National Cancer Institute
CARCINOGENESIS
Technical Report Series
No. 15
1977

BIOASSAY OF

CAPTAN

FOR POSSIBLE CARCINOGENICITY

CAS No. 133-06-2

NCI-CG-TR-15

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health

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Carcinogen Bioassay and Program Resources Branch
Carcinogenesis Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20014

DHEW Publication No. (NIH) 77-815

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CONTRIBUTORS: This report presents the results of the bioassay of captan for possible carcinogenicity, conducted for the Carcinogen Bioassay and Program Resources Branch, Carcinogenesis Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), Bethesda, Maryland. The bioassay was conducted by Gulf South Research Institute, New Iberia, Louisiana, initially under direct contract to NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI carcinogenesis bioassay program.

The experimental design was determined by Drs. J. H. Weisburger[1,2] and R. R. Bates[1,3]; the doses were selected by Drs. T. E. Shellenberger[4,5], J. H. Weisburger, and R. R. Bates. Animal treatment and observation were supervised by Drs. T. E. Shellenberger and H. P. Burchfield[4], with the technical assistance of Ms. D. H. Monceaux[4] and Mr. D. Broussard[4]. Histopathology was performed by Drs. E. Bernal[4] and B. Buratto[4] at Gulf South Research Institute, and the diagnoses included in this report represent the interpretation of these pathologists. Pathologists from NCI and Tracor Jitco have reviewed selected slides and concur with the overall pathologic evaluation of the study.

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute[6]. Statistical analyses were performed by Dr. J. R. Joiner[7], using methods selected for the bioassay program by Dr. J. J. Gart[8]. Chemicals used in this bioassay were analyzed under the direction of Dr. H. P. Burchfield, and the analytical results were reviewed by Dr. S. S. Olin[7].

This report was prepared at Tracor Jitco under the direction of NCI. Those responsible for the report at Tracor Jitco were Dr. Marshall Steinberg[7], Director of the Bioassay Program; Drs. J. F. Robens[7] and O. G. Fitzhugh[7], toxicologists; Mr. W. D. Reichardt[7] and Ms. L. A. Waitz[7], bioscience writers; and Dr. E. W. Gunberg[7], technical editor, assisted by Ms. Y. E. Presley[7].

The statistical analysis was reviewed by a member or members of the Mathematical Statistics and Applied Mathematics Section of NCI (Dr. John J. Gart, Mr. Jun-mo Nam, Dr. Hugh M. Pettigrew, and Dr. Robert E. Tarone served as reviewers on an alternating basis).

The following other scientists at the National Cancer Institute were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings:

Dr. Kenneth C. Chu
Dr. Cipriano Cueto, Jr.
Dr. J. Fielding Douglas
Dr. Dawn G. Goodman
Dr. Richard A. Griesemer
Dr. Thomas W. Orme
Dr. Robert A. Squire[9]
Dr. Jerrold M. Ward

---

[1]Carcinogenesis Program, Divison of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

[2]Now with the Naylor Dana Institute for Disease Prevention, American Health Foundation, Hammond House Road, Valhalla, New York.

[3]Now with the Office of the Commissioner, Food and Drug Administration, Rockville, Maryland.

[4]Gulf South Research Institute, Atchafalaya Basin Laboratories, P. O. Box 1177, New Iberia, Louisiana.

[5]Now with the National Center for Toxicological Research, Jefferson, Arkansas.

[6]EG&G Mason Research Institute, 1530 East Jefferson Street, Rockville, Maryland.

[7]Tracor Jitco, Inc., 1776 East Jefferson Street, Rockville, Maryland.

[8]Mathematical Statistics and Applied Mathematics Section, Biometry Branch, Field Studies and Statistics, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

[9]Now with the Division of Comparative Medicine, Johns Hopkins University, School of Medicine, Traylor Building, Baltimore, Maryland.

SUMMARY

A bioassay of technical-grade captan for possible carcinogenicity was conducted by administering the test material in feed to Osborne-Mendel rats and B6C3F1 mice.

Groups of 50 rats of each sex were administered one of two doses of captan for 80 weeks, then observed for 33 or 34 weeks. The time-weighted average doses for both sexes of rats were 2,525 or 6,050 ppm. Matched controls consisted of groups of 10 untreated rats of each sex; pooled controls, used for statistical evaluation, consisted of the matched controls combined with 75 untreated male and 75 untreated female rats from similar bioassays of six other test chemicals. All surviving rats were killed at 113-114 weeks.

Groups of 50 mice of each sex were administered the test material at one of two doses, either 8,000 or 16,000 ppm, for 80 weeks, then observed for 11 weeks. Matched controls consisted of groups of 10 untreated mice of each sex; pooled controls, used for statistical evaluation, consisted of the matched controls combined with 80 untreated male and 80 untreated female mice from similar bioassays of six other test chemicals. All surviving mice were killed at 90-91 weeks.

The mean body weights of both low- and high-dose rats and high-dose mice were lower than those of the matched controls throughout most of the study. Mortality rates did not show statistically significant dose-related trends in either sex of either species.

In rats, a positive dose-related trend and a difference between incidences of tumors in high-dose and pooled-control groups were found in females when the data for adrenal cortical adenoma were combined with those for adrenal cortical carcinoma (pooled controls 0/64, low-dose 2/50, high-dose 3/47, P = 0.047). There was also a positive dose-related trend for the incidence of

C-cell adenoma of the thyroid in female rats (pooled controls 1/66, low-dose 1/49, high-dose 4/44, P = 0.035). These endocrine tumors in female rats are believed to have been spontaneous, and not related to treatment.

In mice, the incidences of polypoid carcinoma (adenocarcinoma in adenomatous polyp) of the duodenum were statistically significant using tests for a positive dose-related trend both in male mice (pooled controls 0/68, low-dose 1/43, high-dose 3/46, P = 0.033) and in female mice (pooled controls 0/68, low-dose 0/49, high-dose 3/48, P = 0.022). When the incidences of adenomatous polyp, NOS (not otherwise specified), were combined with those of polypoid carcinoma for statistical analysis, the tests for male mice indicated a substantial increase in significance (pooled controls 0/68, low-dose 3/43, high-dose 5/46, P = 0.008).

It is concluded that under the conditions of this bioassay, tumors in the duodenum of B6C3F1 mice were associated with treatment with captan, but there was no convincing evidence that the tumors observed in Osborne-Mendel rats were related to treatment.

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I. INTRODUCTION

Captan (CAS 133-06-2; NCI C00077) is a broad-spectrum fungicide which inhibits mycelial growth from germinating fungus spores (EPA, 1974). As a result, it has effective protective action, although it will not eradicate a preexisting infection (Billings, 1974; EPA, 1974). Because captan is a nonpersistent fungicide (EPA, 1974), directions for use indicate that it should be reapplied every week as necessary to maintain control (Stauffer Chemicals, 1975). It has been one of the most widely used fungicides since its introduction in 1950 (EPA, 1974).

Captan is registered for use in foliar and soil applications for growing vegetables, fruits, nut trees, and ornamental plants, and for treatment of seeds and turf (EPA Compendium, 1975). It is also used as an industrial fungicide in paints, plastics, leather, and certain soaps and shampoos. Residue tolerances on foods range from 2 to 100 ppm (EPA, 1975). The World Health Organization has established an acceptable daily intake of 0-0.1 mg/kg (WHO, 1974).

Captan was selected for screening for carcinogenic activity because there was a potential for long-term human exposure during agricultural, industrial, or other applications, or from residues in food products.

II. MATERIALS AND METHODS

A. Chemical

Captan, the common name for N-((trichloromethyl)thio)-4-cyclohexene-1,2-dicarboximide, was obtained in a single batch (Lot No. 5x-317) from the Chevron Chemical Company, Ortho Division, San Francisco, California, for use in the chronic study. The identity of the chemical was confirmed at Gulf South Research Institute by infrared, nuclear magnetic resonance, and isobutane chemical ionization mass spectra. Gas-liquid chromatography (electron capture detector, 10% DC-200 column) showed a single peak. No attempt was made to identify or quantitate impurities. The chemical was stored at approximately 4°C.

B. Dietary Preparation

All diets were formulated using finely ground Wayne® Lab Blox (Allied Mills, Inc., Chicago, Ill.) to which was added the required amount of captan for each dietary concentration. A given amount of the test chemical was first hand-mixed with an approximately equal amount of feed. This mixture was then added slowly with mechanical mixing to a larger quantity of feed to give the desired concentration of the chemical. Acetone (Mallinckrodt, Inc., St. Louis, Mo.) and corn oil (Louana®, Opelousas Refinery Co., Opelousas, La.) were then added to the

feed, each in an amount corresponding to 2% of the final weight of feed. The diets were mixed mechanically for not less than 25 minutes to assure homogeniety of the mixture and evaporation of the acetone. Formulated diets were stored at approximately 17°C until used, but no longer than 1 week.

The stability of captan in feed was tested by determining the concentration of the chemical in formulated diets at intervals over a 7-day period. Diets containing 8,000 or 16,000 ppm captan showed no change in concentration on standing at ambient temperature for this period.

As a quality control test on the accuracy of preparation of the diets, the concentration of captan was determined in different batches of formulated diets during the chronic study. The results are summarized in Appendix G. At each dietary concentration, the mean of the analytical concentrations for the samples tested was within 2.5% of the theoretical concentration, and the coefficient of variation was never more than 5.9%. Thus, the evidence indicates that the formulated diets were prepared accurately.

C. Animals

Rats and mice of both sexes obtained through contracts of the Division of Cancer Treatment, National Cancer Institute, were

used in these bioassays. The rats were of the Osborne-Mendel strain obtained from Battelle Memorial Institute, Columbus, Ohio, and the mice were B6C3F1 hybrids obtained from Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. Upon arrival at the laboratory, all animals were quarantined for an acclimation period (rats for 6 or 7 days, mice for 15 days) and then assigned to control and test groups.

D. Animal Maintenance

All animals were housed in temperature- and humidity-controlled rooms. The temperature range was 22-24°C, and the relative humidity was maintained at 40-70%. The air in each room was changed 10-12 times per hour. Fluorescent lighting provided illumination 10 hours per day. Food and water were presented *ad libitum*.

The rats were housed individually in hanging galvanized steel mesh cages, and the mice were housed in plastic cages with filter bonnets, five per cage for females, and two or three per cage for males. Initially, rats were transferred one time per week to clean cages; later in the study, cages were changed every 2 weeks. Mice were transferred one time per week to clean cages with filter bonnets; bedding used for the mice was Absorb-Dri® (Lab Products, Inc., Garfield, N.J.). For rats, absorbent sheets

under the cages were changed three times per week. Feeder jars and water bottles were changed and sterilized three times per week.

Cages for control and treated mice were placed on separate racks in the same room. Animal racks for both species were rotated laterally one time per week; at the same time each cage was changed to a different position in the row within the same column. Rats receiving captan, along with their matched controls, were housed in a room by themselves. Mice receiving captan were maintained in a room housing mice administered aldrin (CAS 309-00-2) or photodieldrin (CAS 13366-73-9), together with their respective matched controls.

E. Subchronic Studies

Subchronic studies were conducted to estimate the maximum tolerated doses of captan, on the basis of which low and high concentrations (hereinafter referred to as "low doses" and "high doses") were determined for administration in the chronic studies. In these subchronic studies, captan was added to the animal feed in twofold increasing concentrations, ranging from 500 to 32,000 ppm for both rats and mice. The treated and control groups each consisted of five male and five female animals. The chemical was provided in the feed to the treated

groups for 6 weeks, followed by a period of observation for 2 weeks.

In both male and female rats, weight depression was apparent at 8,000 and 16,000 ppm during the first weeks. Later, these animals appeared to adapt to the test chemical, and gains in weight approached those of the controls. There were no deaths in either male or female rats. The low and high doses for the chronic studies in rats were set at 8,000 and 16,000 ppm.

In male and female mice, there was little, if any, adverse effect on weight gain at dietary concentrations as high as 8,000 ppm. At 16,000 ppm, captan caused a loss in weight among males during the first 2 weeks and among females during the first week of the feeding period; as the study progressed, treated animals of both sexes recovered and their gains in weight were similar to those of the controls. Weight losses were more marked at 32,000 ppm in males and females during the initial weeks, and four males and all females died during the study. The low and high doses for the chronic study in mice were set at 8,000 and 16,000 ppm.

F. Designs of Chronic Studies

The designs of the chronic studies are shown in tables 1 and 2.

Initially, doses of 8,000 or 16,000 ppm were administered to

Table 1. Design of Captan Chronic Feeding Studies in Rats

Sex and Treatment Group	Initial No. of Animals[b]	Captan in Diet (ppm)	Time on Study Treated (weeks)[c]	Time on Study Untreated (weeks)[d]	Time-Weighted Average Dose[e] (ppm)
MALE					
Matched-Control[a]	10	0		114	
Low-Dose	50	4,000	21		
		2,000	59		2,525
		0		33	
High-Dose	50	8,000	41		
		4,000	39		6,050
		0		34	
FEMALE					
Matched-Control[a]	10	0		114	
Low-Dose	50	4,000	21		
		2,000	59		2,525
		0		33	
High-Dose	50	8,000	41		
		4,000	39		6,050
		0		34	

[a]The matched controls consisted of 5 animals of each sex, started with the low-dose animals, and 5 animals of each sex, started with the high-dose animals.

[b]All animals were 35 days of age when placed on study.

[c]Doses of captan were lowered at week 21 during the study, since it was believed that excessive mortality might occur before termination of the study based on the mortality, weight changes, and general condition of rats used in similar bioassays of other chemicals at Gulf South Research Institute.

Table 1. Design of Captan Chronic Feeding Studies in Rats

(continued)

[d]When diets containing captan were discontinued, the high-dose rats and their matched controls were fed the control diet without corn oil for 6 weeks, then the control diet (2% corn oil added) for an additional 28 weeks, while low-dose rats received only the control diet (2% corn oil added) until termination of the study.

[e]Time-weighted average dose $= \frac{\Sigma(\text{dose in ppm x no. of weeks at that dose})}{\Sigma(\text{no. of weeks receiving each dose})}$

Table 2. Design of Captan Chronic Feeding Studies in Mice

Sex and Treatment Group	Initial No. of Animals[a]	Captan in Diet (ppm)	Time on Study	
			Treated (weeks)	Untreated[b] (weeks)
MALE				
Matched-Control	10	0		91
Low-Dose	50	8,000	80	
		0		11
High-Dose	50	16,000	80	
		0		11
FEMALE				
Matched-Control	10	0		90-91
Low-Dose	50	8,000	80	
		0		11
High-Dose	50	16,000	80	
		0		11

[a]All animals were 35 days of age when placed on study.

[b]When diets containing captan were discontinued, all treated mice and their matched controls were fed the control diet (2% corn oil added) until termination of the study.

groups of rats of each sex. Because the chemical was highly toxic at 16,000 ppm, tests at this dose were terminated after 18 weeks. Five matched controls of each sex were also terminated. The groups receiving 8,000 ppm, originally designated "low-dose," were then redesignated "high-dose," as indicated in table 1.

Seven males and one female of the groups fed at 8,000 ppm had also died by week 18. These rats were replaced with healthy animals selected from the groups fed at 16,000 ppm. Additional groups of male and female rats, designated "low-dose" as indicated in table 1, were started at 4,000 ppm 20 weeks after the beginning of the study. At the same time, five additional matched controls of each sex were started. The time-weighted average doses for the rats were 2,525 and 6,050 ppm.

For the mice, the initial doses of 8,000 and 16,000 ppm were maintained throughout the study, as indicated in table 2.

Since the numbers of animals in the matched-control groups were small, pooled-control groups also were used for statistical comparisons. Matched controls from the current studies on captan were combined with matched controls from studies performed on tetrachlorvinphos (CAS 961-11-5), malathion (CAS 121-75-5), toxaphene (CAS 8001-35-2), endrin (CAS 72-20-8), lindane (CAS 58-89-9), and photodieldrin (CAS 13366-73-9). The pooled

controls for statistical tests using rats consisted of 75 males and 75 females; using mice, 80 males and 80 females. The studies on chemicals other than captan were also conducted at Gulf South Research Institute and overlapped the captan study by at least 1 year. The matched-control groups for the different test chemicals were of the same strain and from the same supplier, and they were examined by the same pathologists. Because additional matched controls were started simultaneously with restarted treatment groups for some of these chemicals, the number of animals in the pooled-control groups varied.

G. Clinical and Pathologic Examinations

All animals were observed twice daily for signs of toxicity, weighed at regular intervals, and palpated for masses at each weighing. Animals that were moribund at the time of clinical examination were killed and necropsied.

The pathologic evaluation consisted of gross and microscopic examination of major tissues, major organs, and all gross lesions from killed animals and from animals found dead. The following tissues were examined microscopically: skin, lungs and bronchi, trachea, bone and bone marrow, spleen, lymph nodes, heart, salivary gland, liver, gallbladder (mice), pancreas, stomach, small intestine, large intestine, kidney, urinary bladder,

pituitary, adrenal, thyroid, parathyroid, mammary gland, prostate or uterus, testis or ovary, and brain. Occasionally, additional tissues were also examined microscopically. The different tissues were preserved in 10% buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Special staining techniques were utilized when indicated for more definitive diagnosis.

A few tissues from some animals were not examined, particularly from those animals that died early. Also, some animals were missing, cannibalized, or judged to be in such an advanced state of autolysis as to preclude histopathologic evaluation. 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 experiment in each group.

H. Data Recording and Statistical Analyses

Pertinent data on this experiment have been recorded in an automatic data processing system, 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). Data tables were generated for verification of data transcription and for statistical review.

These data were analyzed using the statistical techniques described in this section. Those analyses of the experimental results that bear on the possibility of carcinogenicity are discussed in the statistical narrative sections.

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) extensions of Cox's methods for testing for a dose-related trend. One-tailed P values have been reported for all tests except the departure from linearity test, which is only reported when its two-tailed P value is less than 0.05.

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals in which that site is examined (denominator). In most instances,

the denominators included only those animals for which that site was examined histologically. However, when macroscopic examination was required to detect lesions prior to histologic sampling (e.g., skin or mammary tumors), or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

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

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971), was also used. Under the assumption of a linear trend, this test determines if the slope

of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend is a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

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

When appropriate, 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 animals died naturally or were sacrificed was entered as the time point of tumor observation. Cox's methods of comparing these curves were used for two groups;

Tarone's extension to testing for linear trend was used for three groups. The statistical tests for the incidence of tumors which used life-table methods were one-tailed and, unless otherwise noted, in the direction of a positive dose relationship. Significant departures from linearity ($P < 0.05$, two-tailed test) were also noted.

The approximate 95 percent confidence interval for the relative risk of each treated group compared to its control was calculated from the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as p_t/p_c where p_t is the true binomial probability of the incidence of a specific type of tumor in a treated group of animals and p_c is the true probability of the spontaneous incidence of the same type of tumor in a control group. The hypothesis of equality between the true proportion of a specific tumor in a treated group and the proportion in a control group corresponds to a relative risk of unity. Values in excess of unity represent the condition of a larger proportion in the treated group than in the control.

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 treated 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 (a $P < 0.025$ one-tailed test when the control incidence is not zero, $P < 0.050$ when the control incidence is zero) has occurred. 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)

The mean body weights of both male and female low- and high-dose rats were less than those of their corresponding controls throughout the study (figure 1). During the first year of study, the treated animals were generally comparable to the controls in appearance and behavior.

Clinical signs including rough hair coats, alopecia, pale mucous membranes, dermatitis, tachypnea, and hematuria were noted at a low incidence in all treated groups of rats during the first half of the second year, with a gradually increasing frequency during the remainder of the study. A few treated females showed evidence of vaginal bleeding.

B. Survival (Rats)

The Kaplan and Meier curves estimating the probabilities of survival for male and female rats receiving captan at the doses of this experiment, together with the controls, are shown in figure 2.

In neither sex was the Tarone test result significant at the 0.05 level for positive dose-related trend in mortality over the period. In male rats, 46% of the high-dose group, 58% of the

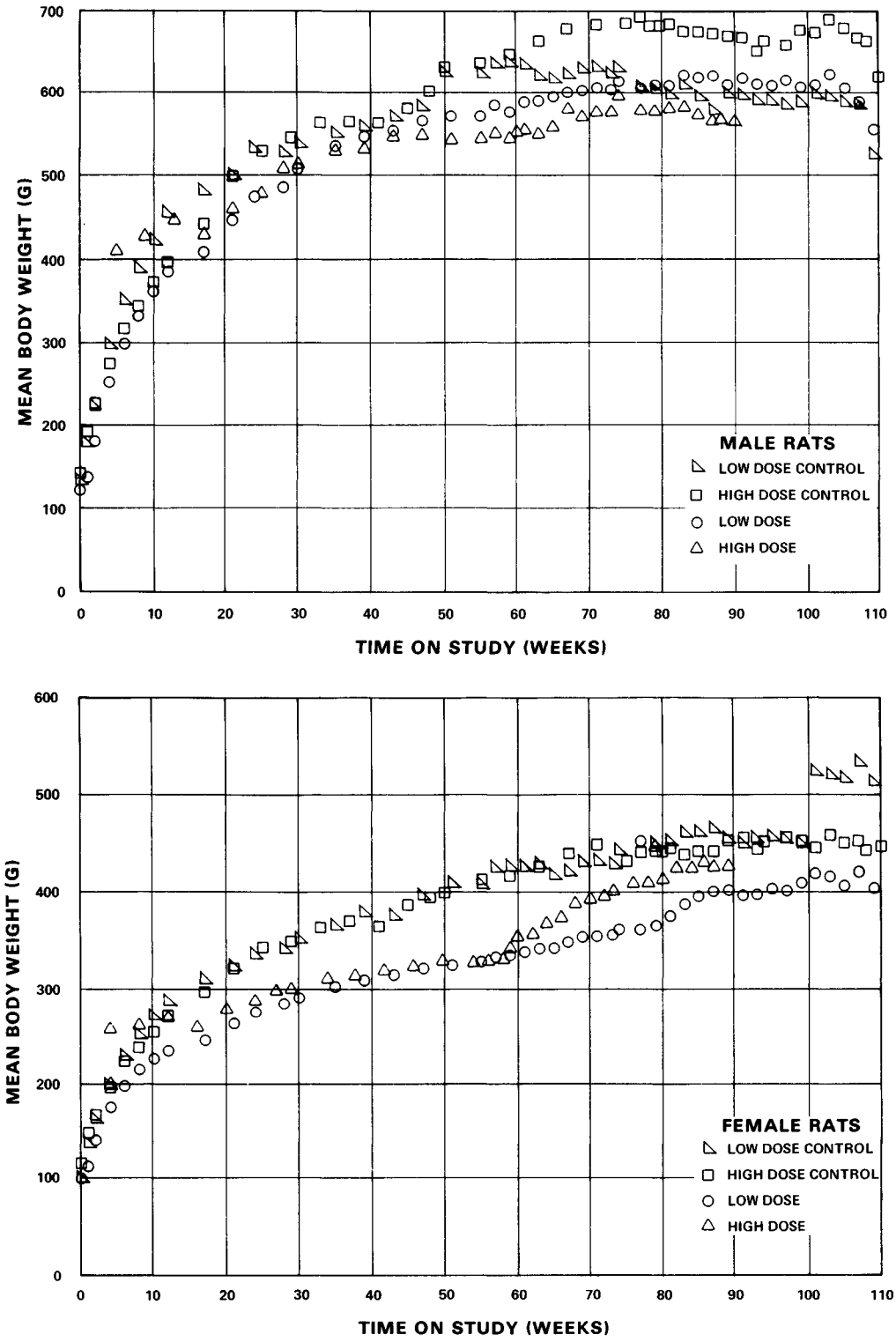


Figure 1. Growth Curves for Rats Fed Captan in the Diet

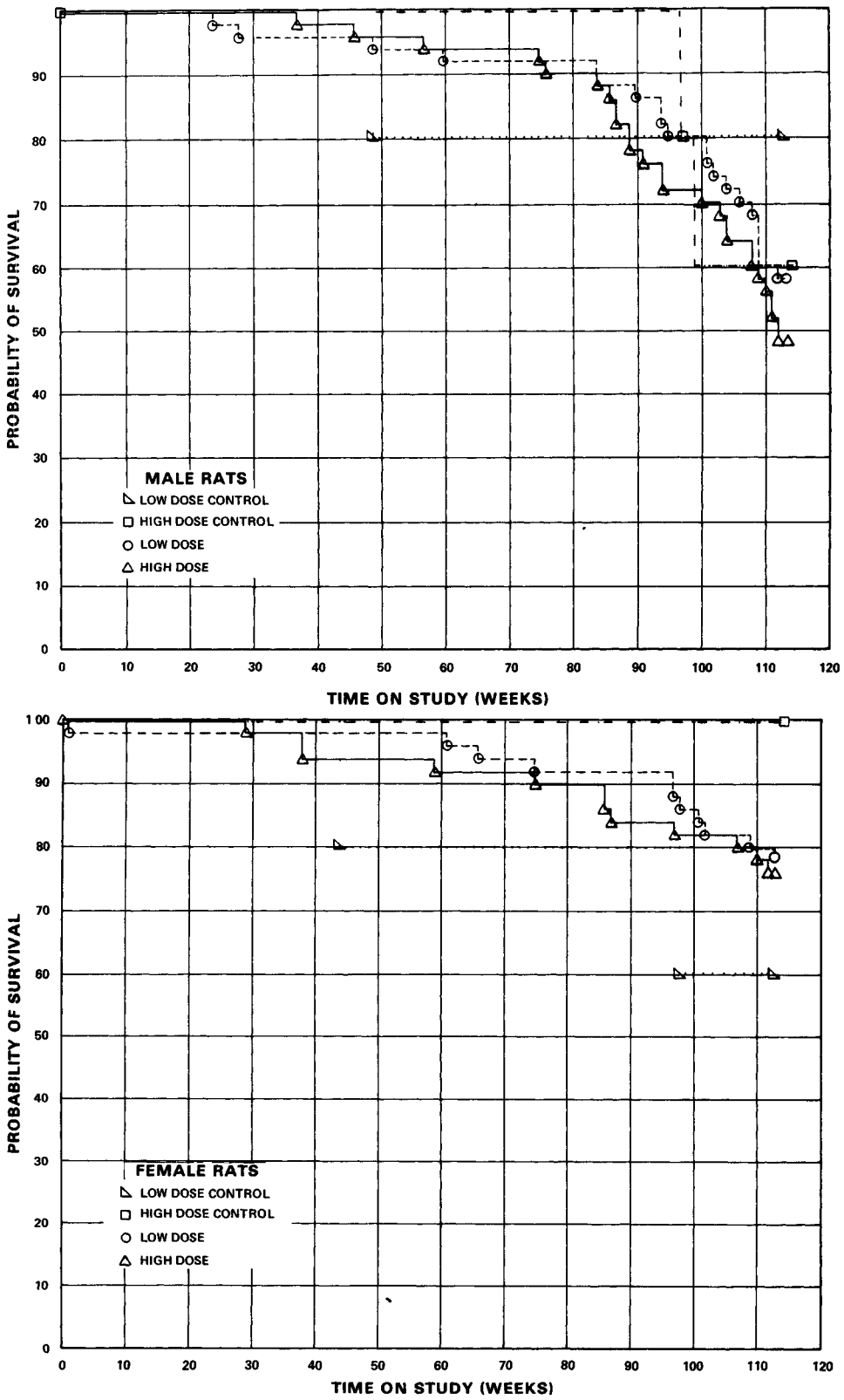


Figure 2. Survival Curves for Rats Fed Captan in the Diet

low-dose group, 80% of the low-dose controls, and 60% of the high-dose controls survived to the end of the study. Survival in female rats was higher, with over 75% of the treated animals, 60% of the low-dose controls, and all of the high-dose controls living to termination of the study. Survival was sufficient for meaningful statistical analyses of late-developing tumors.

C. Pathology (Rats)

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

The types of tumors observed are not uncommon for this strain of rat, and the distribution and frequency among animals of the matched-control and captan-treated groups do not indicate any trend of carcinogenic activity induced by the chemical. Therefore, these lesions are considered to have occurred spontaneously.

Likewise, a great variety of nonneoplastic lesions were observed either sporadically or with approximately equal frequency among animals of the control and treated groups. These lesions frequently have been found in rats used in other experiments independent of treatment.

The incidence and distribution of the neoplastic and non-neoplastic lesions occurring in the rats in this study do not implicate captan as the causative agent.

D. Statistical Analyses of Results (Rats)

Tables E1 and E2 in Appendix E contain the statistical analyses of the incidences of those specific primary tumors that were observed in at least 5% of one or more treated groups of either sex.

In male rats, neither the results of the Cochran-Armitage test for dose-related linear trend nor of the Fisher exact test for the incidence of tumors at any specific site is significant at the 0.05 level. Due to the early deaths in the high-dose males, time-adjusted analyses, eliminating animals that died before 1 year on study, were performed on the incidence of chromophobe adenoma of the pituitary; however, no significant result was obtained.

When the incidences of cortical adenoma and cortical carcinoma of the adrenal gland in female rats are combined, the Cochran-Armitage test for positive linear dose-related trend has a probability of 0.047, using the pooled controls. The Fisher exact test results are not significant. The 95% confidence interval for the relative risk in the high-dose group compared

with the pooled controls has a lower limit of 0.813, which is a value less than one, indicating the possibility that no true difference exists between these two groups. The incidence of C-cell adenoma in the thyroid also has a positive linear trend (P = 0.035), but the results of the Fisher exact test are not significant. No other tumor or combination of tumors appears in significantly larger numbers in the treated groups than in either control group. The statistical conclusion is that there is insufficient evidence for the dose association of the chemical with the tumors in rats.

When groupings of types of tumors are made, as in cortical adenoma or carcinoma of the adrenal gland in female rats, the incidences of the individual components of the grouping are not included in tables E1 and E2 unless the statistical tests are significant. A list of the incidences of each type of tumor is provided in Appendix A, tables A1 and A2.

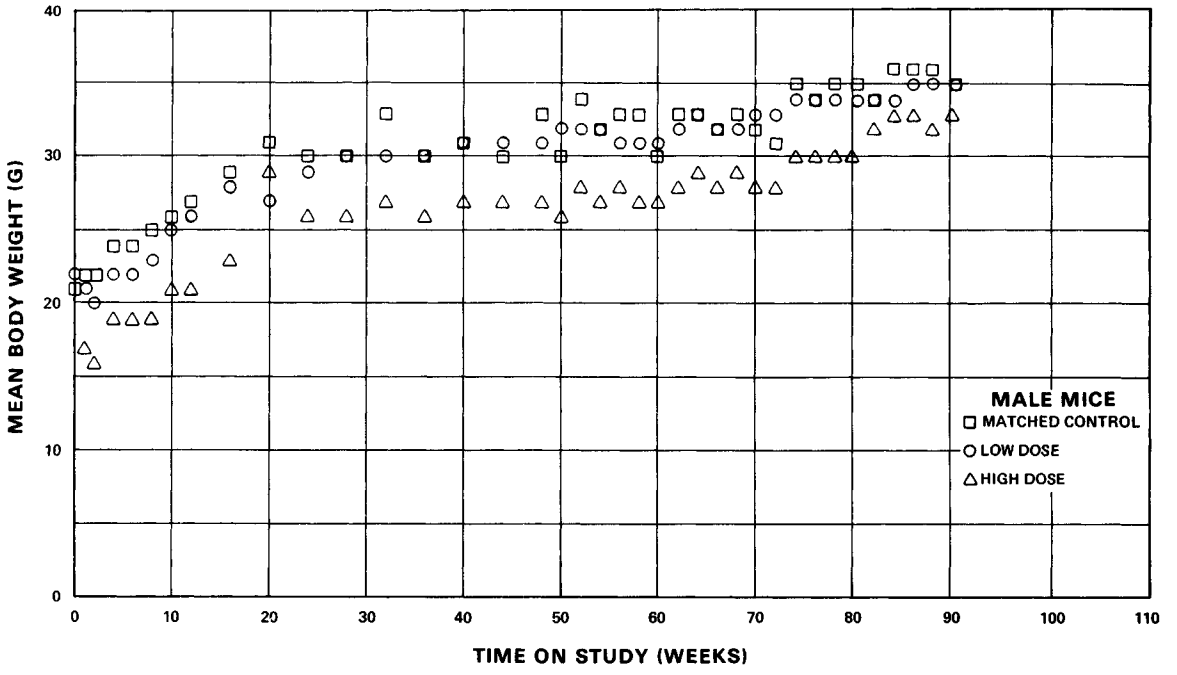
IV. RESULTS - MICE

A. Body Weights and Clinical Signs

Throughout the study, the mean body weights of the high-dose male and female mice were notably lower than those of their controls, whereas the mean body weights of the low-dose male and female mice were only slightly lower (figure 3).

During the first 4 months of the study, the treated animals were generally comparable to the controls in appearance and behavior, except during the first 2 weeks, when the treated animals showed loss of weight. At week 24, all of the high-dose females were very excitable and a few had slight tremors (tremors were not noted after this time). At the same time, a slight weight loss occurred in high-dose females. At week 24, the high-dose males showed a considerable weight loss but did not appear excitable. During week 36, both treated and control animals showed weight loss.

After 50 weeks, clinical signs including rough hair coats, alopecia, and abdominal distention were observed in the treated groups. At week 71 all of the low- and high-dose males appeared to be very excitable. At week 80, all of the low- and high-dose males evidenced abdominal distention. During the last 6 weeks of the study, one low-dose male and one high-dose male had a



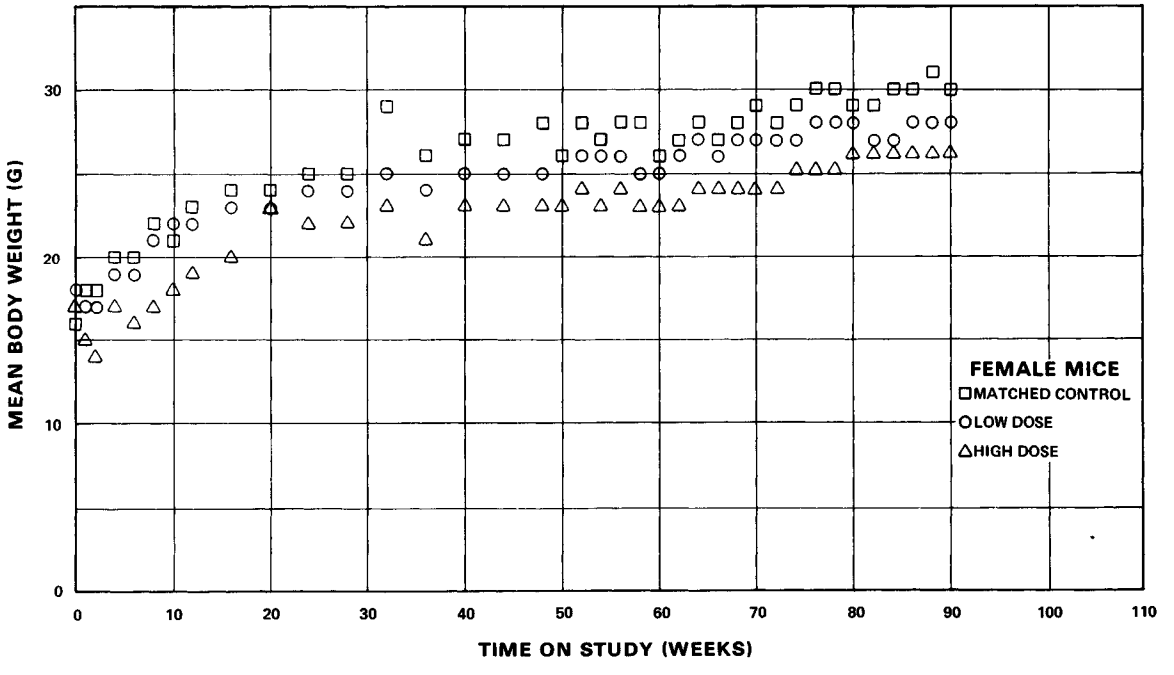


Figure 3. Growth Curves for Mice Fed Captan in the Diet

purulent discharge from the penis. The perineal areas of a few high-dose males were irritated and red in appearance.

B. Survival (Mice)

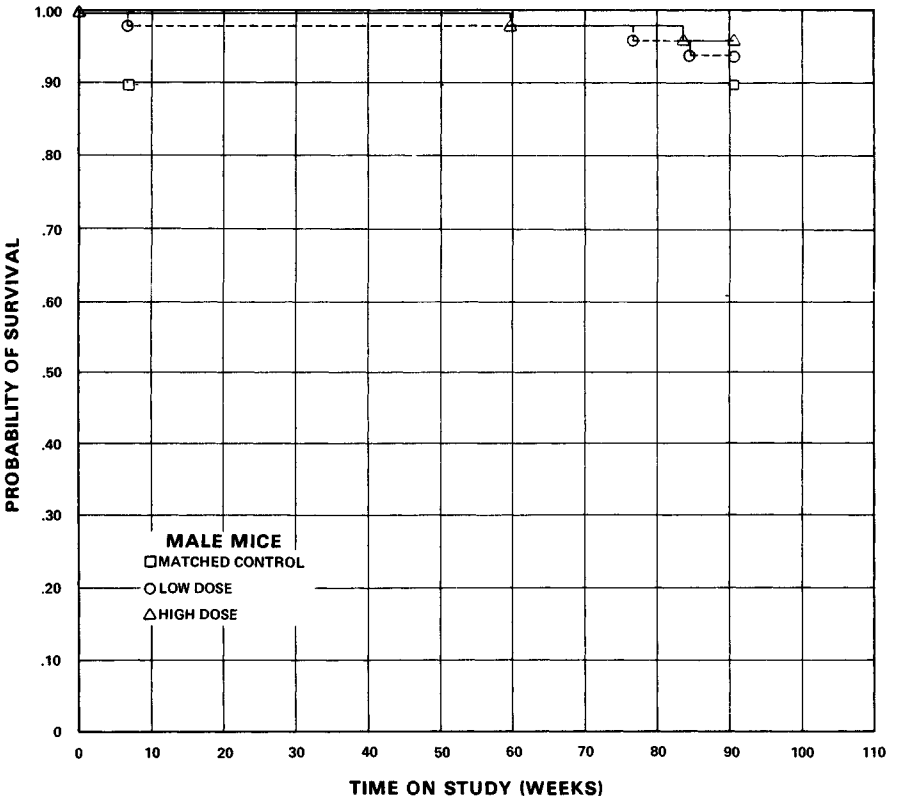
The Kaplan and Meier curves estimating the probabilities of survival for male and female mice receiving captan at the doses of this experiment, together with the controls, are shown in figure 4.

In neither sex was the Tarone test result significant for positive dose-related trend in mortality over the period. More than 90% of the animals survived to the end of the study, providing sufficient numbers of animals for meaningful statistical analyses of late-developing tumors.

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.

With the exception of the proliferative and/or neoplastic lesions observed in the duodenum of both male and female treated mice, the pathologic changes observed were not considered to be related to the administration of captan.



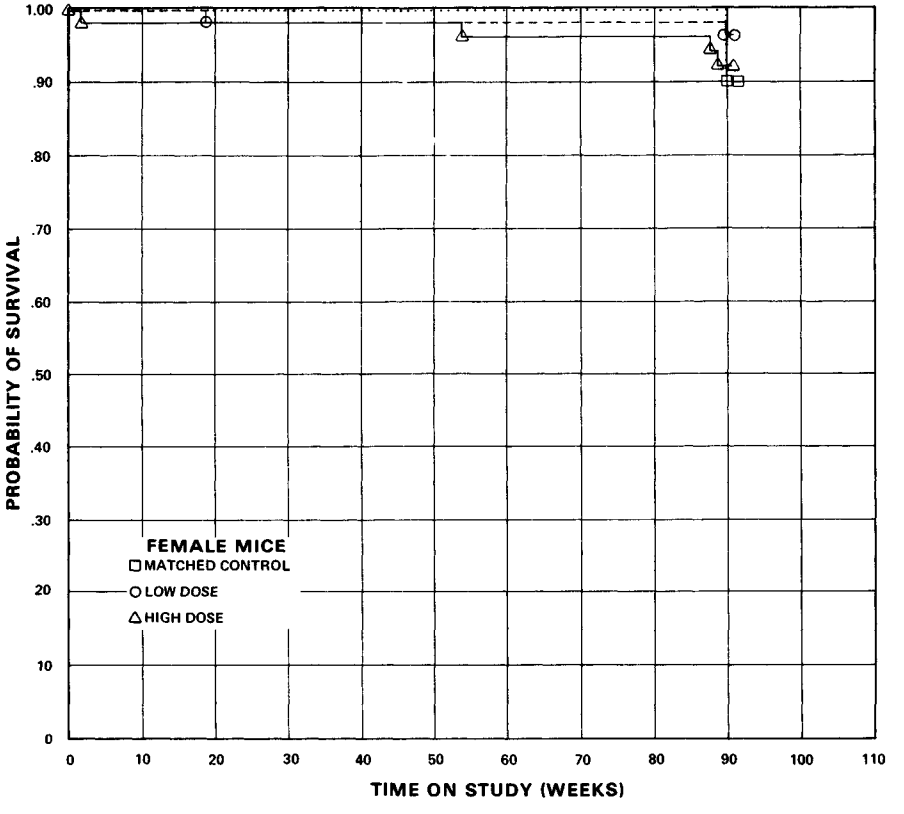


Figure 4. Survival Curves for Mice Fed Captan in the Diet

The duodenal lesions were located approximately 1 cm posterior to the pylorus, usually in the antimesenteric portion of the duodenal mucosa. Grossly, they were either single, well-circumscribed (3-5 mm across) and slightly elevated (1-2 mm) areas, or single, thin mucosal projections up to 5 mm in height. The lesions were inconspicuous on the serosal surface. Microscopically, the following three different lesions were classified:

(1) mucosal hyperplasia--a duplication of glands and villi,

(2) adenomatous polyp--a more accentuated proliferative process with glandular structures and villi aggregated and branched around supporting stalks made up of connective tissue (features of malignancy were not observed), and

(3) adenocarcinoma in adenomatous polyp (polypoid carcinoma)--the most advanced and aggressive-appearing lesion, consisting of cellular polypoid structures with numerous mitotic figures, disorganized microacini, and areas where neoplastic infiltration was evident.

Tinctorial changes (basophilia) were also present.

The classification of these lesions was frequently difficult. Nevertheless, the location and some common cellular character-

istics suggest that they are different developmental stages of the same type of lesion. The distribution and incidence of the duodenal alteration were as follows:

	Males			Females		
	Controls	Low Dose	High Dose	Controls	Low Dose	High Dose
Number examined	(9)	(43)	(46)	(9)	(49)	(48)
Adenocarcinoma	0	1	3	0	0	3
Adenomatous polyp	0	2	2	1	1	0
Mucosal hyperplasia	0	0	3	0	0	0

The rarity of these lesions in the strain of mouse used suggests that the lesions were caused by captan.

The nonneoplastic pathological changes were either inflammatory or degenerative in nature, and their incidence and distribution do not appear to be associated with captan treatment.

D. Statistical Analyses of Results (Mice)

Tables F1 and F2 in Appendix F contain the statistical analyses of the incidences of those specific primary tumors that were observed in at least 5% of one or more treated groups of either sex.

The incidences of adenocarcinoma in adenomatous polyp of the duodenum are in a significant linear trend for both male and female mice, with Cochran-Armitage probability levels of 0.033

and 0.022, respectively, using the pooled controls. The Fisher exact test results for both sexes are not significant. When the incidences of adenocarcinoma in adenomatous polyp of the duodenum are combined with those of adenomatous polyp, NOS (not otherwise specified), for statistical analysis, the tests for male mice show a substantial increase in significance when compared with pooled controls. The test for positive linear trend is significant (P = 0.008), the Fisher exact test in the high-dose male mice has a probability level of 0.009, and the 95% confidence interval for relative risk has a lower limit of 1.849 using pooled controls. The incidence of these combined tumors in female mice is not significant. The overall consideration of these various statistics suggests a dose association of the test chemical with tumors in the duodenum in male mice.

Significant trends and results in the negative direction were observed due to a lower incidence of liver tumors in the treated groups of male mice than in either set of controls. When tumors at the same site are grouped, as in neoplastic nodule and hepatocellular carcinoma in male mice, the incidences of the individual components of the grouping are not indicated in the statistical analyses in the tables when they do not occur individually at less than 5% incidence. No other incidences of

tumors were significant in the mice. A list of the incidences of each type of tumor is provided in Appendix B, tables B1 and B2.

In each of the 95% confidence intervals for relative risk, shown in the tables, with the exception of adenomatous polyp, NOS, or adenocarcinoma in adenomatous polyp of the duodenum in high-dose male mice, the lower limit is below the value of one; this indicates the negative aspects of the results. It should also be noted that each of the intervals, with the exception of liver tumors in low-dose male mice, has an upper limit greater than one, indicating the theoretical possibility of the induction of tumors by this chemical, which could not be detected under the conditions of this test.

V. DISCUSSION

The doses of captan used in this bioassay adversely affected both rats and mice. Mean body weights of both low- and high-dose rats and high-dose mice were generally lower than controls throughout most of the study. General clinical signs that were noted, particularly during the second year of the study, included rough hair coats, alopecia, pale mucous membranes, dermatitis, tachypnea, and hematuria for treated rats, and rough hair coats, alopecia, and abdominal distention for treated mice. The high-dose female mice and both low- and high-dose males had periods of excitability, and a few had slight tremors. Mortality rates, however, did not show statistically significant dose-related trends in either sex of either species.

In rats, there was a positive dose-related trend ($P = 0.047$) for the combined incidence of cortical adenoma and cortical carcinoma of the adrenal gland in high-dose females compared with the incidence in the pooled controls. However, the spontaneous incidence is variable in this strain of rat, and the incidence of tumors was very low; one adrenal cortical adenoma and one carcinoma were found in the low-dose animals and two adrenal cortical adenomas and one carcinoma in the high-dose group. There was also a positive dose-related trend for the incidence of

C-cell adenoma of the thyroid in female rats (pooled controls 1/66, low-dose 1/49, high-dose 4/44, P = 0.035). The relationship of these tumors to treatment is not clearly established.

In mice, duodenal lesions, which are usually rare, occurred in both sexes of treated animals. They were located approximately 1 cm posterior to the pylorus, usually in the antimesenteric portion of the duodenal mucosa. Microscopically, the three different lesions that were classified were mucosal hyperplasia, adenomatous polyp, NOS, and adenocarcinoma in adenomatous polyp (polypoid carcinoma). Among males, the mucosal hyperplasia was found in three high-dose animals. Incidences of polypoid carcinoma (adenocarcinoma in adenomatous polyp) of the duodenum were statistically significant using tests for a positive dose-related trend both in male mice (pooled controls 0/68, low-dose 1/43, high-dose 3/46, P = 0.033) and in female mice (pooled controls 0/68, low-dose 0/49, high-dose 3/48, P = 0.022). When the incidences of adenomatous polyp, NOS, were combined with those of polypoid carcinoma for statistical analysis, the tests for male mice indicated a substantial increase in significance (pooled controls 0/68, low-dose 3/43, high-dose 5/46, P = 0.008). Only two females, a control and a low-dose animal, had adenomatous polyp, and none had hyperplasia. Three high-dose females had polypoid carcinoma; this incidence was significant,

using the test for positive dose-related trend, but was not significant for direct comparison of the incidences in the high-dose and control groups.

The absence of carcinogenicity of captan in rats in the present bioassay agrees with findings of other studies reported in the literature. In one study (Weir, 1956) groups of 10 rats of each sex were fed diets containing 1,000 or 5,000 ppm of technical-grade captan for 2 years. The incidence of tumors in each treated group did not differ significantly from that in their comparable control group. In a second study (Reyna et al., 1974b), groups containing 50 male and 50 female rats were fed diets containing 1,000 or 5,000 ppm of technical-grade captan for 2 years; the incidence of tumors was no higher in these treated groups than in their comparable controls.

Previous studies using mice also reported negative findings. Innes et al. (1969) treated groups of 18 mice of two hybrid strains with captan for 18 months. Beginning with 7-day-old mice, a dose of 215 mg/kg body weight of captan was given daily by gavage for a period of 3 weeks; thereafter, a corresponding dose of 560 ppm captan was added to the diet for the remainder of the 18 months. There was no significant increase in the incidence of tumors in the captan-treated groups compared with

that in the controls. In another 18-month study (Reyna et al., 1974a), three groups each of 50 male and 50 female Swiss mice were fed diets containing 0, 3,700, or 7,500 ppm of technical-grade captan. No difference in the incidence of tumors was found in treated and control groups. These negative findings in mice are not in agreement with the results of the present bioassay. The differences may be related to the strains of mice used, since C57BL/6 x C3H/Anf and C57BL/6 x AKR mice were used in the Innes study, Swiss mice were used in the Reyna study, and B6C3F1 (C57BL/6 x C3H/He) mice were used in the present study. It should also be noted that the Innes study particularly considered hepatomas, pulmonary tumors, and lymphomas, and the intestine may not have been adequately examined.

It is concluded that under the conditions of this bioassay, tumors in the duodenum in B6C3F1 mice were associated with treatment with captan, but there was no convincing evidence that the tumors observed in Osborne-Mendel rats were related to treatment.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS FED CAPTAN IN THE DIET

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS FED CAPTAN IN THE DIET

	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	5	10	50	50
ANIMALS NECROPSIED	5	5	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	5	5	49	49
INTEGUMENTARY SYSTEM				
*SKIN	(5)	(5)	(50)	(49)
SQUAMOUS CELL CARCINOMA				1 (2%)
FIBROMA			1 (2%)	
FIBROSARCOMA			1 (2%)	
FIBROUS HISTIOCYTOMA, MALIGNANT				1 (2%)
*SUBCUT TISSUE	(5)	(5)	(50)	(49)
FIBROMA			1 (2%)	1 (2%)
LIPOMA				1 (2%)
RESPIRATORY SYSTEM				
#LUNG	(4)	(5)	(48)	(49)
TRANSITIONAL-CELL CARCINOMA, MET			1 (2%)	
MIXED TUMOR, METASTATIC				1 (2%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(5)	(5)	(50)	(49)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)	
#SPLEEN	(4)	(5)	(49)	(47)
HEMANGIOMA			1 (2%)	
HEMANGIOSARCOMA			1 (2%)	
#LIVER	(5)	(5)	(47)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
CIRCULATORY SYSTEM				
#HEART	(4)	(5)	(48)	(49)
RHABDOMYOSARCOMA			1 (2%)	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
#MYOCARDIUM	(4)	(5)	(48)	(49)
FIBROMA			1 (2%)	
DIGESTIVE SYSTEM				
#LIVER	(5)	(5)	(47)	(49)
BILE DUCT CARCINOMA				1 (2%)
NEOPLASTIC NODULE	1 (20%)		1 (2%)	2 (4%)
#ESOPHAGUS			(7)	(5)
FIBROUS HISTIOCYTOMA, MALIGNANT				1 (20%)
#STOMACH	(5)	(5)	(47)	(44)
SQUAMOUS CELL PAPILLOMA				1 (2%)
HAMARTOMA			1 (2%)	
URINARY SYSTEM				
#KIDNEY	(5)	(5)	(49)	(49)
TRANSITIONAL-CELL CARCINOMA			1 (2%)	
TUBULAR-CELL ADENOMA				1 (2%)
FIBROUS HISTIOCYTOMA, MALIGNANT				1 (2%)
MIXED TUMOR, MALIGNANT		1 (20%)	1 (2%)	1 (2%)
†HAMARTOMA				1 (2%)
#URINARY BLADDER	(5)	(5)	(46)	(40)
FIBROUS HISTIOCYTOMA, MALIGNANT				1 (3%)
ENDOCRINE SYSTEM				
#PITUITARY	(5)	(5)	(43)	(45)
CARCINOMA,NOS		1 (20%)		1 (2%)
CHROMOPHOBE ADENOMA	1 (20%)	1 (20%)	9 (21%)	5 (11%)
#ADRENAL	(5)	(5)	(47)	(47)
PHEOCHROMOCYTOMA				1 (2%)
#THYROID	(5)	(5)	(42)	(47)
C-CELL ADENOMA			1 (2%)	1 (2%)
#PANCREATIC ISLETS	(4)	(5)	(45)	(47)
ISLET-CELL ADENOMA			1 (2%)	1 (2%)

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

†This is considered to be a benign form of the malignant mixed tumor of the kidney and consists of lipocytes, tubular structures, and fibroblasts in varying proportions.

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(5)	(5)	(50)	(49)
ADENOCARCINOMA, NOS			1 (2%)	
FIBROMA			1 (2%)	
LIPOMA				1 (2%)
*SEMINAL VESICLE	(5)	(5)	(50)	(49)
ADENOCARCINOMA, NOS			1 (2%)	
#TESTIS	(5)	(5)	(48)	(48)
INTERSTITIAL-CELL TUMOR			2 (4%)	
NERVOUS SYSTEM				
#BRAIN	(5)	(5)	(47)	(45)
GRANULAR-CELL TUMOR, BENIGN			2 (4%)	
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(5)	(5)	(50)	(49)
FIBROUS HISTIOCYTOMA, MALIGNANT			1 (2%)	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	5	10	50	50
NATURAL DEATH@		1	6	12
MORIBUND SACRIFICE	1	1	15	15
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	4	3	29	23
ANIMAL MISSING				
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	2	2	28	20
TOTAL PRIMARY TUMORS	2	3	32	24
TOTAL ANIMALS WITH BENIGN TUMORS	1	1	20	14
TOTAL BENIGN TUMORS	1	1	21	14
TOTAL ANIMALS WITH MALIGNANT TUMORS		1	10	5
TOTAL MALIGNANT TUMORS		2	10	8
TOTAL ANIMALS WITH SECONDARY TUMORS#			1	1
TOTAL SECONDARY TUMORS			1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1		1	2
TOTAL UNCERTAIN TUMORS	1		1	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

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS FED CAPTAN IN THE DIET

	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	5	10	50	50
ANIMALS NECROPSIED	4	5	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	4	5	50	50
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(4)	(5)	(50)	(50)
FIBROUS HISTIOCYTOMA, MALIGNANT			1 (2%)	
AMELOBLASTOMA			1 (2%)	
RESPIRATORY SYSTEM				
#LUNG	(4)	(5)	(50)	(49)
BILE DUCT CARCINOMA, METASTATIC			1 (2%)	
CORTICAL CARCINOMA, METASTATIC				1 (2%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(4)	(5)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE				1 (2%)
#SPLEEN	(4)	(5)	(49)	(50)
BILE DUCT CARCINOMA, METASTATIC			1 (2%)	
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(4)	(5)	(49)	(50)
NEOPLASTIC NODULE			4 (8%)	
HEPATOCELLULAR CARCINOMA				1 (2%)
*BILE DUCT	(4)	(5)	(50)	(50)
BILE DUCT ADENOMA				1 (2%)

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
BILE DUCT CARCINOMA			1 (2%)	
HAMARTOMA		1 (20%)		
#PANCREAS	(4)	(4)	(45)	(48)
BILE DUCT CARCINOMA, METASTATIC			1 (2%)	
#SMALL INTESTINE	(4)	(5)	(47)	(49)
BILE DUCT CARCINOMA, METASTATIC			1 (2%)	
URINARY SYSTEM				
#KIDNEY	(4)	(5)	(49)	(47)
TUBULAR-CELL ADENOMA			1 (2%)	
MIXED TUMOR, BENIGN			1 (2%)	
MIXED TUMOR, MALIGNANT			1 (2%)	
† HAMARTOMA			1 (2%)	1 (2%)
#URINARY BLADDER	(4)	(5)	(48)	(43)
BILE DUCT CARCINOMA, METASTATIC			1 (2%)	
ENDOCRINE SYSTEM				
#PITUITARY	(4)	(4)	(48)	(45)
CARCINOMA,NOS				1 (2%)
ADENOMA, NOS			1 (2%)	
CHROMOPHOBE ADENOMA	2 (50%)	1 (25%)	12 (25%)	4 (9%)
#ADRENAL	(4)	(5)	(50)	(47)
CORTICAL ADENOMA			1 (2%)	2 (4%)
CORTICAL CARCINOMA			1 (2%)	1 (2%)
PHEOCHROMOCYTOMA			1 (2%)	1 (2%)
#THYROID	(4)	(5)	(49)	(44)
FOLLICULAR-CELL ADENOMA		1 (20%)		
C-CELL ADENOMA			1 (2%)	4 (9%)
C-CELL CARCINOMA			1 (2%)	
#PANCREATIC ISLETS	(4)	(4)	(45)	(48)
ISLET-CELL ADENOMA	1 (25%)			3 (6%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(4)	(5)	(50)	(50)
ADENOMA, NOS			3 (6%)	1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
† This is considered to be a benign form of the malignant mixed tumor of the kidney and consists of lipocytes, tubular structures, and fibroblasts in varying proportions.

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
ADENOCARCINOMA, NOS				1 (2%)
SWEAT GLAND CARCINOMA				1 (2%)
INFILTRATING DUCT CARCINOMA				1 (2%)
FIBROMA			2 (4%)	3 (6%)
FIBROADENOMA			4 (8%)	5 (10%)
#UTERUS	(4)	(5)	(48)	(45)
CARCINOMA,NOS				1 (2%)
SARCOMA, NOS			1 (2%)	
ENDOMETRIAL STROMAL POLYP	1 (25%)	1 (20%)	6 (13%)	7 (16%)
#OVARY	(4)	(5)	(49)	(46)
THECOMA			1 (2%)	
GRANULOSA-CELL CARCINOMA			1 (2%)	
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*PERITONEUM	(4)	(5)	(50)	(50)
BILE DUCT CARCINOMA, METASTATIC			1 (2%)	
SARCOMA, NOS				1 (2%)
ALL OTHER SYSTEMS				
NONE				

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	5	10	50	50
NATURAL DEATH@	1		2	3
MORIBUND SACRIFICE	1		10	9
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	3	5	38	38
ANIMAL MISSING				
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	3	4	36	32
TOTAL PRIMARY TUMORS	4	4	47	41
TOTAL ANIMALS WITH BENIGN TUMORS	3	4	30	25
TOTAL BENIGN TUMORS	4	4	36	32
TOTAL ANIMALS WITH MALIGNANT TUMORS			7	8
TOTAL MALIGNANT TUMORS			7	9
TOTAL ANIMALS WITH SECONDARY TUMORS#			1	1
TOTAL SECONDARY TUMORS			6	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			4	
TOTAL UNCERTAIN TUMORS			4	
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 CAPTAN IN THE DIET

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE FED CAPTAN IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	9	48	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	9	47	49
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(9)	(47)	(49)
HEPATOCELLULAR CARCINOMA, METAST	1 (11%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (22%)	2 (4%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	
HEMATOPOIETIC SYSTEM			
#CECUM			(1)
MALIGNANT LYMPHOMA, NOS			1 (100%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(9)	(46)	(49)
NEOPLASTIC NODULE			1 (2%)
HEPATOCELLULAR CARCINOMA	3 (33%)	1 (2%)	2 (4%)
#DUODENUM	(9)	(43)	(46)
ADENOMATOUS POLYP, NOS		2 (5%)	2 (4%)
ADENOCA IN ADENOMATOUS POLYP		1 (2%)	3 (7%)
URINARY SYSTEM			
NONE			

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

	CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	10	50	50
NATURAL DEATH@	1	3	1
MORIBUND SACRIFICE			1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	9	47	48
ANIMAL MISSING			

@ 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*	5	7	10
TOTAL PRIMARY TUMORS	5	7	10
TOTAL ANIMALS WITH BENIGN TUMORS	2	4	3
TOTAL BENIGN TUMORS	2	4	3
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	3	6
TOTAL MALIGNANT TUMORS	3	3	6
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		
TOTAL SECONDARY TUMORS	1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			1
TOTAL UNCERTAIN TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE FED CAPTAN IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	50	48
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
NONE			
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(10)	(50)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (10%)	1 (2%)	1 (2%)
LYMPHOCYTIC LEUKEMIA			1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(10)	(49)	(47)
NEOPLASTIC NODULE	1 (10%)	1 (2%)	1 (2%)
#STOMACH	(10)	(49)	(47)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
#DUODENUM	(9)	(49)	(48)
ADENOMATOUS POLYP, NOS	1 (11%)	1 (2%)	
ADENOCA IN ADENOMATOUS POLYP			3 (6%)
URINARY SYSTEM			
NONE			

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(10)	(50)	(49)
ADENOMA, NOS		1 (2%)	
#OVARY	(10)	(46)	(45)
CYSTADENOMA, NOS			1 (2%)
HEMANGIOMA			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	10	50	50
NATURAL DEATH@		2	2
MORIBUND SACRIFICE	1		2
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	9	48	46
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	3	5	8
TOTAL PRIMARY TUMORS	3	5	8
TOTAL ANIMALS WITH BENIGN TUMORS	1	3	2
TOTAL BENIGN TUMORS	1	3	2
TOTAL ANIMALS WITH MALIGNANT TUMORS	1	1	5
TOTAL MALIGNANT TUMORS	1	1	5
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	1	1
TOTAL UNCERTAIN TUMORS	1	1	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 CAPTAN IN THE DIET

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS FED CAPTAN IN THE DIET

	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	5	10	50	50
ANIMALS NECROPSIED	5	5	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	5	5	49	49
INTEGUMENTARY SYSTEM				
NONE				
RESPIRATORY SYSTEM				
#LUNG	(4)	(5)	(48)	(49)
ATELECTASIS			1 (2%)	
CONGESTION, NOS			1 (2%)	
EDEMA, NOS			1 (2%)	
BRONCHOPNEUMONIA SUPPURATIVE				1 (2%)
PNEUMONIA, CHRONIC MURINE				1 (2%)
BRONCHOPNEUMONIA, CHRONIC			1 (2%)	
INFLAMMATION, CHRONIC FOCAL			1 (2%)	1 (2%)
GRANULOMA, NOS				1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU				1 (2%)
CALCIFICATION, METASTATIC				1 (2%)
#LUNG/ALVEOLI	(4)	(5)	(48)	(49)
EMPHYSEMA, NOS	1 (25%)	1 (20%)	1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM				
#SPLEEN	(4)	(5)	(49)	(47)
FIBROSIS, FOCAL			1 (2%)	
PERIARTERITIS	1 (25%)		1 (2%)	
HEMOSIDEROSIS			1 (2%)	
HEMATOPOIESIS			1 (2%)	1 (2%)
CIRCULATORY SYSTEM				
#MYOCARDIUM	(4)	(5)	(48)	(49)
INFLAMMATION, CHRONIC		1 (20%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, CHRONIC FOCAL				1 (2%)
FIBROSIS, DIFFUSE			1 (2%)	
*AORTA	(5)	(5)	(50)	(49)
MEDIAL CALCIFICATION				1 (2%)
CALCIFICATION, METASTATIC				1 (2%)
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(5)	(5)	(47)	(43)
INFLAMMATION, CHRONIC			1 (2%)	
#LIVER	(5)	(5)	(47)	(49)
PERIARTERITIS	1 (20%)			
DEGENERATION, BALLOONING			1 (2%)	
DEGENERATION PARENCHYMATOUS		2 (40%)	5 (11%)	10 (20%)
METAMORPHOSIS FATTY		1 (20%)	9 (19%)	14 (29%)
FOCAL CELLULAR CHANGE			1 (2%)	5 (10%)
ANGIECTASIS	1 (20%)		4 (9%)	3 (6%)
*BILE DUCT	(5)	(5)	(50)	(49)
INFLAMMATION, CHRONIC			1 (2%)	
HYPERPLASIA, NOS	1 (20%)			
#PANCREAS	(4)	(5)	(45)	(47)
THROMBOSIS, NOS				1 (2%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
PERIARTERITIS	1 (25%)	1 (20%)	1 (2%)	4 (9%)
#STOMACH	(5)	(5)	(47)	(44)
EROSION			1 (2%)	
NECROSIS, FOCAL				1 (2%)
CALCIFICATION, NOS				1 (2%)
#GASTRIC MUCOSA	(5)	(5)	(47)	(44)
HEMORRHAGE			1 (2%)	
CALCIFICATION, METASTATIC				1 (2%)
URINARY SYSTEM				
#KIDNEY	(5)	(5)	(49)	(49)
INFLAMMATION, CHRONIC	3 (60%)	5 (100%)	25 (51%)	33 (67%)
INFLAMMATION, CHRONIC FOCAL				1 (2%)
GLOMERULOSCLEROSIS, NOS				1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM				
#PITUITARY	(5)	(5)	(43)	(45)
MULTIPLE CYSTS			2 (5%)	
CONGESTION, NOS		1 (20%)		
HEMORRHAGE		1 (20%)		
DEGENERATION, CYSTIC			2 (5%)	
HYPERPLASIA, NOS	1 (20%)		2 (5%)	
ANGIECTASIS			6 (14%)	1 (2%)
#ADRENAL	(5)	(5)	(47)	(47)
DEGENERATION, CYSTIC			1 (2%)	
ANGIECTASIS				1 (2%)
#ADRENAL CORTEX	(5)	(5)	(47)	(47)
HEMORRHAGE			1 (2%)	3 (6%)
NECROSIS, FOCAL			1 (2%)	
METAMORPHOSIS FATTY			1 (2%)	3 (6%)
#THYROID	(5)	(5)	(42)	(47)
FOLLICULAR CYST, NOS			2 (5%)	1 (2%)
HEMORRHAGE			1 (2%)	
HYPERPLASIA, C-CELL	1 (20%)	1 (20%)	1 (2%)	1 (2%)
HYPERPLASIA, FOLLICULAR-CELL		2 (40%)	1 (2%)	6 (13%)
#PARATHYROID	(3)	(2)	(21)	(33)
HYPERPLASIA, NOS			1 (5%)	2 (6%)
HYPERPLASIA, SECONDARY				1 (3%)
REPRODUCTIVE SYSTEM				
#PROSTATE	(4)	(5)	(44)	(45)
INFLAMMATION, ACUTE				1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE				1 (2%)
#TESTIS	(5)	(5)	(48)	(48)
EDEMA, NOS			3 (6%)	1 (2%)
PERIARTERITIS				4 (8%)
DEGENERATION, NOS			2 (4%)	2 (4%)
ATROPHY, NOS	3 (60%)	1 (20%)	14 (29%)	6 (13%)
ATROPHY, FOCAL				2 (4%)
*EPIDIDYMIS	(5)	(5)	(50)	(49)
HEMORRHAGE				1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, CHRONIC				1 (2%)
FIBROSIS				1 (2%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAI SYSTEM				
*FEMUR	(5)	(5)	(50)	(49)
OSTEOPOROSIS				1 (2%)
BODY CAVITIES				
*MESENTERY	(5)	(5)	(50)	(49)
PERIARTERITIS	1 (20%)	1 (20%)	1 (2%)	8 (16%)
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED			3	4
AUTO/NECROPSY/NO HISTO			1	
AUTOLYSIS/NO NECROPSY				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 CAPTAN IN THE DIET

	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	5	10	50	50
ANIMALS NECROPSIED	4	5	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	4	5	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(4)	(5)	(50)	(50)
DEGENERATION, CYSTIC				1 (2%)
RESPIRATORY SYSTEM				
#LUNG	(4)	(5)	(50)	(49)
EMPHYSEMA, NOS				1 (2%)
ATELECTASIS				1 (2%)
INFLAMMATION, FOCAL			1 (2%)	1 (2%)
PNEUMONIA, ASPIRATION	1 (25%)			
PNEUMONIA, CHRONIC MURINE				1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU				1 (2%)
NECROSIS, NOS			1 (2%)	
HEMATOPOIETIC SYSTEM				
#SPLEEN	(4)	(5)	(49)	(50)
CONGESTION, CHRONIC PASSIVE			1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)	
FIBROSIS			1 (2%)	
HYPERPLASIA, NOS			1 (2%)	
HYPERPLASIA, LYMPHOID			1 (2%)	
HEMATOPOIESIS				1 (2%)
#LYMPH NODE	(4)	(5)	(44)	(41)
INFLAMMATION, NOS				1 (2%)
#CERVICAL LYMPH NODE	(4)	(5)	(44)	(41)
INFLAMMATION ACUTE AND CHRONIC		1 (20%)		
CIRCULATORY SYSTEM				
#MYOCARDIUM	(4)	(4)	(50)	(50)
INFLAMMATION, INTERSTITIAL				1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
#ENDOCARDIUM	(4)	(4)	(50)	(50)
FIBROSIS, FOCAL				1 (2%)
DIGESTIVE SYSTEM				
#LIVER	(4)	(5)	(49)	(50)
DEGENERATION PARENCHYMATOUS	2 (50%)	3 (60%)	1 (2%)	6 (12%)
NECROSIS, FOCAL				1 (2%)
METAMORPHOSIS FATTY	1 (25%)		4 (8%)	5 (10%)
FOCAL CELLULAR CHANGE			1 (2%)	2 (4%)
ANGIECTASIS		1 (20%)	3 (6%)	8 (16%)
*BILE DUCT	(4)	(5)	(50)	(50)
INFLAMMATION, CHRONIC		1 (20%)		
FIBROSIS			1 (2%)	
HYPERPLASIA, NOS			2 (4%)	
#GASTRIC MUCOSA	(4)	(5)	(49)	(49)
EROSION			1 (2%)	
URINARY SYSTEM				
#KIDNEY	(4)	(5)	(49)	(47)
CYST, NOS				1 (2%)
INFLAMMATION, CHRONIC		2 (40%)	7 (14%)	4 (9%)
ENDOCRINE SYSTEM				
#PITUITARY	(4)	(4)	(48)	(45)
CYST, NOS				1 (2%)
CONGESTION, NOS			1 (2%)	
HEMORRHAGIC CYST				1 (2%)
DEGENERATION, CYSTIC				1 (2%)
HYPERPLASIA, NOS		1 (25%)	2 (4%)	1 (2%)
HYPERPLASIA, FOCAL				1 (2%)
ANGIECTASIS			8 (17%)	2 (4%)
#ADRENAL	(4)	(5)	(50)	(47)
CONGESTION, NOS			1 (2%)	1 (2%)
HEMORRHAGE			4 (8%)	2 (4%)
DEGENERATION, CYSTIC	1 (25%)			
NECROSIS, NOS			1 (2%)	1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
METAMORPHOSIS FATTY			1 (2%)	1 (2%)
HEMOSIDEROSIS				1 (2%)
HYPERPLASIA, NOS				1 (2%)
ANGIECTASIS			1 (2%)	
#ADRENAL CORTEX	(4)	(5)	(50)	(47)
HEMORRHAGE			2 (4%)	1 (2%)
DEGENERATION, CYSTIC	1 (25%)		1 (2%)	
NECROSIS, NOS			1 (2%)	
NECROSIS, HEMORRHAGIC			1 (2%)	
METAMORPHOSIS FATTY				1 (2%)
ATROPHY, NOS				1 (2%)
HYPERPLASIA, FOCAL	1 (25%)			
ANGIECTASIS			2 (4%)	
#THYROID	(4)	(5)	(49)	(44)
FOLLICULAR CYST, NOS	1 (25%)			
HYPERPLASIA, C-CELL			3 (6%)	2 (5%)
HYPERPLASIA, FOLLICULAR-CELL		1 (20%)	1 (2%)	2 (5%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(4)	(5)	(50)	(50)
HYPERPLASIA, NOS				2 (4%)
*MAMMARY LOBULE	(4)	(5)	(50)	(50)
HYPERPLASIA, NOS		1 (20%)		3 (6%)
#OVARY	(4)	(5)	(49)	(46)
FOLLICULAR CYST, NOS				1 (2%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*BONE	(4)	(5)	(50)	(50)
OSTEOPOROSIS				1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	LOW DOSE CONTROL	HIGH DOSE CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED			6	4
AUTOLYSIS/NO NECROPSY	1			

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE FED CAPTAN IN THE DIET

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE FED CAPTAN IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	9	48	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	9	47	49
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(9)	(47)	(49)
HYPERPLASIA, ALVEOLAR EPITHELIUM		2 (4%)	
HEMATOPOIETIC SYSTEM			
#MESENTERIC L. NODE	(9)	(37)	(41)
CONGESTION, CHRONIC PASSIVE		1 (3%)	
INFLAMMATION, NOS			1 (2%)
CIRCULATORY SYSTEM			
#MYOCARDIUM	(9)	(47)	(49)
DEGENERATION, NOS		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(9)	(46)	(49)
DEGENERATION PARENCHYMATOUS		2 (4%)	
NECROSIS, FOCAL		1 (2%)	
#PANCREAS	(9)	(47)	(49)
DILATATION/DUCTS			1 (2%)
INFLAMMATION, NOS			1 (2%)
#DUODENUM	(9)	(43)	(46)
HYPERPLASIA, FOCAL			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
#DUODENAL MUCOSA	(9)	(43)	(46)
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, FOCAL			2 (4%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	4	35	34

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
AUTO/NECRCPSY/NO HISTO		1	
AUTOLYSIS/NO NECROPSY	1	2	1

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

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE FED CAPTAN IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	50	48
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(10)	(49)	(48)
HYPERPLASIA, ALVEOLAR EPITHELIUM		1 (2%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(10)	(49)	(48)
CONGESTION, ACUTE		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
HEMATOPOIESIS		1 (2%)	
#MESENTERIC L. NODE	(10)	(42)	(36)
INFLAMMATION, NOS		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(10)	(49)	(47)
INFLAMMATION, NOS	1 (10%)		
DEGENERATION PARENCHYMATOUS		7 (14%)	
METAMORPHOSIS FATTY	1 (10%)		1 (2%)
#PANCREAS	(10)	(48)	(47)
HEMATOPOIESIS	1 (10%)		

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	(8)	(50)	(48)
INFLAMMATION, CHRONIC		1 (2%)	
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
#UTERUS	(10)	(45)	(43)
HEMORRHAGE		1 (2%)	
#UTERUS/ENDOMETRIUM	(10)	(45)	(43)
HYPERPLASIA, CYSTIC	1 (10%)	3 (7%)	3 (7%)
#OVARY	(10)	(46)	(45)
INFLAMMATION, NOS	3 (30%)		
INFLAMMATION, SUPPURATIVE	1 (10%)	3 (7%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

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	29	38
AUTO/NECROPSY/NO HISTO			1
AUTOLYSIS/NO NECROPSY			1

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

APPENDIX E

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS FED CAPTAN IN THE DIET

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Captan in the Diet[a]

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Thyroid: C-cell Adenoma[b]	2/65 (3)	0/10 (0)	1/42 (2)	1/47 (2)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			0.774	0.691
Lower Limit			0.013	0.012
Upper Limit			14.321	12.844
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.014	0.012
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	113	75
Pancreatic Islets: Islet-cell Adenoma[b]	3/72 (4)	0/9 (0)	1/45 (2)	1/47 (2)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			0.533	0.511
Lower Limit			0.010	0.010
Upper Limit			6.370	6.108
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.012	0.011
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	--	114

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Captan in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma[b]	8/62 (13)	2/10 (20)	9/43 (21)	5/45 (11)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			1.622	0.861
Lower Limit			0.603	0.235
Upper Limit			4.414	2.768
Relative Risk (Matched Control)[f]			1.047	0.556
Lower Limit			0.283	0.116
Upper Limit			9.208	5.436
Weeks to First Observed Tumor	--	113	60	86
Liver: Neoplastic Nodule[b]	2/73 (3)	1/10 (10)	1/47 (2)	2/49 (4)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			0.777	1.490
Lower Limit			0.013	0.111
Upper Limit			14.431	19.881
Relative Risk (Matched Control)[f]			0.213	0.408
Lower Limit			0.003	0.025
Upper Limit			16.378	23.619
Weeks to First Observed Tumor	--	113	--	114

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Captan in the Diet[a]

(continued)

[a]Treated groups received time-weighted average doses of 2,525 or 6,050 ppm.

[b]Number of tumor-bearing animals/number of animals examined at site (percent).

[c]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when $P < 0.05$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched-control group (*) or with the pooled-control group (**) when $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

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

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each treated group and the specified control group.

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Captan in the Diet[a]

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma[b]	12/62 (19)	3/8 (38)	12/48 (25)	4/45 (9)
P Values[c,d]	N.S.	P = 0.014(N)	N.S.	N.S.
Relative Risk (Pooled Control)[f]			1.292	0.459
Lower Limit			0.581	0.115
Upper Limit			2.842	1.398
Relative Risk (Matched Control)[f]			0.667	0.237
Lower Limit			0.266	0.059
Upper Limit			3.220	1.433
Weeks to First Observed Tumor	--	113	97	97
Liver: Neoplastic Nodule[b]	1/71 (1)	0/9 (0)	4/49 (8)	0/50 (0)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.010			
Relative Risk (Pooled Control)[f]			5.796	0.000
Lower Limit			0.594	0.000
Upper Limit			279.251	26.485
Relative Risk (Matched Control)[f]			Infinite	--
Lower Limit			0.192	--
Upper Limit			Infinite	--
Weeks to First Observed Tumor	--	--	113	--

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Captan in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Liver: Neoplastic Nodule or Hepatocellular Carcinoma[b]	1/71 (1)	0/9 (0)	4/49 (8)	1/50 (2)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.039			
Relative Risk (Pooled Control)[f]			5.796	1.420
Lower Limit			0.594	0.018
Upper Limit			279.251	109.277
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.192	0.011
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	113	114
Adrenal: Cortical Adenoma or Cortical Carcinoma[b]	0/64 (0)	0/9 (0)	2/50 (4)	3/47 (6)
P Values[c,d]	P = 0.047	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			Infinite	Infinite
Lower Limit			0.377	0.813
Upper Limit			Infinite	Infinite
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.060	0.130
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	113	87

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Captan in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Pancreatic Islets: Islet-cell Adenoma[b]	1/69 (1)	1/8 (13)	0/45 (0)	3/48 (6)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			0.000	4.313
Lower Limit			0.000	0.359
Upper Limit			28.540	221.533
Relative Risk (Matched Control)[f]			0.000	0.500
Lower Limit			0.000	0.051
Upper Limit			3.329	25.730
Weeks to First Observed Tumor	--	98	--	114
Mammary Gland: Adenocarcinoma, NOS, Adenoma, NOS, or Infiltrating Duct Carcinoma[b]	0/67 (0)	0/9 (0)	3/50 (6)	3/50 (6)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			Infinite	Infinite
Lower Limit			0.800	0.800
Upper Limit			Infinite	Infinite
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.122	0.122
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	97	114

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Captan in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Mammary Gland: Fibroma[b]	1/72 (1)	0/9 (0)	2/50 (4)	3/50 (6)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			2.880	4.320
Lower Limit			0.155	0.358
Upper Limit			166.479	222.074
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.060	0.122
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	102	114
Mammary Gland: Fibroadenoma[b]	8/72 (11)	0/9 (0)	4/50 (8)	5/50 (10)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			0.720	0.900
Lower Limit			0.166	0.244
Upper Limit			2.523	2.920
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.188	0.257
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	75	38

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Captan in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Mammary Gland: Adenoma, NOS, or Fibroadenoma[b]	8/72 (11)	0/9 (0)	7/50 (14)	6/50 (12)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			1.260	1.080
Lower Limit			0.413	0.328
Upper Limit			3.701	3.311
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.396	0.326
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	75	38
Uterus: Endometrial Stromal Polyp[b]	7/67 (10)	2/9 (22)	6/48 (13)	7/45 (16)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			1.196	1.489
Lower Limit			0.354	0.476
Upper Limit			3.876	4.608
Relative Risk (Matched Control)[f]			0.563	0.700
Lower Limit			0.134	0.178
Upper Limit			5.293	6.391
Weeks to First Observed Tumor	--	113	66	114

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Captan in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Thyroid: C-cell Adenoma[b]	1/66 (2)	0/9 (0)	1/49 (2)	4/44 (9)
P Values[c,d]	P = 0.035	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			1.347	6.000
Lower Limit			0.017	0.619
Upper Limit			103.614	288.319
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.011	0.214
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	113	114
Thyroid: C-cell Adenoma or Carcinoma[b]	2/66 (3)	0/9 (0)	2/49 (4)	4/44 (9)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			1.347	3.000
Lower Limit			0.101	0.451
Upper Limit			17.968	31.881
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.061	0.214
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	113	107

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Captan in the Diet[a]

(continued)

[a]Treated groups received time-weighted average doses of 2,525 or 6,050 ppm.

[b]Number of tumor-bearing animals/number of animals examined at site (percent).

[c]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when $P < 0.05$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched-control group (*) or with the pooled-control group (**) when $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

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

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each treated group and the specified control group.

APPENDIX F

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN MICE FED CAPTAN IN THE DIET

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed Captan in the Diet[a]

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma[b]	5/66 (8)	2/9 (22)	3/47 (6)	1/49 (2)
P Values[c,d]	N.S.	P = 0.034(N)	N.S.	N.S.
Relative Risk (Pooled Control)[f]			0.843	0.269
Lower Limit			0.136	0.006
Upper Limit			4.093	2.296
Relative Risk (Matched Control)[f]			0.287	0.092
Lower Limit			0.043	0.002
Upper Limit			3.205	1.657
Weeks to First Observed Tumor	--	91	91	91

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed Captan in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Liver: Neoplastic Nodule or Heptatocellular Carcinoma[b]	14/76 (18)	3/9 (33)	1/46 (2)	3/49 (6)
P Values[c,d]	P = 0.012(N)	N.S.	P = 0.012*(N) P = 0.006**(N)	P = 0.042*(N) P = 0.041**(N)
Departure from Linear Trend[e]		P = 0.003		
Relative Risk (Pooled Control)[f]			0.118	0.332
Lower Limit			0.003	0.064
Upper Limit			0.729	1.109
Relative Risk (Matched Control)[f]			0.065	0.184
Lower Limit			0.001	0.033
Upper Limit			0.738	1.233
Weeks to First Observed Tumor	--	91	91	84

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed Captan in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Duodenum: Adenomatous Polyp, NOS[b]	0/68 (0)	0/9 (0)	2/43 (5)	2/46 (4)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			Infinite	Infinite
Lower Limit			0.463	0.433
Upper Limit			Infinite	Infinite
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.069	0.065
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	91	91
Duodenum: Adenocarcinoma in Adenomatous Polyp[b]	0/68 (0)	0/9 (0)	1/43 (2)	3/46 (7)
P Values[c,d]	P = 0.033	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			Infinite	Infinite
Lower Limit			0.085	0.882
Upper Limit			Infinite	Infinite
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.012	0.132
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	91	91

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed Captan in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Duodenum: Adenomatous Polyp, NOS, or Adenocarcinoma in Adenomatous Polyp[b]	0/68 (0)	0/9 (0)	3/43 (7)	5/46 (11)
P Values[c,d]	P = 0.008	N.S.	N.S.	P = 0.009**
Relative Risk (Pooled Control)[f]			Infinite	Infinite
Lower Limit			0.943	1.849
Upper Limit			Infinite	Infinite
Relative Risk (Matched Control)[f]			Infinite	Infinite
Lower Limit			0.142	0.280
Upper Limit			Infinite	Infinite
Weeks to First Observed Tumor	--	--	91	91

[a]Treated groups received doses of 8,000 or 16,000 ppm.

[b]Number of tumor-bearing animals/number of animals examined at site (percent).

[c]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when $P < 0.05$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched-control group (*) or with the pooled-control group (**) when $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed Captan in the Diet[a]

(continued)

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

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each treated group and the specified control group.

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed Captan in the Diet[a]

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Liver: Neoplastic Nodule[b]	2/67 (3)	1/10 (10)	1/49 (2)	1/47 (2)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			0.684	0.713
Lower Limit			0.012	0.012
Upper Limit			12.716	13.241
Relative Risk (Matched Control)[f]			0.204	0.213
Lower Limit			0.003	0.003
Upper Limit			15.723	16.378
Weeks to First Observed Tumor	--	91	91	91
Duodenum: Adenomatous Polyp, NOS[b]	1/68 (1)	1/9 (11)	1/49 (2)	0/48 (0)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			1.388	0.000
Lower Limit			0.018	0.000
Upper Limit			106.757	26.404
Relative Risk (Matched Control)[f]			0.184	0.000
Lower Limit			0.003	0.000
Upper Limit			14.153	3.512
Weeks to First Observed Tumor	--	--	91	--

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed Captan in the Diet[a]

(continued)

Topography: Morphology	Pooled Control	Matched Control	Low Dose	High Dose
Duodenum: Adenocarcinoma in Adenomatous Polyp[b]	0/68 (0)	0/9 (0)	0/49 (0)	3/48 (6)
P Values[c,d]	P = 0.022	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			--	Infinite
Lower Limit			--	0.844
Upper Limit			--	Infinite
Relative Risk (Matched Control)[f]			--	Infinite
Lower Limit			--	0.127
Upper Limit			--	Infinite
Weeks to First Observed Tumor	--	--	--	91
Duodenum: Adenomatous Polyp, NOS, or Adenocarcinoma in Adenomatous Polyp[b]	1/68 (1)	1/9 (11)	1/49 (2)	3/48 (6)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Pooled Control)[f]			1.388	4.250
Lower Limit			0.018	0.351
Upper Limit			106.757	218.317
Relative Risk (Matched Control)[f]			0.184	0.563
Lower Limit			0.003	0.056
Upper Limit			14.153	28.937
Weeks to First Observed Tumor	--	--	91	91

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed Captan in the Diet[a]

(continued)

[a]Treated groups received doses of 8,000 or 16,000 ppm.

[b]Number of tumor-bearing animals/number of animals examined at site (percent).

[c]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when $P < 0.05$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched-control group (*) or with the pooled-control group (**) when $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

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

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each treated group and the specified control group.

APPENDIX G

ANALYSIS OF FORMULATED DIETS FOR CONCENTRATIONS OF CAPTAN

APPENDIX G

Analysis of Formulated Diets for Concentrations of Captan

A 10-g sample of the diet mixture was shaken with 125 ml of benzene at room temperature for 16 hours, then filtered through Celite with benzene washes. The extracts were evaporated almost to dryness under dry nitrogen. After appropriate dilutions, the solution was quantitatively analyzed for captan by gas-liquid chromatography (electron capture detector, 10% DC-200 on Gas Chrom Q column). Recoveries were checked with spiked samples, and external standards were used for calibration.

Theoretical Concentrations in Diet (ppm)	No. of Samples	Sample Analytical Mean (ppm)	Coefficient of Variation (%)	Range (ppm)
2,000	12	2,014	3.6%	1,870-2,130
4,000	18	4,012	5.9%	3,550-4,340
8,000	31	8,186	5.0%	7,250-9,230
16,000	26	15,748	4.9%	14,100-17,350

☆U.S. GOVERNMENT PRINTING OFFICE: 1977— 260-899.3134

DHEW Publication No. (NIH) 77-815