	18.6	0.7
28	19.7	22.0	1.1	22.9	1.2
32	23.1	22.0	1.0	19.0	0.8
37	19.3	21.1	1.1	19.9	1.0
40	22.1	21.1	1.0	19.1	0.9
45	23.4	21.0	0.9	20.4	0.9
48	24.9	23.1	0.9	20.4	0.8
52	25.6	24.4	1.0	21.9	0.9
57	27.7	25.4	0.9	23.6	0.9
61	28.1	26.3	0.9	24.1	0.9
64	24.7	21.3	0.9	19.7	0.8
69	23.0	19.9	0.9	19.3	0.8
72	23.4	20.1	0.9	18.7	0.8
76	20.0	19.0	1.0	17.9	0.9
81	21.9	21.3	1.0	18.6	0.8
84	21.1	20.3	1.0	17.0	0.8
89	21.1	18.6	0.9	16.6	0.8
93	25.6	21.3	0.8	19.9	0.8
97	23.9	21.7	0.9	19.9	0.8
101	21.6	17.4	0.8	19.6	0.9
Mean	22.4	20.5	0.9	19.2	0.9
SD (c)	3.1	2.9	0.1	2.8	0.1
CV (d)	13.8	14.1	11.1	14.6	11.1

(a) Grams of feed consumed per animal per day.

(b) Ratio of feed consumption per day for the dosed group to that for the controls.

(c) Standard Deviation.

(d) Coefficient of variation (Standard Deviation divided by mean) x 100.

Table F-2. Feed Consumption by Female Rats Receiving Guar Gum

Week	Control	Low		High	
	Grams Feed/ Day (a)	Grams Feed/ Day (a)	Low/ Control (b)	Grams Feed/ Day (a)	High/ Control (b)
4	14.9	16.3	1.1	19.1	1.3
8	18.3	14.7	0.8	9.4	0.5
12	18.9	12.1	0.6	12.4	0.7
16	16.9	12.6	0.7	12.1	0.7
20	15.9	10.9	0.7	8.7	0.5
24	20.9	19.4	0.9	13.7	0.7
28	17.4	19.9	1.1	23.1	1.3
32	22.1	20.0	0.9	16.3	0.7
36	19.6	19.3	1.0	17.7	0.9
40	19.7	16.4	0.8	13.6	0.7
44	22.3	19.7	0.9	16.0	0.7
49	20.6	17.9	0.9	15.1	0.7
53	18.6	16.6	0.9	15.1	0.8
56	22.1	18.4	0.8	16.7	0.7
61	22.1	19.0	0.9	15.9	0.7
65	24.1	19.1	0.8	15.7	0.7
68	21.6	17.9	0.8	15.6	0.7
72	22.6	17.6	0.8	15.4	0.7
73	23.7	16.6	0.7	15.1	0.6
77	21.0	15.6	0.7	14.7	0.7
80	19.6	16.9	0.9	16.6	1.8
81	16.1	18.1	1.1	16.0	1.0
85	12.6	17.0	1.3	15.3	1.2
88	14.7	13.3	0.9	13.9	0.9
92	24.3	14.6	0.6	19.7	0.8
97	20.9	16.4	0.8	16.6	0.8
100	15.1	13.3	0.9	16.6	1.1
Mean	19.5	16.6	0.9	15.4	0.9
SD (c)	3.2	2.6	0.2	2.9	0.2
CV (d)	16.4	15.6	22.2	18.8	22.2

(a) Grams of feed consumed per animal per day.

(b) Ratio of feed consumption per day for the dosed group to that for the controls.

(c) Standard Deviation.

(d) Coefficient of variation (Standard Deviation divided by mean) x 100.

Table F-3. Feed Consumption by Male Mice Receiving Guar Gum

Week	Control	Low		High	
	Grams Feed/ Day (a)	Grams Feed/ Day (a)	Low/ Control (b)	Grams Feed/ Day (a)	High/ Control (b)
4	8.6	7.7	0.9	7.0	0.8
8	9.1	8.4	0.9	8.3	0.9
12	8.3	7.1	0.9	8.4	1.0
16	9.0	7.4	0.8	7.4	0.8
20	9.7	8.6	0.9	8.0	0.8
24	8.9	8.1	0.9	8.1	0.9
28	7.9	8.1	1.0	7.9	1.0
32	6.1	5.6	0.9	5.6	0.9
36	8.3	7.9	1.0	7.3	0.9
40	8.1	7.4	0.9	7.1	0.9
44	7.3	6.1	0.8	5.7	0.8
48	7.6	6.4	0.8	6.9	0.9
52	7.1	5.6	0.8	5.1	0.7
56	7.6	5.9	0.8	6.3	0.8
60	8.0	6.9	0.9	6.9	0.9
64	6.9	5.9	0.9	6.0	0.9
68	7.6	4.9	0.6	6.3	0.8
72	8.6	6.6	0.8	7.0	0.8
76	9.3	5.9	0.6	9.9	1.1
80	8.7	6.4	0.7	6.6	0.8
84	9.4	7.9	0.8	6.9	0.7
88	8.0	6.0	0.8	6.0	0.8
92	7.7	5.9	0.8	6.4	0.8
96	8.6	6.1	0.7	6.1	0.7
100	10.3	7.1	0.7	7.4	0.7
Mean	8.3	6.8	0.9	7.0	0.9
SD (c)	0.9	1.0	0.1	1.1	0.1
CV (d)	10.8	14.7	11.1	15.7	11.1

(a) Grams of feed consumed per animal per day.

(b) Ratio of feed consumption per day for the dosed group to that for the controls.

(c) Standard Deviation.

(d) Coefficient of variation (Standard Deviation divided by mean) x 100.

Table F-4. Feed Consumption by Female Mice Receiving Guar Gum

Week	Control	Low		High	
	Grams Feed/ Day (a)	Grams Feed/ Day (a)	Low/ Control (b)	Grams Feed/ Day (a)	High/ Control (b)
4	8.1	8.3	1.0	7.6	0.9
8	9.7	9.0	0.9	9.3	1.0
12	10.0	10.1	1.0	9.3	0.9
16	9.6	9.4	1.0	9.6	1.0
20	10.4	10.1	1.0	7.6	0.7
24	10.3	10.0	1.0	10.6	1.0
28	9.7	9.0	0.9	10.0	1.0
32	8.6	7.0	0.8	8.4	1.0
36	8.3	8.6	1.0	9.4	1.1
40	10.1	8.7	0.9	8.6	0.9
44	7.7	7.1	0.9	7.6	1.0
48	8.7	7.7	0.9	8.7	1.0
52	8.7	7.6	0.9	8.1	0.9
56	9.3	6.7	0.7	7.3	0.8
60	9.1	7.6	0.8	8.3	0.9
64	8.1	7.1	0.9	6.3	0.8
68	9.3	8.1	0.9	8.6	0.9
72	9.1	9.0	1.0	9.0	1.0
76	11.1	8.9	0.8	9.9	0.9
80	10.7	9.1	0.9	8.9	0.8
84	11.6	8.4	0.7	8.6	0.7
88	10.0	7.0	0.7	8.0	0.8
92	8.4	6.0	0.7	8.1	1.0
96	9.1	8.1	0.9	8.7	1.0
100	8.7	7.4	0.9	8.6	1.0
Mean	9.4	8.3	0.9	8.6	0.9
SD (c)	1.0	1.1	0.1	0.9	0.1
CV (d)	10.6	13.2	11.1	10.5	11.1

(a) Grams of feed consumed per animal per day.

(b) Ratio of feed consumption per day for the dosed group to that for the controls.

(c) Standard Deviation.

(d) Coefficient of variation (Standard Deviation divided by mean) x 100.

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