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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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BIOASSAY OF

DIBROMOCHLOROPROPANE

FOR POSSIBLE CARCINOGENICITY

Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20014

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REPORT ON THE BIOASSAY OF DIBROMOCHLOROPROPANE
FOR POSSIBLE CARCINOGENICITY

CARCINOGENESIS PROGRAM, DIVISION OF CANCER CAUSE AND PREVENTION
NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH

CONTRIBUTORS: This report presents the results of the bioassay of dibromochloropropane (DBCP) conducted for the Carcinogen Bioassay and Program Resources Branch, Carcinogenesis Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), National Institutes of Health, Bethesda, Maryland. This bioassay was conducted by Hazleton Laboratories America, Inc., Vienna, Virginia, initially under direct contract to the NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI Carcinogenesis Bioassay Program.

The experimental design was determined by the NCI Project Officers, Dr. J. H. Weisburger (1,2) and Dr. E. K. Weisburger (1). The principal investigators for the contract were Dr. M. B. Powers (3), Dr. R. W. Voelker (3), Dr. W. A. Olson (3,4) and Dr. W. M. Weatherholtz (3). Chemical analysis was performed by Dr. C. L. Guyton (3,5); the technical supervisor of animal treatment and observation was Ms. K. J. Petrovics (3).

Histopathology was performed by Dr. R. H. Habermann (3) and reviewed by Dr. R. W. Voelker (3) at the Hazleton Laboratories America, Inc., and the diagnoses included in this report represent the interpretation of these pathologists. Pathologists from NCI (1) and Tracor Jitco (6) have reviewed selected slides and concur with the overall pathologic evaluation of the study.

Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute (7); the statistical analysis was performed by Dr. J. R. Joiner (6) and Mr. W. W. Belew (8), using methods selected for the Bioassay Program by Dr. J. J. Gart (9).

This report was prepared at METREK, a Division of The MITRE Corporation (8) under the direction of the NCI. Those responsible for this report at METREK are the project coordinator, Dr. L. W. Thomas (8), the task leader, Dr. M. R. Kornreich (8), and the senior biologist, Ms. P. Walker (8). The final report was reviewed by members of the participating organizations.

The statistical analysis was reviewed by a member or members of the Mathematical Statistics and Applied Mathematics Section of the NCI: Dr. J. J. Gart (9), Mr. J. Nam (9), Dr. H. M. Pettigrew (9), and Dr. R. E. Tarone (9).

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SUMMARY

A bioassay for possible carcinogenicity of technical-grade dibromochloropropane (DBCP) was conducted using Osborne-Mendel rats and B6C3F1 mice. DBCP in corn oil was administered by gavage 5 days a week, at either of two dosages, to groups of 50 male and 50 female animals of each species.

Initial dosage levels for the chronic bioassay were selected on the basis of a preliminary subchronic toxicity test. Subsequent dosage adjustments were made during the course of the chronic bioassay. The time-weighted average dosages of DBCP in the chronic study were 29 mg/kg/day for the high dose rats of both sexes, and 15 mg/kg/day for the low dose rats of both sexes. The time-weighted average concentrations for the high dose male and female mice were 219 and 209 mg/kg/day, respectively. The time-weighted average concentrations for the low dose male and female mice were 114 and 110 mg/kg/day, respectively.

For each species, 20 animals of each sex were placed on test as vehicle controls. These animals were intubated with corn oil at the same time that dosed animals were intubated with DBCP mixtures. Twenty animals of each sex were placed on test as untreated controls for each species. These animals received no gavage treatments.

DBCP was administered to the high dose male and high dose female rats for 64 weeks prior to sacrifice, and to the low dose female rats for 73 weeks prior to sacrifice. The low dose male rats were treated for 78 weeks followed by an additional 5 weeks of observation. The high dose male and female mice were treated for 47 weeks prior to sacrifice; the low dose male mice were treated for 59 or 60 weeks prior to sacrifice, and the low dose female mice were treated for 60 weeks prior to sacrifice.

In rats and mice of both sexes, statistically significant incidences of squamous-cell carcinomas of the forestomach occurred in each dosed group and a significant positive association existed between dosage level and tumor incidence. The incidences of adenocarcinomas of the mammary gland were statistically significant in female rats when the treated groups were compared to the controls. Toxic nephropathy was also observed at elevated incidences in all of the treated rats and mice when compared to their respective untreated or vehicle control groups.

Under the conditions of this study, DBCP is a stomach carcinogen in rats and mice of both sexes and is carcinogenic to the mammary gland in female rats.

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I. INTRODUCTION

Dibromochloropropane (DBCP) (NCI No. C00500), a halogenated aliphatic hydrocarbon and agricultural pesticide, was one of several widely used pesticides selected for bioassay by the National Cancer Institute. At that time there was a lack of adequate chronic toxicity data on this compound.

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is 1,2-dibromo-3-chloropropane.* It is also known in the agricultural trade as Nemagon®, Fumazone® and DBCP.

DBCP is used primarily as a soil fumigant for control of nematodes and is suitable for protection of a wide variety of field crops, vegetables, fruits, nuts, and ornamental plants. In 1971, the most recent year for which such data are available, approximately 255,000 acres of U.S. agricultural land were treated with 3.6 million pounds of the nematocide, with more than 59 percent of total usage occurring in the Pacific region (Andrilenas, 1974).

Recent production statistics for DBCP are considered proprietary and are, therefore, not available; however, domestic production in 1969 amounted to more than 8.6 million pounds (Fowler and Mahan, 1975) while domestic sales in 1972 exceeded 15 million pounds (U.S. International Trade Commission, 1977).

*The CAS registry number is 96-12-8.

Workers at pesticide formulating plants and agricultural workers engaged in pesticide application may be exposed to DBCP either through inhalation or skin contact. Since the compound is classified as moderately volatile (evaporating at a rate similar to ethanol) and undergoes biological degradation in moist soils (Shell Chemical Company, 1972) exposure of the general population via ingestion of contaminated food crops is probably negligible.

DBCP is harmful to humans following inhalation or ingestion; however, toxic amounts may also be absorbed through the skin. Inhalational intoxication results in nausea, irritation of the respiratory tract membranes, narcosis, and possible pulmonary congestion following prolonged or repeated exposure to high vapor concentrations. Symptoms of acute ingestion include gastrointestinal distress and congestion and edema of the lungs (Shell Chemical Company, 1972). DBCP is irritating to the skin, with repeated applications resulting in necrosis of the dermis and mild erythema. Permanent eye injury may result from chronic eye contact with vapors (Gleason et al., 1969). DBCP was found to be mutagenic in bacteria, causing base-substitution mutations in a histidine-requiring strain of Salmonella typhimurium (The Ames Test using strain TA1530) (Rosenkranz, 1975).

In July and August, 1977, at least 60 male chemical plant workers involved with the manufacture or formulation of DBCP pesticides were found to be sterile (Peterson and Shinoff, 1977a; 1977b). Earlier

studies indicated sterility in laboratory animals (Torkelson et al., 1961). Rats, guinea pigs, rabbits, and monkeys received at least 50 seven-hour exposures to 12 ppm DBCP in air. The most striking observation at autopsy was severe atrophy and degeneration of the testes of all species. In the rats this was characterized by degenerative changes in the seminiferous tubules, an increase in Sertoli cells, reduction in the number of sperm cells, and development of abnormal forms of sperm cells (Torkelson et al., 1961).

II. MATERIALS AND METHODS

A. Chemicals

One batch of technical-grade 1,2-dibromo-3-chloropropane (DBCP) was purchased from Shell Chemical Company, Incorporated. Analysis was performed by Hazleton Laboratories America, Inc., Vienna, Virginia. Gas-liquid chromatography (GLC) suggested a purity greater than 90 percent with 16 minor impurities. The infrared analysis was not inconsistent with the structure of the compound.

A second GLC analysis, performed 24 months later, suggested a similar degree of purity although some changes in the nature and quantity of the impurities were noted in the chromatogram. Those changes were reflected in a slightly altered infrared spectra.

Throughout this report the term DBCP is used to represent this technical-grade material.

B. Dosage Preparation

Fresh mixtures of DBCP in Duke's® corn oil (S. F. Sauer Company), were prepared weekly, sealed, and stored in dark bottles at 34°F. These DBCP solutions were considered generally stable for 10 days under the indicated storage conditions. The concentrations of DBCP in the corn oil were 1.0 to 1.5 percent for rats and 1.0 to 2.6 percent for mice.

C. Animals

Two animal species, rats and mice, were used in the carcinogenicity bioassay. The Osborne-Mendel rat was selected on the basis of a

comparative study of the tumorigenic responsiveness to carbon tetrachloride of five different strains of rats (Reuber and Glover, 1970). The B6C3F1 mouse was selected because it has been used by the NCI for carcinogenesis bioassays and has proved satisfactory in this capacity.

Rats and mice of both sexes were obtained through contracts of the Division of Cancer Treatment at the National Cancer Institute. The Osborne-Mendel rats were procured from the Battelle Memorial Institute, Columbus, Ohio, and the B6C3F1 mice were obtained from the Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. Upon receipt, animals were quarantined for at least 10 days, observed for visible signs of disease or parasites, and assigned to the various treatment and control groups.

D. Animal Maintenance

All animals were housed by species in temperature- and humidity-controlled rooms. The temperature range was 20° to 24°C and the relative humidity was maintained between 45 and 55 percent. The air conditioning system in the laboratory provided filtered air at a rate of 12 complete changes of room air per hour. Fluorescent lighting was provided on a 12-hour-daily cycle. The rats were individually housed in suspended galvanized-steel wire-mesh cages with perforated floors, while mice were housed by sex in groups of 10 in solid-bottom polypropylene cages with filter tops. Sanitized cages with fresh bedding (Sanichips®, Shurfire) were provided once each week for mice. Rats received sanitized cages with no bedding with the same frequency.

Food hoppers were changed and heat-sterilized once a week for the first 10 weeks and once a month thereafter. Fresh heat-sterilized glass water bottles were provided three times a week. Food (Wayne Lab-Blox®, Allied Mills, Inc.) and water were available ad libitum.

DBCP-treated rats and their vehicle controls were housed in the same room with rats treated with* trichloroethylene (79-01-6), carbon disulfide (75-15-0), 1,1-dichloroethane (75-34-3), and 1,2-dichloroethane (107-06-2). Untreated control rats for the DBCP bioassay were housed in another room with rats treated with 1,1,2,2-tetrachloroethane (79-34-5), chloroform (67-66-3), 1,2-dibromoethane (106-93-4), carbon tetrachloride (56-23-5), and allyl chloride (107-05-1). DBCP-treated and both vehicle and untreated control mice were maintained in the same room as mice receiving iodoform (75-47-8), 1,1,2-trichloroethane (79-00-5), 3-sulfolene (77-79-2), carbon disulfide (75-15-0), 1,1,2,2-tetrachloroethane (79-34-5), allyl chloride (107-05-1), 1,2-dichloroethane (107-06-2), carbon tetrachloride (56-23-5), chloroform (67-66-3), chloropicirin (76-06-2), tetrachloroethylene (127-18-4), methylchloroform (71-55-6), hexachloroethane (67-72-1), 1,1-dichloroethane (75-34-3), trichloroethylene (79-01-6), trichlorofluoromethane (75-69-4), and 1,2-dibromoethane (106-93-4).

E. Gastric Intubation

Intubation was performed for five consecutive days per week on a mg/kg body weight basis utilizing the most recently observed group

*CAS registry numbers are given in parentheses.

mean body weight as a guide for determining the dose. Mean body weights for each group were recorded at weekly intervals for the first 10 weeks and at monthly intervals thereafter. All animals of one sex within a treatment group received the same dose. Animals were gavaged with test solutions under a hood to minimize extraneous exposure of other animals and laboratory personnel to the chemical.

F. Selection of Initial Dose Levels

In order to establish the maximum tolerated dosages of DBCP for administration to treated animals in the chronic studies, subchronic toxicity tests were conducted with both rats and mice. Six groups, each consisting of five males and five females, were utilized for each animal species. DBCP dissolved in corn oil was administered by gavage to five of the six rat groups at concentrations of 25, 40, 63, 100, and 160 mg/kg/day and to five of the six mouse groups at concentrations of 100, 160, 251, 398 and 631 mg/kg/day. The sixth group of each species served as a control group and was gavaged only with corn oil. Intubation occurred 5 days per week for 6 weeks, followed by a 2-week observation period to detect any delayed toxicity.

A dosage inducing no mortality and resulting in a retardation in body weight gain of approximately 20 percent was to be selected as the initial high dose. When weight gain criteria were not applicable, mortality data alone were utilized.

All the male rats treated with 25 and 40 mg/kg/day and all the female rats treated with 25 mg/kg/day survived the entire 6-week

treatment period and the 2-week observation period, while deaths were observed at higher doses. Body weight gain retardation, expressed as a percentage of the weight gained by the controls, was 22 percent in males and 33 percent in females receiving dosages of 25 mg/kg/day. The initial high dose selected for use in the chronic bioassay was 24 mg/kg/day for both male and female rats.

All mice receiving dosages of 398 mg/kg/day or more died before the subchronic study was completed. All other mice (with the exception of one male and one female) treated with 251 mg/kg/day or less survived the entire 8-week period. No retardation in mean body weight gain was observed in any of the male or female treated groups. The initial high doses selected for the chronic bioassay were 160 and 120 mg/kg/day for males and females, respectively.

G. Experimental Design

The experimental design parameters for the chronic study (species, sex, group size, dosages administered, duration of treated and untreated observation periods, and the time-weighted average dosages) are summarized in Tables 1 and 2.

The low dose, high dose, and vehicle control rats were all approximately 7 weeks old at the time the bioassay began. The untreated controls were approximately 16 weeks younger than the other three groups, and were started on test a corresponding 16 weeks after the other groups. They were observed for a total of 109 weeks. The untreated controls were approximately 6 weeks old when they were

TABLE 1

DESIGN SUMMARY FOR OSBORNE-MENDEL RATS
DBCP GAVAGE EXPERIMENT

	INITIAL GROUP SIZE	DBCP DOSAGE[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE DOSAGE[b]
MALE					
UNTREATED CONTROL	20	0		109	0
VEHICLE CONTROL[c]	20	0	78	5	0
LOW DOSE[c]	50	12 15 0	9 69	 5	15
HIGH DOSE[d]	50	24 30	9 55	 0	29
FEMALE					
UNTREATED CONTROL	20	0		109	0
VEHICLE CONTROL[c]	20	0	78	5	0
LOW DOSE[e]	50	12 15	9 64	 0	15
HIGH DOSE[d]	50	24 30	9 55	 0	29

[a] Dosage, given in mg/kg body weight, was administered by gavage five consecutive days per week.

[b] Time-weighted average dosage = $\frac{\Sigma(\text{dosage X number of weeks received})}{\Sigma(\text{weeks receiving treatment})}$

[c] These animals were sacrificed during week 83.

[d] These animals were sacrificed during week 64.

[e] These animals were sacrificed during week 73.

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
DBCP GAVAGE EXPERIMENT

	INITIAL GROUP SIZE	DBCP DOSAGE[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE DOSAGE[b]
MALE					
UNTREATED CONTROL[c]	20	0	0	78	0
VEHICLE CONTROL[d]	20	0	59	0	0
LOW DOSE[e]	50	80 100 130	11 14 35	0	114
HIGH DOSE[f]	50	160 200 260	11 14 22	0	219
FEMALE					
UNTREATED CONTROL	20	0	0	90	0
VEHICLE CONTROL[e]	20	0	60	0	0
LOW DOSE[e]	50	60 100 130	11 14 35	0	110
HIGH DOSE[f]	50	120 200 260	11 14 22	0	209

[a] Dosage, given in mg/kg body weight, was administered by gavage five consecutive days per week.

[b] Time-weighted average dosage = $\frac{\Sigma \text{ (dosage X number of weeks received)}}{\Sigma \text{ (weeks receiving treatment)}}$

[c] These animals were sacrificed during week 78.

[d] These animals were sacrificed during week 59.

[e] These animals were sacrificed during week 60.

[f] These animals were sacrificed during week 47.

started on test. The high and low dosages of DBCP initially utilized for rats of both sexes were 24 and 12 mg/kg/day, respectively. Intubation was performed five consecutive days per week. In week 10, dosages were raised to 30 and 15 mg/kg/day and maintained at these levels until the end of the bioassay. High dose male and female rats were sacrificed during week 64. Low dose female rats were sacrificed in week 73. Low dose male rats and vehicle control rats of both sexes were treated for 78 weeks, observed without treatment for 5 additional weeks, and then sacrificed.

The low dose, high dose, and vehicle control mice were approximately 5 weeks old when the first gavage treatments were administered. Male mice received initial high and low dosages of 160 and 80 mg/kg/day, respectively, while female mice received high and low dosages of 120 and 60 mg/kg/day, respectively. In week 12, high and low dosages administered to both male and female mice were increased to 200 and 100 mg/kg/day, respectively. Dosages were raised again in week 26, to 260 and 130 mg/kg/day and these were the respective high and low dosages utilized for the remainder of the bioassay.

Due to poor survival among the mice, all surviving high dose males and females were sacrificed during week 47. All surviving male vehicle control mice were sacrificed during week 59 and surviving male and female low dose mice or female vehicle control mice were sacrificed during weeks 59 and 60.

For both the rat and mouse control groups, the animals were maintained and observed in the same manner as the dosed groups. The untreated controls received no DBCP or corn oil, while the vehicle controls received pure corn oil by gavage.

H. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment. From the first day, all animals were inspected daily for mortality. Body weights, food consumption, and data concerning appearance, behavior, signs of toxic effects, and incidence, size, and location of tissue masses were recorded at weekly intervals for the first 10 weeks and at monthly intervals thereafter. The presence of tissue masses was determined by observation and palpation of each animal.

A necropsy was performed on each animal regardless of whether it died, was killed when moribund, or was sacrificed at the end of the bioassay. The animals were euthanized by exsanguination under sodium pentobarbital anesthesia, and were immediately necropsied. The histopathologic examination consisted of gross and microscopic examination of major tissues, organs, or gross lesions taken from sacrificed animals and, whenever possible, from animals found dead.

Slides were prepared from the following tissues: skin, subcutaneous tissue, lungs and bronchi, trachea, bone marrow, spleen, lymph nodes, thymus, heart, salivary gland, liver, gallbladder (mice) and bile duct, pancreas, esophagus, stomach, small intestine, large

intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, pancreatic islets, testis, prostate, seminal vesicle, brain, eye, muscle, uterus, mammary gland, and ovary.

Tissues for which slides were prepared were preserved in 10 percent buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin prior to microscopic examination. An occasional section was subjected to special staining techniques for more definitive diagnosis.

A few tissues were not examined for some animals, particularly for those that died early. Also, some animals were missing, cannibalized, or judged to be in such an advanced state of autolysis as to preclude histopathologic interpretation. Thus, the number of animals for which particular organs, tissues, or lesions were examined microscopically varies and does not necessarily represent the number of animals that were placed on experiment in each group.

I. 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 used Tarone's (1975) extensions of Cox's methods for testing 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 was 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, pp. 48-52) was used to compare the tumor incidence of a control group to 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, pp. 6-10) 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, pp. 362-365), was also used. Under the assumption of a linear trend, this test determined 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 was 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 dosed 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 percent 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. CHRONIC TESTING RESULTS: RATS

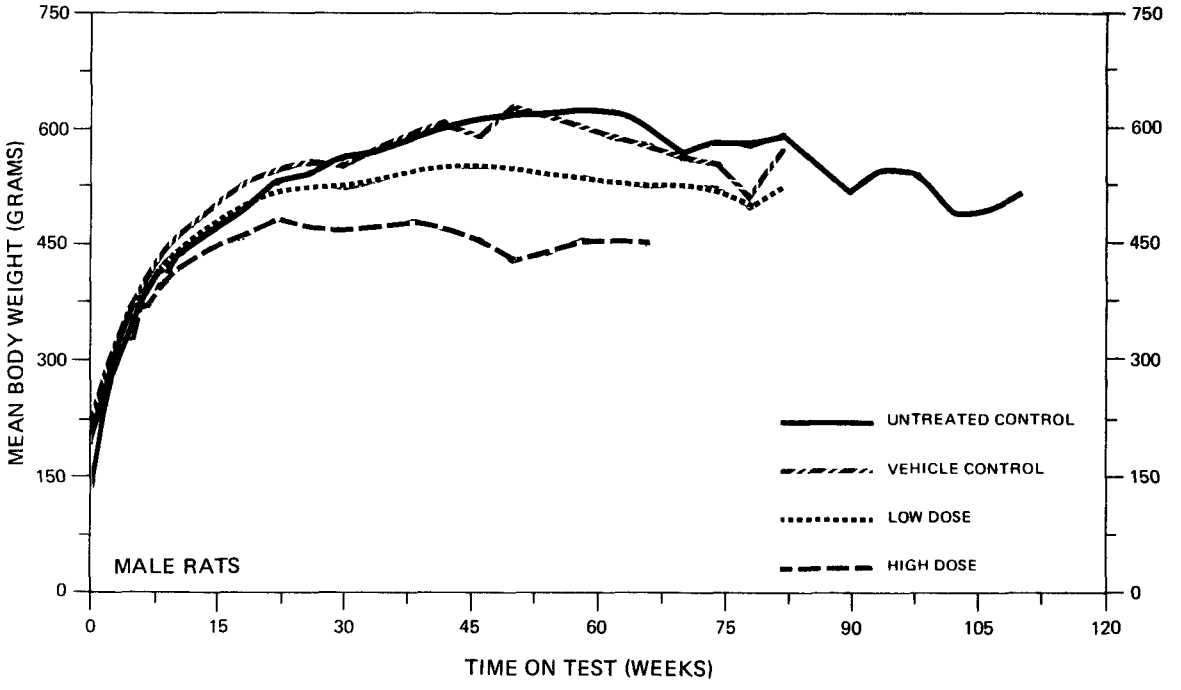
A. Body Weights and Clinical Observations

After the first 5 months of treatment, dose-related body weight gain retardation was apparent in male and female rats (Figure 1).

All animals exhibited generally normal appearance and behavior during the first 14 weeks of the study with the exception of occasional hunched appearance in a few treated rats. Beginning in week 18, an increasing number of treated males and females showed a hunched appearance and by week 34, this observation was evident in approximately 80 percent of the treated rats.

Urine staining of the abdominal area was the other predominant clinical sign noted in this study. It was first observed in a few high dose females in week 6, and in slightly increasing numbers of treated males and females thereafter. By week 34, approximately 15 percent of the low dose and 50 percent of the high dose rats showed abdominal urine stains. Urine stains were infrequently noted in the vehicle controls during the first 15 months of the study, but more frequently thereafter.

A declining survival rate, apparently from compound-related toxicity, was observed beginning in week 30 in the treated females. In week 36, 10 high dose females with large palpable tissue masses were sacrificed. The majority of these masses were histopathologically diagnosed as mammary adenocarcinomas. Increasing mortality was evident as the study progressed, particularly in the high dose rats.



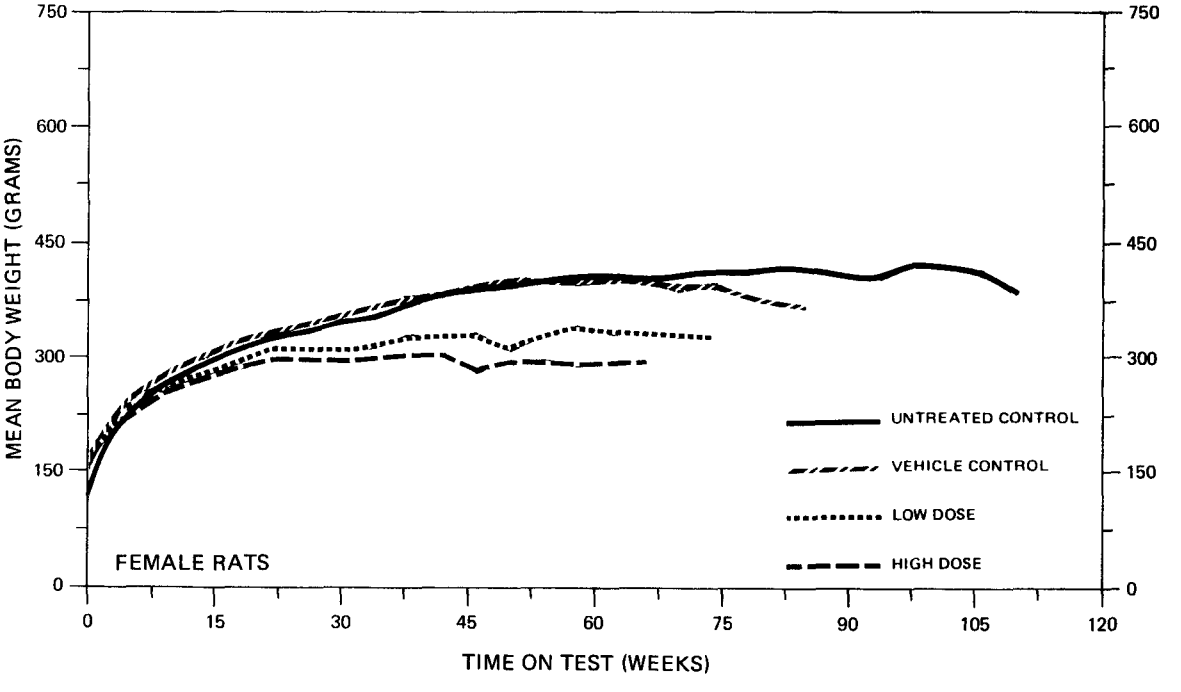


FIGURE 1
GROWTH CURVES FOR DBCP CHRONIC STUDY RATS

For most of the DBCP-treated animals that died naturally or were sacrificed, gross necropsy revealed tumors of the stomach, with metastases to adjacent organs in many cases.

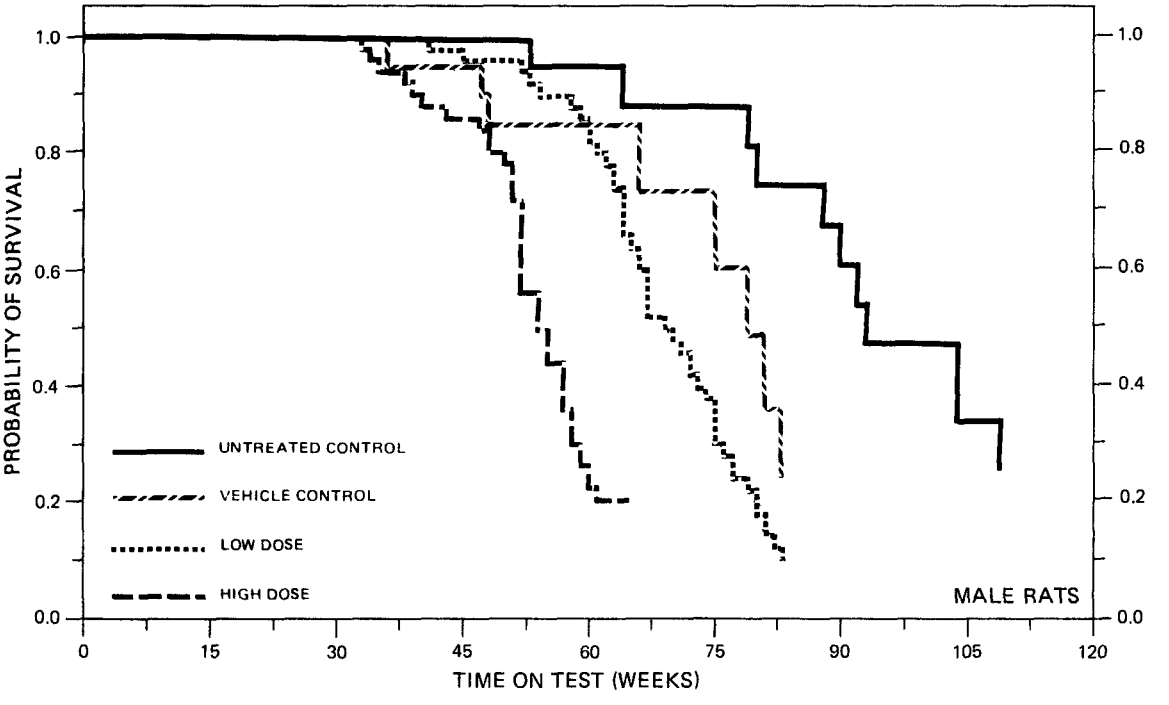
Respiratory signs characterized by labored respiration, wheezing, and/or nasal discharge were noted at a comparable and moderate incidence in all groups, including the vehicle controls, during the study. The incidence increased as the animals aged. Other signs commonly associated with aging that were noted at a similar rate in the vehicle controls and treated animals included sores on the body and/or extremities, localized alopecia, reddish discharge or brown crust around body orifices, and rough or stained fur. Isolated, apparently spontaneous clinical signs in one or two treated rats included head tilt, circling, tremors, and unusual gait.

Palpable nodules or tissue masses were observed as early as week 14 in a low dose female rat and were evident in a greater number of treated animals than controls during the study. The increased incidence of mammary adenocarcinomas in the DBCP-treated females was confirmed by subsequent histopathology.

B. Survival

The estimated probabilities of survival for male and female rats in the control and DBCP-treated groups are shown in Figure 2.

In male rats the Tarone test indicated a significant ($P < 0.001$) positive association between increased dosage and accelerated mortality. The departure from linear trend was also significant ($P < 0.001$),



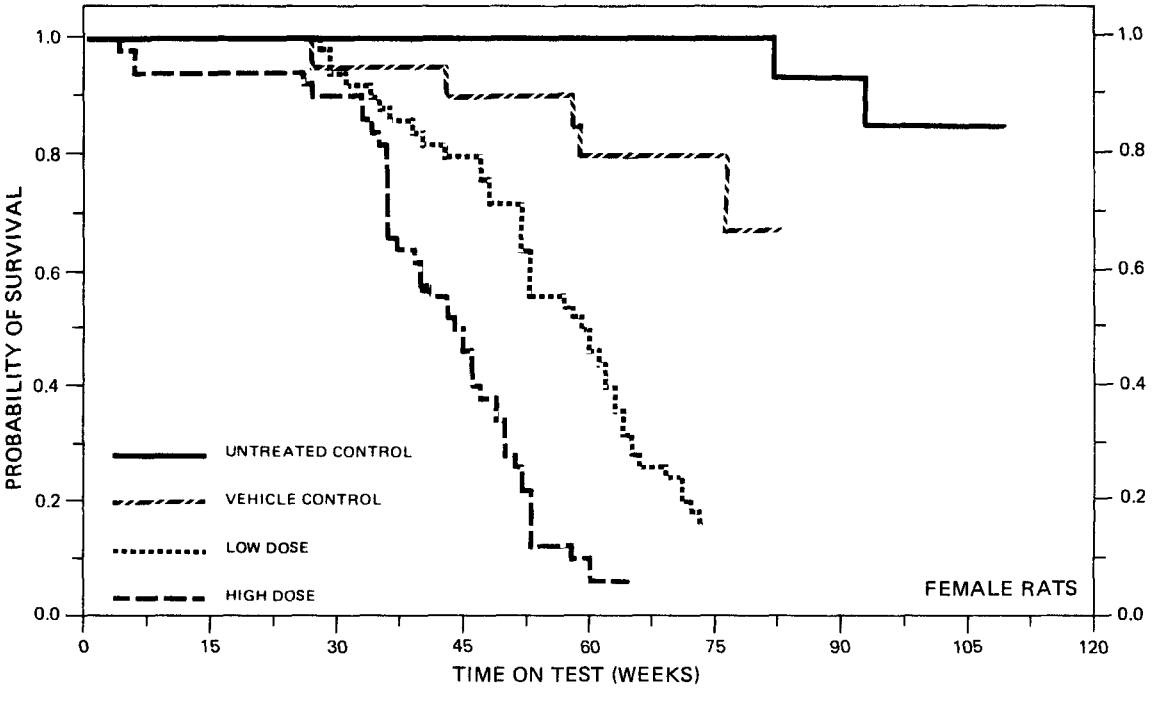


FIGURE 2
SURVIVAL COMPARISONS OF DBCP CHRONIC STUDY RATS

primarily because of the accelerated mortality noted in several of the groups. Eighty percent of the high dose males had died by week 62; the other 10 were sacrificed in week 64. Ninety percent of the low dose males were dead by week 83, at which point the remaining five rats were sacrificed. Ten vehicle control rats were sacrificed in week 64 and two in week 83; the others all died before week 83. Despite the sacrifice of five rats in week 60, survival in the untreated control group was adequate, with 55 percent of the male rats surviving at least 88 weeks. Early deaths in the dosed males may well have been tumor-related, since in both high and low dose groups 47/50 (94 percent) had squamous-cell carcinomas of the stomach.

In female rats the Tarone test indicated a significant ($P < 0.001$) positive association between dosage and mortality. The departure from linear trend was also significant ($P = 0.010$), primarily because of the accelerated mortality noted in treated rats. Ninety-four percent of the high dose females were dead by week 61, the remaining three were sacrificed in week 64. Eighty-four percent of the low dose group were dead by week 73, at which point the remaining eight were sacrificed. Seventy-five percent of the vehicle controls were dead by week 77, including ten rats sacrificed in week 65; the remaining five vehicle control rats were sacrificed in week 83. Survival in the untreated controls was high; despite the sacrifice of five animals in week 60, 65 percent of the rats survived until the end of

the study. Early deaths in the treated females may have been tumor-related, since squamous-cell carcinomas of the stomach were discovered in 38/50 (76 percent) of the low dose and 29/49 (59 percent) of the high dose female rats.

C. Pathology

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

Squamous-cell carcinomas of the forestomach occurred in 47/50 (94 percent) low dose males, 47/50 (94 percent) high dose males, 38/50 (76 percent) low dose females, and 29/49 (59 percent) high dose females. These tumors were not observed in control rats. Grossly, the neoplasms appeared as white fibrous lesions in the forestomach. Raised white and pale streaks were observed on the serosal surface. Adhesions to adjacent abdominal organs and tissues were present in some rats. Microscopically, the mucosal surface was acanthotic and hyperkeratotic. The basal epithelial layer contained papillary cords and nests of anaplastic squamous epithelium supported by dense bands of fibrous connective tissue. The carcinoma extended through the muscularis mucosa, submucosa, muscular layers, and serosa and metastasized (transcoelomic) to adjacent tissues. Pulmonary metastases were observed in lung sections from 5/50 (10 percent) low dose males, 5/50 (10 percent) high dose males, and 3/44 (7 percent) high dose females.

Squamous-cell papillomas of the stomach occurred in 1/50 (2 percent) low dose males, 2/50 (4 percent) high dose males, 1/50 (2 percent) low dose females, and 9/49 (18 percent) high dose females. These tumors were not observed in control rats.

In stomach sections from rats that did not have tumors of the forestomach, both acanthosis and hyperkeratosis occurred in two high dose males, two low dose males, nine high dose females, and four low dose females. Acanthosis in the absence of hyperkeratosis occurred in one low dose female.

Adenocarcinomas of the mammary gland were observed primarily in treated females, 24/50 (48 percent) in the low dose group, 31/50 (62 percent) in the high dose group, and 2/20 (10 percent) in the untreated controls. Mammary adenocarcinomas were also found in 1/50 (2 percent) low dose and 1/20 (5 percent) untreated control male rats. Grossly, the neoplasms were light pink to red, subcutaneous, firm and nodular, weighing 1 to 150 grams. Microscopically, these adenocarcinomas were characterized by irregular acini lined by anaplastic epithelium and supported by a dense fibrous stroma. Acini were frequently lined by multiple layers of epithelium, and papillary infoldings or projections were present. Larger hyperchromatic cells were present and mitoses were frequent in the more anaplastic adenocarcinomas.

Hemangiosarcomas occurred in the spleens of 9/50 (18 percent) low dose males and 4/42 (10 percent) low dose females, but were not observed in the high dose or control rats.

The other neoplasms that occurred in this study were comparable in frequency and morphology to those tumors occurring naturally in untreated Osborne-Mendel rats.

Toxic nephropathy occurred in 50/50 low dose males, 49/50 high dose males, 42/42 low dose females, and 44/44 high dose females but not in controls of either sex. Microscopically, toxic nephropathy was characterized by degenerative changes in the proximal convoluted tubules at the junction of the cortex and medulla, with cloudy swelling, fatty degeneration, and necrosis of the tubular epithelium. Some affected tubules were empty; others were filled with hyaline casts. Occasionally the damaged tubules contained large basophilic regenerative cells. At this stage, the kidneys often had infiltration of inflammatory cells, fibrosis, and calcium deposition.

Other inflammatory, proliferative, and degenerative lesions as seen in the control and treated animals were similar in number and kind to lesions occurring naturally in untreated rats.

In this study, DBCP treatment was associated with squamous-cell carcinomas in the forestomach of male and female rats at both doses and adenocarcinomas of the mammary gland in the female rats. This chemical was also toxic to the kidneys, producing a toxic tubular nephropathy in both male and female rats.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in rats are summarized in Tables 3 and 4. The analysis for every type

TABLE 3

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE RATS TREATED WITH DBCP[a]

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibroma[b]	0/20(0.00)	0/20(0.00)	3/50(0.06)	0/50(0.00)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.047	P = 0.047	---	---
Relative Risk (Untreated Control)[f]	---	---	Infinite	---
Lower Limit	---	---	0.250	---
Upper Limit	---	---	Infinite	---
Relative Risk (Vehicle Control)[f]	---	---	Infinite	---
Lower Limit	---	---	0.250	---
Upper Limit	---	---	Infinite	---
Weeks to First Observed Tumor	---	---	41	---
Stomach: Squamous Cell Carcinoma[b]	0/20(0.00)	0/19(0.00)	47/50(0.94)	47/50(0.94)
P Values[c,d]	P < 0.001	P < 0.001	P < 0.001* P < 0.001**	P < 0.001* P < 0.001**
Departure from Linear Trend[e]	P < 0.001	P < 0.001	---	---
Relative Risk (Untreated Control)[f]	---	---	Infinite	Infinite
Lower Limit	---	---	7.114	7.114
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Vehicle Control)[f]	---	---	Infinite	Infinite
Lower Limit	---	---	6.779	6.779
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	52	34
Stomach: Squamous Cell Papilloma[b]	0/20(0.00)	0/19(0.00)	1/50(0.02)	2/50(0.04)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[f]	---	---	Infinite	Infinite
Lower Limit	---	---	0.022	0.123
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Vehicle Control)[f]	---	---	Infinite	Infinite
Lower Limit	---	---	0.021	0.117
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	58	33

TABLE 3
(CONTINUED)

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
All Sites: Hemangiosarcoma or Hemangioma[b]	0/20(0.00)	0/20(0.00)	13/50(0.26)	2/50(0.04)
P Values[c,d]	N.S.	N.S.	P = 0.008* P = 0.008**	N.S.
Departure from Linear Trend[e]	P< 0.001	P< 0.001	---	---
Relative Risk (Untreated Control)[f]	---	---	Infinite	Infinite
Lower Limit	---	---	1.674	0.123
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Vehicle Control)[f]	---	---	Infinite	Infinite
Lower Limit	---	---	1.674	0.123
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	45	52
Thyroid: Follicular-Cell Adenoma[b]	0/19(0.00)	0/20(0.00)	3/48(0.06)	2/49(0.04)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[f]	---	---	Infinite	Infinite
Lower Limit	---	---	0.248	0.119
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Vehicle Control)[f]	---	---	Infinite	Infinite
Lower Limit	---	---	0.261	0.125
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	83	57
Thyroid: Follicular-Cell Adenoma or Carcinoma[b]	1/19(0.05)	0/20(0.00)	5/48(0.10)	3/49(0.06)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[f]	---	---	1.979	1.163
Lower Limit	---	---	0.246	0.103
Upper Limit	---	---	91.529	59.809
Relative Risk (Vehicle Control)[f]	---	---	Infinite	Infinite
Lower Limit	---	---	0.547	0.255
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	90	---	81	57

TABLE 3
(CONCLUDED)

[a]Treated groups received time-weighted average doses of 15 and 29 mg/kg by gavage.

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

[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 untreated control group (*) or with the vehicle 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 4

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE RATS TREATED WITH DBCP[a]

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Stomach: Squamous Cell Carcinoma[b]	0/20(0.00)	0/20(0.00	38/50(0.76)	29/49(0.59)
P Values[c,d]	P = 0.001	P = 0.001	P < 0.001* P < 0.001**	P < 0.001* P < 0.001**
Departure from Linear Trend[e]	P < 0.001	P < 0.001	---	---
Relative Risk (Untreated Control)[f]	---	---	Infinite	Infinite
Lower Limit	---	---	5.402	4.108
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Vehicle Control)[f]	---	---	Infinite	Infinite
Lower Limit	---	---	5.402	4.108
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	47	33
Stomach: Squamous Cell Papilloma[b]	0/20(0.00)	0/20(0.00)	1/50(0.02)	9/49(0.18)
P Values[c,d]	P = 0.003	P = 0.003	N.S.	P = 0.036* P = 0.036**
Relative Risk (Untreated Control)[f]	---	---	Infinite	Infinite
Lower Limit	---	---	0.022	1.119
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Vehicle Control)[f]	---	---	Infinite	Infinite
Lower Limit	---	---	0.022	1.119
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	57	36
All Sites: Hemangiosarcoma or Hemangioma[b]	1/20(0.05)	0/20(0.00)	6/50(0.12)	1/50(0.02)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	---	P = 0.015	---	---
Relative Risk (Untreated Control)[f]	---	---	2.400	0.400
Lower Limit	---	---	0.325	0.005
Upper Limit	---	---	108.020	30.802
Relative Risk (Vehicle Control)[f]	---	---	Infinite	Infinite
Lower Limit	---	---	0.667	0.022
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	109	---	52	45

TABLE 4
(CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Mammary Gland: Adenocarcinoma, NOS[b]	2/20(0.10)	0/20(0.00)	24/50(0.48)	31/50(0.62)
P Values[c,d]	P < 0.001	P < 0.001	P < 0.001** P = 0.002*	P < 0.001** P < 0.001*
Relative Risk (Untreated Control)[f]	---	---	4.800	6.200
Lower Limit	---	---	1.390	1.860
Upper Limit	---	---	38.983	48.724
Relative Risk (Vehicle Control)[f]	---	---	Infinite	Infinite
Lower Limit	---	---	3.281	4.322
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	109	---	34	33
Mammary Gland: Adenocarcinoma, NOS or Fibroadenoma[b]	4/20(0.20)	1/20(0.05)	24/50(0.48)	31/50(0.62)
P Values[c,d]	P = 0.002	P < 0.001	P = 0.027* P < 0.001**	P = 0.002* P < 0.001**
Relative Risk (Untreated Control)[f]	---	---	2.400	3.100
Lower Limit	---	---	0.989	1.328
Upper Limit	---	---	8.461	10.464
Relative Risk (Vehicle Control)[f]	---	---	9.600	12.400
Lower Limit	---	---	1.794	2.391
Upper Limit	---	---	380.129	479.476
Weeks to First Observed Tumor	60	83	34	33

[a]Treated groups received time-weighted average doses of 15 and 29 mg/kg by gavage.

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

[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 untreated control group(*) or with the vehicle 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.

of tumor that was observed in more than 5 percent of any of the DBCP-dosed groups of either sex is included.

Both male and female dosed rats developed a significant number of squamous-cell carcinomas of the forestomach. For both sexes the Cochran-Armitage test indicated a significant ($P = 0.001$) positive association between increased dosage and elevated tumor incidence when the dosed groups were compared to either the untreated controls or the vehicle controls. However, the departure from linear trend was significant ($P < 0.001$) due to the very high incidence levels observed in not only the high dose but the low dose groups as well. The Fisher exact tests comparing dosed groups to control groups were all significant ($P < 0.001$); all confidence intervals on the relative risk had a lower limit greater than the value one. The incidence rates observed in the controls were not significantly different from the historical spontaneous incidence rates observed to date for Osborne-Mendel rats in the NCI Bioassay Program (male vehicle control 0/748; female vehicle control 0/741; male untreated control 0/196; and female untreated control 1/198).

Squamous-cell papillomas of the stomach were also found in dosed rats. For females the Cochran-Armitage test indicated a significant ($P = 0.003$) positive dose-response association in females; the Fisher exact tests comparing high dose group to either control had a probability level of $P = 0.034$, a marginal result which was not significant

under the Bonferroni criteria. For the male rats the incidence of papillomas was not statistically significant.

Based upon these results, the statistical conclusion is that the administration of DBCP was associated with a significantly increased incidence of cancer of the forestomach in Osborne-Mendel rats under the conditions of this experiment.

Among low dose males the incidence of either hemangioma or hemangiosarcoma was significantly higher ($P = 0.008$) than in either of the control groups. This finding was not supported by significant results in the high dose group. However, it is possible that some of the high dose males were not at risk long enough to develop this tumor.

For females, when the dosed groups were compared to either control group, the Cochran-Armitage test indicated a significant ($P < 0.001$) association between dosage and an increased incidence of adenocarcinomas of the mammary gland. Fisher exact tests confirmed these results ($P < 0.003$) when comparing either the high dose or the low dose group to either control; for all comparisons the lower limit of the confidence interval on the relative risk was greater than the value one. When female rats with either an adenocarcinoma or a fibroadenoma of the mammary gland were considered, all of the tests remained significant.

Based upon these results, the statistical conclusion is that the administration of DBCP at the dose levels of this experiment is associated with the increased incidence of adenocarcinomas of the mammary gland in female Osborne-Mendel rats.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

No appreciable differences in body weight gain patterns were apparent among male or female mice (Figure 3).

During the first 34 weeks of the study, DBCP-treated and vehicle control mice displayed essentially comparable appearance and behavior. Clinical signs characterized by a hunched or thin appearance and apparent compound-related deaths were observed in the high dose animals beginning in week 38 of the study. The incidence of clinical signs and deaths in the high dose groups increased as the study progressed. Gross necropsy of most of the DBCP-treated mice revealed a high incidence of stomach tumors with metastases to adjacent organs in many of the animals.

Signs often observed in group-housed laboratory mice were noted at a comparable rate among control and treated mice. These signs included sores on the body (more common in males due to fighting), penile/anal/vulvar irritation (sometimes with anal prolapse), hunched posture, reddened or squinted eyes, soft feces, alopecia, and palpable nodules. A bloated appearance and swelling along the abdominal area were more frequently noted in the treated mice than in the vehicle controls.

B. Survival

The estimated probabilities of survival for male and female mice in the control and DBCP-treated groups are shown in Figure 4.

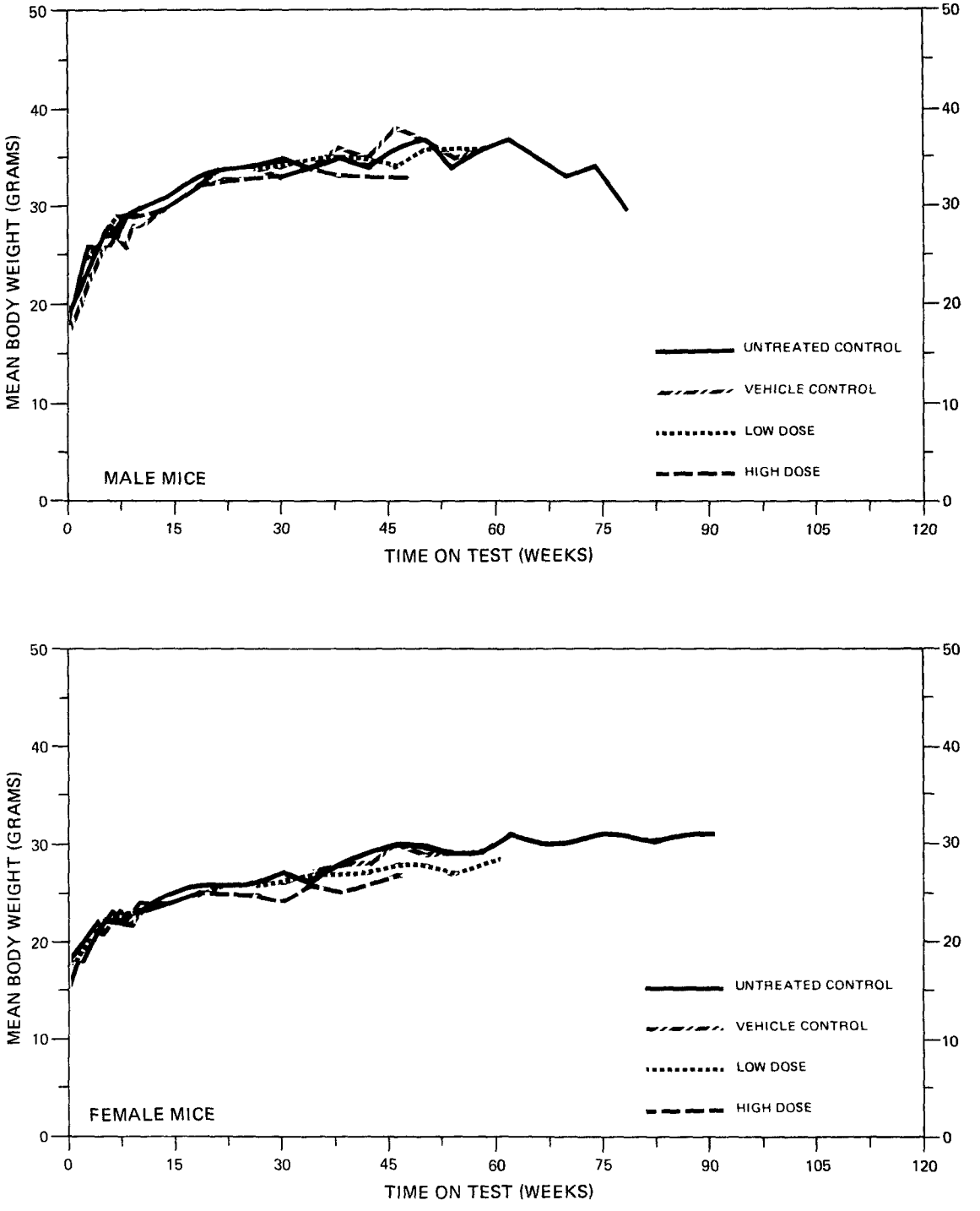
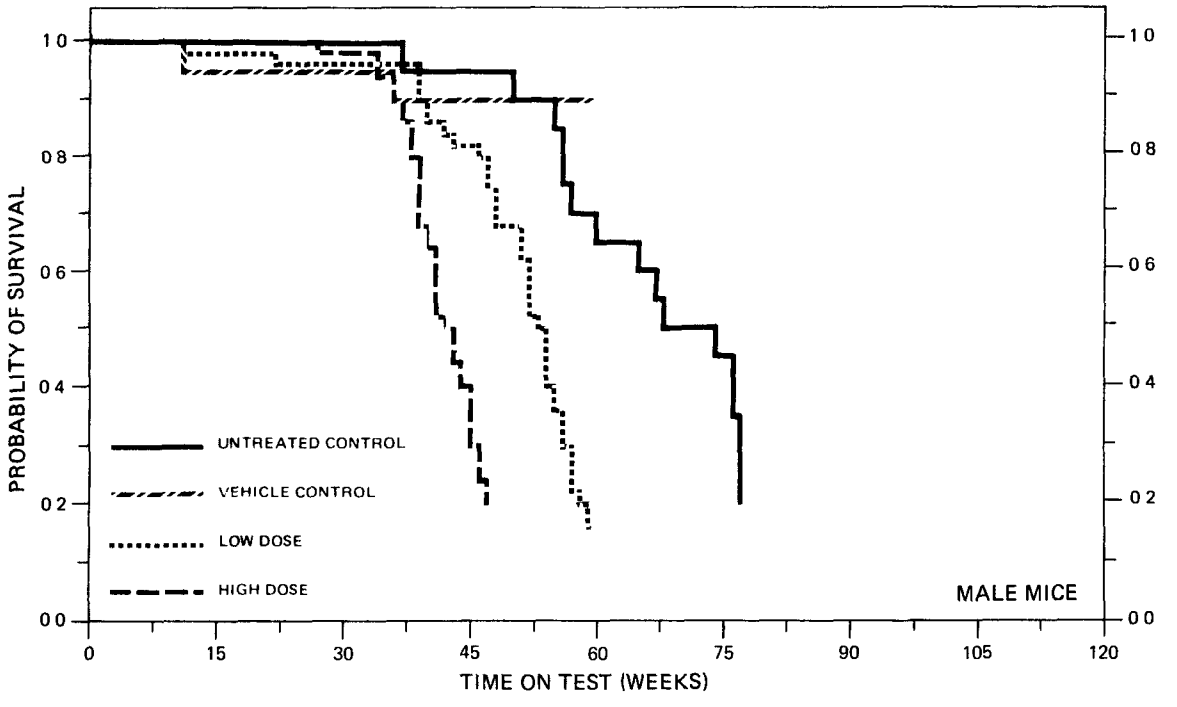


FIGURE 3
GROWTH CURVES FOR DBCP CHRONIC STUDY MICE



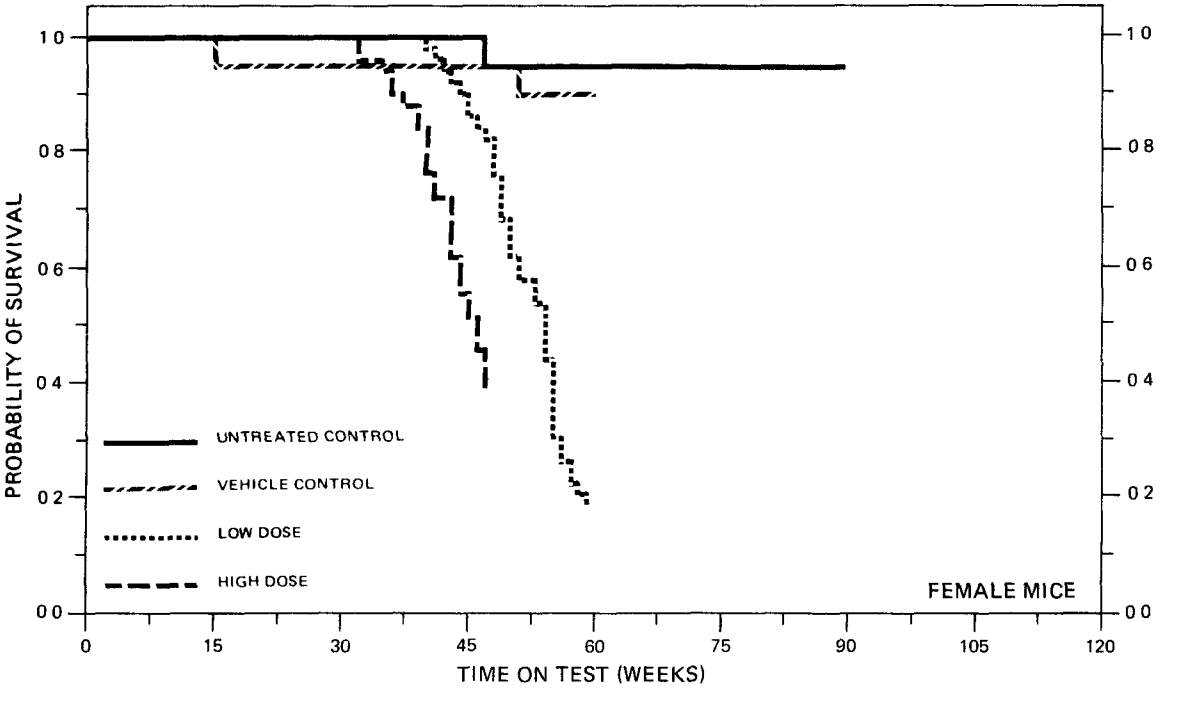


FIGURE 4
SURVIVAL COMPARISONS OF DBCP CHRONIC STUDY MICE

In both male and female mice the Tarone test indicated a significant ($P < 0.001$) positive association between increased dosage and accelerated mortality. In males the departure from linear trend was significant ($P < 0.001$) due to the accelerated mortality in dosed groups.

Among the males, 80 percent of the high dose group died by the end of week 47, at which point the remaining 10 mice were sacrificed. Eighty-four percent of the low dose group died by week 59, after which the 8 remaining mice were sacrificed. Ninety percent of the vehicle control males were still alive by week 58, but these 18 mice were sacrificed in week 59. Eighty percent of the untreated control mice died by the end of week 77, after which the remaining 4 mice were sacrificed.

Among the female mice, 61 percent of the high dose group died by the end of week 47. The remaining 19 mice were sacrificed in week 47. Eighty-two percent of the low dose mice died by week 60, at which point the remaining 9 mice were sacrificed. All 18 vehicle control animals (90 percent) still alive in week 58 were sacrificed in weeks 59 and 60. Ninety-five percent of the untreated controls survived until the end of the study.

Early deaths in the treated mice may have been tumor-related as over 90 percent of each dosed group was found to have squamous-cell carcinomas of the stomach.

C. Pathology

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

Squamous-cell carcinomas of the stomach occurred in 43/46 (93 percent) low dose males, 47/49 (96 percent) high dose males, 50/50 (100 percent) low dose females, and 47/48 (98 percent) high dose females but in no male or female controls. Microscopically, the neoplasms of the forestomach were similar in appearance to the squamous-cell carcinomas seen in the rats, with frequent metastases to the abdominal viscera. Pulmonary metastases occurred in 4/46 (9 percent) low dose males, 3/48 (6 percent) high dose males, 10/50 (20 percent) low dose females, and 3/46 (7 percent) high dose females.

Other neoplasms that occurred in this study were observed at similar incidences in control and treated mice.

Toxic nephropathy occurred in 11/46 (24 percent) low dose males, 45/48 (94 percent) high dose males, 14/50 (28 percent) low dose females, and 43/46 (93 percent) high dose females but in no male or female controls. Microscopically, toxic nephropathy in the mice occurred primarily in the proximal tubules and was comparable in appearance to renal lesions in the rats.

Other inflammatory, proliferative, and degenerative lesions seen in the treated mice were similar to those seen in controls.

In this study DBCP treatment was associated with squamous-cell carcinomas of the forestomach in male and female mice at both high and low doses. This chemical was also toxic to the kidneys, producing a toxic tubular nephropathy in both male and female mice.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in mice are summarized in Tables 5 and 6. The analysis for every type of tumor that was observed in more than 5 percent of any of the DBCP-treated groups of either sex is included.

Both male and female dosed mice developed a significant number of squamous-cell carcinomas of the stomach. For both sexes the Cochran-Armitage test indicated a significant ($P = 0.001$) positive association between increased dosage and elevated incidence when the dosed groups were compared to either the untreated controls or the vehicle controls. The Fisher exact tests comparing dosed groups to control groups were all significant ($P < 0.001$); all confidence intervals on the relative risk had a lower limit greater than the value one. Additionally, the incidence rates observed in the controls were not significantly different from the historical spontaneous incidence rates observed to date for B6C3F1 mice in the NCI Bioassay Program (male vehicle control 1/887; female vehicle control 1/877; male untreated control 1/1544; and female untreated control 0/1503).

Based upon these results, the statistical conclusion is that DBCP was a stomach carcinogen in B6C3F1 mice under the conditions of this experiment.

TABLE 5

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE MICE TREATED WITH DBCP[a]

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Stomach: Squamous Cell Carcinoma[b]	0/20(0.00)	0/20(0.00)	43/46(0.93)	47/49(0.96)
P Values[c,d]	P < 0.001	P < 0.001	P < 0.001* P < 0.001**	P < 0.001* P < 0.001**
Departure from Linear Trend[e]	P < 0.001	P < 0.001	---	---
Relative Risk (Untreated Control)[f]	---	---	Infinite	Infinite
Lower Limit	---	---	7.052	7.416
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Vehicle Control)[f]	---	---	Infinite	Infinite
Lower Limit	---	---	7.052	7.416
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	39	27

[a] Treated groups received time-weighted average doses of 114 and 219 mg/kg.

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

[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 untreated control group (*) or with the vehicle 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 6

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN FEMALE MICE TREATED WITH DBCP[a]

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Stomach: Squamous Cell Carcinoma[b]	0/20(0.00)	0/20(0.00)	50/50(0.100)	47/48(0.98)
P Values[c,d]	P < 0.001	P < 0.001	P < 0.001* P < 0.001**	P < 0.001* P < 0.001**
Departure from Linear Trend[e]	P < 0.001	P < 0.001	---	---
Relative Risk (Untreated Control)[f]	---	---	Infinite	Infinite
Lower Limit	---	---	8.661	7.845
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Vehicle Control)[f]	---	---	Infinite	Infinite
Lower Limit	---	---	8.661	7.845
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	40	32

[a] Treated groups received time-weighted average doses of 110 and 209 mg/kg.

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

[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 untreated control group (*) or with the vehicle 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.

V. DISCUSSION

Under the conditions of this bioassay, administration of technical-grade DBCP was associated with a high incidence of squamous-cell carcinomas of the forestomach and toxic nephropathy in male and female rats and mice and with a high incidence of mammary adenocarcinoma in female rats.

The untreated controls for the rat bioassay were approximately 16 weeks younger than the dosed and vehicle control rats, were started on test a corresponding 16 weeks later, and were housed in a separate room. These differences in age and room assignments did not, however, complicate statistical evaluation since vehicle controls are the preferred controls for a gavage study and statistical tests were applied to the vehicle controls. In addition, there were no significant differences in tumor incidence between untreated and vehicle controls in this bioassay.

Among the rats, squamous-cell carcinomas of the forestomach were observed in 47/50 (94 percent) high dose males, 47/50 (94 percent) low dose males, 29/49 (59 percent) high dose females, and 38/50 (76 percent) low dose females but in none of the untreated or vehicle controls. When the incidences of these neoplasms in the treated animals were statistically compared to those in the control groups, there was a significant positive association between dosage and incidence of these neoplasms. Some of these carcinomas were accompanied by pulmonary metastases. Squamous-cell papillomas were also found in dosed

rats of both sexes, but not in vehicle or untreated controls. The Cochran-Armitage test showed a significant association between increased dosage and increased incidence of squamous-cell papillomas for females but not for males.

Squamous-cell carcinomas and papillomas of the forestomach are uncommon lesions in control animals, and the high incidences of these lesions in treated animals indicates that they are related to DBCP treatment. It is possible, however, that the method of administration might have played a role in inducing these neoplasms, as DBCP is a skin and mucous membrane irritant (Shell Chemical Company, 1972) and proliferative lesions of the forestomach have been noted in other bioassays where chemical irritants have been administered by gavage.

Adenocarcinomas of the mammary gland in females were an indication of the capacity of DBCP to induce tumors at other than the site of application. These tumors occurred in 2/20 (10 percent), 24/50 (48 percent), and 31/50 (62 percent) of the untreated control, low dose, and high dose groups, respectively. When the treated groups were statistically compared to either control group, a significant association between dosage and increased incidence of these tumors was indicated.

Among mice, squamous-cell carcinomas of the forestomach were observed in 47/48 (98 percent) high dose males, 43/46 (93 percent) low dose males, 47/48 (98 percent) high dose females, and 50/50 (100 percent) low dose females but in none of the untreated or vehicle

control males or females. Statistically, there was a significant association between dosage and incidence of these neoplasms when the treated animals were compared to either of their respective control groups. These carcinomas were frequently accompanied by metastases to the abdominal viscera and occasionally by metastases to the lung.

The animals survived sufficiently long to develop the previously mentioned tumors despite the frequency with which toxic nephropathy occurred in the treated animals. This severely toxic lesion occurred in 100 percent of the treated female and low dose male rats and 98 percent of the high dose male rats but in none of the untreated or vehicle control rats. Additionally, toxic nephropathy in mice occurred in 45/48 (94 percent) high dose males, 11/46 (24 percent) low dose males, 43/46 (93 percent) high dose females, and 14/50 (28 percent) low dose females, but in none of the untreated or vehicle control groups.

Under the conditions of this study DBCP is a stomach carcinogen in Osborne-Mendel rats and B6C3F1 mice of both sexes and is carcinogenic to the mammary glands of female rats. Chronic exposure to DBCP also caused toxic nephropathy in both rats and mice.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH DBCP

TABLE A1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH DBCP

	CONTROL(UNTR) 01-031M	CONTROL(VEH) 01-051M	LOW DOSE 01-052M	HIGH DOSE 01-053M
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	20	20	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(20)	(20)	(50)	(50)
BASAL-CELL CARCINOMA				1 (2%)
KERATOACANTHOMA			1 (2%)	
FIBROSARCOMA			2 (4%)	1 (2%)
*SUBCUT TISSUE	(20)	(20)	(50)	(50)
FIBROMA			3 (6%)	
FIBROSARCOMA	1 (5%)			
HEMANGIOSARCOMA			1 (2%)	
RESPIRATORY SYSTEM				
#LUNG	(20)	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			5 (10%)	5 (10%)
HEMANGIOSARCOMA			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(20)	(20)	(50)	(50)
LYMPHOCYTIC LEUKEMIA	1 (5%)			
GRANULOCYTIC LEUKEMIA				2 (4%)
*ABDOMINAL CAVITY	(20)	(20)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (2%)
#SPLEEN	(20)	(20)	(50)	(49)
SQUAMOUS CELL CARCINOMA, METASTA			17 (34%)	21 (43%)
HEMANGIOMA			2 (4%)	
HEMANGIOSARCOMA			9 (18%)	
#CERVICAL LYMPH NODE	(19)	(20)	(44)	(48)
FIBROSARCOMA				1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-051M	LOW DOSE 01-052M	HIGH DOSE 01-053M
#MESENTERIC L. NODE	(19)	(20)	(44)	(48)
SQUAMOUS CELL CARCINOMA, METASTA			2 (5%)	4 (8%)
HEMANGIOSARCOMA, METASTATIC				1 (2%)
#THYMUS	(13)	(5)	(8)	(2)
SQUAMOUS CELL CARCINOMA, METASTA				1 (50%)
CIRCULATORY SYSTEM				
#ENDOCARDIUM	(20)	(20)	(50)	(50)
SARCOMA, NOS			1 (2%)	
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(14)	(2)	(5)	
CARCINOMA,NOS	1 (7%)			
#LIVER	(20)	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			20 (40%)	27 (54%)
HEMANGIOSARCOMA			1 (2%)	
#PANCREAS	(20)	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			16 (32%)	18 (36%)
HEMANGIOSARCOMA			2 (4%)	
HEMANGIOSARCOMA, METASTATIC				1 (2%)
#STOMACH	(20)	(19)	(50)	(50)
SQUAMOUS CELL PAPILLOMA			1 (2%)	2 (4%)
SQUAMOUS CELL CARCINOMA			47 (94%)	47 (94%)
HEMANGIOSARCOMA				1 (2%)
#SMALL INTESTINE	(20)	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			5 (10%)	5 (10%)
FIBROSARCOMA	1 (5%)			
HEMANGIOSARCOMA, METASTATIC				1 (2%)
#DUODENUM	(20)	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	
#LARGE INTESTINE	(19)	(20)	(49)	(49)
SQUAMOUS CELL CARCINOMA, METASTA			3 (6%)	3 (6%)
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			2 (4%)	4 (8%)
HAMARTOMA+			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 PROLIFERATIVE LIPOCYTES, TUBULAR STRUCTURES, FIBROBLASTS, AND VASCULAR SPACES IN VARYING PROPORTIONS.

TABLE A1 (CONTINUED)

	CONTROL(UNTR) 01-031M	CONTROL(VEH) 01-051M	LOW DOSE 01-052M	HIGH DOSE 01-053M
#URINARY BLADDER	(19)	(19)	(49)	(46)
SQUAMOUS CELL CARCINOMA, METASTA			3 (6%)	1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY	(20)	(20)	(49)	(48)
CHROMOPHOBE ADENOMA	2 (10%)		1 (2%)	1 (2%)
FIBROSARCOMA			1 (2%)	
#ADRENAL	(20)	(20)	(49)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			3 (6%)	8 (16%)
CORTICAL CARCINOMA	2 (10%)			
#THYROID	(19)	(20)	(48)	(49)
FOLLICULAR-CELL ADENOMA			3 (6%)	2 (4%)
FOLLICULAR-CELL CARCINOMA	1 (5%)		2 (4%)	1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(20)	(20)	(50)	(50)
CARCINOMA,NOS				1 (2%)
ADENOCARCINOMA, NOS	1 (5%)		1 (2%)	
FIBROADENOMA	1 (5%)	1 (5%)		
#PROSTATE	(20)	(16)	(39)	(12)
SQUAMOUS CELL CARCINOMA, METASTA			1 (3%)	
#TESTIS	(20)	(19)	(50)	(49)
SQUAMOUS CELL CARCINOMA, METASTA			7 (14%)	5 (10%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				

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

TABLE A-1 (CONCLUDED)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-051M	LOW DOSE 01-052M	HIGH DOSE 01-053M
BODY CAVITIES				
*ABDOMINAL CAVITY	(20)	(20)	(50)	(50)
HEMANGIOSARCOMA			1 (2%)	1 (2%)
*MESENTERY	(20)	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			2 (4%)	
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	11	8	42	30
MORIBUND SACRIFICE			3	10
SCHEDULED SACRIFICE	5	10		
ACCIDENT. LY KILLED				
TERMINAL SACRIFICE	4	2	5	10
ANIMAL MISSING				
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	6	1	49	48
TOTAL PRIMARY TUMORS	11	1	81	62
TOTAL ANIMALS WITH BENIGN TUMORS	2	1	8	5
TOTAL BENIGN TUMORS	3	1	12	5
TOTAL ANIMALS WITH MALIGNANT TUMORS	6		48	47
TOTAL MALIGNANT TUMORS	8		69	57
TOTAL ANIMALS WITH SECONDARY TUMORS#			28	34
TOTAL SECONDARY TUMORS			87	105
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 A2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH DBCP

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-051F	LOW DOSE 01-054F	HIGH DOSE 01-055F
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	20	20	50	50
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(20)	(20)	(50)	(50)
FIBROMA				1 (2%)
HEMANGIOSARCOMA			2 (4%)	
RESPIRATORY SYSTEM				
#LUNG	(20)	(20)	(42)	(44)
SQUAMOUS CELL CARCINOMA, METASTA				3 (7%)
ADENOCARCINOMA, NOS, METASTATIC			4 (10%)	3 (7%)
GRANULOSA-CELL CARCINOMA, METAST			1 (2%)	
HEMANGIOSARCOMA				1 (2%)
HEMATOPOIETIC SYSTEM				
#SPLEEN	(20)	(20)	(42)	(44)
SQUAMOUS CELL CARCINOMA, METASTA			5 (12%)	3 (7%)
HEMANGIOSARCOMA			4 (10%)	
#MESENTERIC L. NODE	(20)	(18)	(23)	(43)
SQUAMOUS CELL CARCINOMA, METASTA			1 (4%)	1 (2%)
GRANULOSA-CELL CARCINOMA, METAST			1 (4%)	
CIRCULATORY SYSTEM				
#HEART	(20)	(20)	(42)	(44)
SARCOMA, NOS			1 (2%)	
MIXED TUMOR, METASTATIC	1 (5%)			
DIGESTIVE SYSTEM				
#LIVER	(20)	(20)	(42)	(44)
SQUAMOUS CELL CARCINOMA, METASTA			6 (14%)	8 (18%)
HEPATOCELLULAR CARCINOMA	1 (5%)		1 (2%)	
HEMANGIOSARCOMA			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-051F	LOW DOSE 01-054F	HIGH DOSE 01-055F
#PANCREAS	(20)	(19)	(42)	(44)
SQUAMOUS CELL CARCINOMA, METASTA			3 (7%)	7 (16%)
HEMANGIOSARCOMA			1 (2%)	
#STOMACH	(20)	(20)	(50)	(49)
SQUAMOUS CELL PAPILLOMA			1 (2%)	9 (18%)
SQUAMOUS CELL CARCINOMA			38 (76%)	29 (59%)
#SMALL INTESTINE	(20)	(20)	(42)	(44)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	1 (2%)
#LARGE INTESTINE	(19)	(19)	(42)	(44)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(42)	(44)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	1 (2%)
TRANSITIONAL-CELL CARCINOMA			1 (2%)	
ADENOCARCINOMA, NOS, METASTATIC				1 (2%)
TUBULAR-CELL ADENOMA			1 (2%)	
MIXED TUMOR, MALIGNANT	1 (5%)			
HAMARTOMA+	2 (10%)			
ENDOCRINE SYSTEM				
#PITUITARY	(19)	(20)	(40)	(41)
CHROMOPHOBE ADENOMA	6 (32%)	1 (5%)		
#ADRENAL	(20)	(20)	(40)	(44)
SQUAMOUS CELL CARCINOMA, METASTA			1 (3%)	1 (2%)
CORTICAL ADENOMA		1 (5%)		
CORTICAL CARCINOMA			1 (3%)	
#THYROID	(20)	(20)	(39)	(44)
C-CELL ADENOMA	2 (10%)			
C-CELL CARCINOMA	2 (10%)			
#PANCREATIC ISLETS	(20)	(19)	(42)	(44)
ISLET-CELL ADENOMA	1 (5%)			

\# 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 PROLIFERATIVE LIPOCYTES, TUBULAR STRUCTURES, FIBROBLASTS, AND VASCULAR SPACES IN VARYING PROPORTIONS.

TABLE A2 (CONTINUED)

	CONTROL(UNTR) 01-031F	CONTROL(VEH) 01-051F	LOW DOSE 01-054F	HIGH DOSE 01-055F
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(20)	(20)	(50)	(50)
ADENOCARCINOMA, NOS	2 (10%)		24 (48%)	31 (62%)
FIBROADENOMA	2 (10%)	1 (5%)		
#UTERUS	(20)	(20)	(39)	(43)
SQUAMOUS CELL CARCINOMA, METASTA			1 (3%)	
ENDOMETRIAL STROMAL POLYP		1 (5%)		1 (2%)
HEMANGIOMA	1 (5%)			
#OVARY	(20)	(20)	(39)	(43)
SQUAMOUS CELL CARCINOMA, METASTA			2 (5%)	
CYSTADENOCARCINOMA, NOS	1 (5%)			
GRANULOSA-CELL TUMOR			1 (3%)	
GRANULOSA-CELL CARCINOMA			1 (3%)	
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*MESENTERY	(20)	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	1 (2%)
ALL OTHER SYSTEMS				
NONE				

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

TABLE A2 (CONCLUDED)

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-051F	LOW DOSE 01-054F	HIGH DOSE 01-055F
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	2	5	31	25
MORIBUND SACRIFICE			11	22
SCHEDULED SACRIFICE	5	10		
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	13	5	8	3
ANIMAL MISSING				
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	14	4	44	43
TOTAL PRIMARY TUMORS	21	4	78	72
TOTAL ANIMALS WITH BENIGN TUMORS	12	4	2	11
TOTAL BENIGN TUMORS	14	4	2	11
TOTAL ANIMALS WITH MALIGNANT TUMORS	6		44	42
TOTAL MALIGNANT TUMORS	7		75	61
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		12	13
TOTAL SECONDARY TUMORS	1		29	30
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 B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH DBCP

TABLE B1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH DBCP

	CONTROL(UNTR) 02-M061	CONTROL(VEH) 02-M051	LOW DOSE 02-M052	HIGH DOSE 02-M053
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	19	20	47	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	20	45	50
INTEGUMENTARY SYSTEM				
*SKIN	(19)	(20)	(47)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			8 (17%)	5 (10%)
*SUBCUT TISSUE	(19)	(20)	(47)	(50)
FIBROSARCOMA	1 (5%)			
RESPIRATORY SYSTEM				
#LUNG	(18)	(20)	(46)	(48)
SQUAMOUS CELL CARCINOMA, METASTA			4 (9%)	3 (6%)
ALVEOLAR/BRONCHIOLAR ADENOMA				1 (2%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(19)	(20)	(47)	(50)
MALIG.LYMPHOMA, UNDIFFER-TYPE	1 (5%)			
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (5%)			
GRANULOCYTIC LEUKEMIA	1 (5%)			
#SPLEEN	(19)	(20)	(45)	(47)
SQUAMOUS CELL CARCINOMA, METASTA			8 (18%)	14 (30%)
#LYMPH NODE	(18)	(18)	(39)	(42)
SQUAMOUS CELL CARCINOMA, METASTA			1 (3%)	
#CERVICAL LYMPH NODE	(18)	(18)	(39)	(42)
SQUAMOUS CELL CARCINOMA, METASTA			3 (8%)	
CIRCULATORY SYSTEM				
NONE				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE B1 (CONTINUED)

	CONTROL (UNTR) 02-M061	CONTROL (VEH) 02-M051	LOW DOSE 02-M052	HIGH DOSE 02-M053
DIGESTIVE SYSTEM				
#LIVER	(19)	(20)	(46)	(48)
SQUAMOUS CELL CARCINOMA, METASTA			20 (43%)	17 (35%)
NEOPLASTIC NODULE		1 (5%)		
HEPATOCELLULAR CARCINOMA		1 (5%)	1 (2%)	
*GALLBLADDER	(19)	(20)	(47)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			2 (4%)	2 (4%)
#PANCREAS	(19)	(19)	(45)	(48)
SQUAMOUS CELL CARCINOMA, METASTA			19 (42%)	14 (29%)
#ESOPHAGUS	(18)		(3)	(7)
SQUAMOUS CELL CARCINOMA, METASTA			1 (33%)	2 (29%)
#STOMACH	(20)	(20)	(46)	(49)
SQUAMOUS CELL CARCINOMA			43 (93%)	47 (96%)
#SMALL INTESTINE	(18)	(19)	(44)	(47)
SQUAMOUS CELL CARCINOMA, METASTA			2 (5%)	
#DUODENUM	(18)	(19)	(44)	(47)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	
#COLON	(19)	(19)	(46)	(47)
SQUAMOUS CELL CARCINOMA, METASTA			2 (4%)	
URINARY SYSTEM				
#KIDNEY	(19)	(20)	(46)	(48)
SQUAMOUS CELL CARCINOMA, METASTA			4 (9%)	4 (8%)
#URINARY BLADDER	(17)	(19)	(46)	(47)
SQUAMOUS CELL CARCINOMA, METASTA			2 (4%)	
ENDOCRINE SYSTEM				
#ADRENAL	(19)	(20)	(42)	(49)
SQUAMOUS CELL CARCINOMA, METASTA			21 (50%)	13 (27%)
REPRODUCTIVE SYSTEM				
#PROSTATE	(18)	(20)	(33)	(38)
SQUAMOUS CELL CARCINOMA, METASTA			1 (3%)	1 (3%)

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

TABLE B1 (CONTINUED)

	CONTROL(UNTR) 02-M061	CONTROL(VEH) 02-M051	LOW DOSE 02-M052	HIGH DOSE 02-M053
*SEMINAL VESICLE	(19)	(20)	(47)	(50)
SQUAMOUS CELL CARCINOMA, METASTA				1 (2%)
*TESTIS	(19)	(20)	(45)	(48)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	3 (6%)
*EPIDIDYMIS	(19)	(20)	(47)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			8 (17%)	5 (10%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EYE	(19)	(20)	(47)	(50)
MALIGNANT MELANOMA	1 (5%)			
MUSCULOSKELETAL SYSTEM				
*MUSCLE OF TRUNK	(19)	(20)	(47)	(50)
FIBROSARCOMA			1 (2%)	
*MUSCLE HIP/THIGH	(19)	(20)	(47)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	1 (2%)
BODY CAVITIES				
*ABDOMINAL CAVITY	(19)	(20)	(47)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	1 (2%)
*MESENTERY	(19)	(20)	(47)	(50)
SQUAMOUS CELL CARCINOMA, METASTA				1 (2%)
ALL OTHER SYSTEMS				
DIAPHRAGM				
SQUAMOUS CELL CARCINOMA, METASTA				1

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

TABLE B1 (CONCLUDED)

	CONTROL (UNTR) 02-M061	CONTROL (VEH) 02-M051	LOW DOSE 02-M052	HIGH DOSE 02-M053
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	16	2	41	39
MORIBUND SACRIFICE			1	1
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	4	18	8	10
ANIMAL MISSING				
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	5	2	43	47
TOTAL PRIMARY TUMORS	5	2	45	48
TOTAL ANIMALS WITH BENIGN TUMORS				1
TOTAL BENIGN TUMORS				1
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	1	43	47
TOTAL MALIGNANT TUMORS	5	1	45	47
TOTAL ANIMALS WITH SECONDARY TUMORS#			36	30
TOTAL SECONDARY TUMORS			110	88
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 TREATED WITH DBCP

	CONTROL(UNTR) 02-F061	CONTROL(VEH) 02-F051	LOW DOSE 02-F054	HIGH DOSE 02-F055
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS MISSING				1
ANIMALS NECROPSIED	20	20	50	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	20	50	47
INTEGUMENTARY SYSTEM				
*SKIN	(20)	(20)	(50)	(47)
SQUAMOUS CELL CARCINOMA, METASTA			13 (26%)	8 (17%)
*SUBCUT TISSUE	(20)	(20)	(50)	(47)
SQUAMOUS CELL CARCINOMA, METASTA				6 (13%)
RESPIRATORY SYSTEM				
#LUNG	(20)	(20)	(50)	(46)
CARCINOMA, NOS, METASTATIC	1 (5%)			
SQUAMOUS CELL CARCINOMA, METASTA			10 (20%)	3 (7%)
ADENOCARCINOMA, NOS, METASTATIC				1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA				2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(20)	(20)	(50)	(47)
MALIG.LYMPHOMA, UNDIFFER-TYPE				1 (2%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	4 (20%)			
MALIGNANT LYMPHOMA, MIXED TYPE	1 (5%)			
#SPLEEN	(20)	(20)	(50)	(46)
SQUAMOUS CELL CARCINOMA, METASTA			10 (20%)	11 (24%)
#LYMPH NODE	(20)	(19)	(46)	(39)
SQUAMOUS CELL CARCINOMA, METASTA				1 (3%)
#CERVICAL LYMPH NODE	(20)	(19)	(46)	(39)
SQUAMOUS CELL CARCINOMA, METASTA			15 (33%)	5 (13%)
#MESENTERIC L. NODE	(20)	(19)	(46)	(39)
SQUAMOUS CELL CARCINOMA, METASTA			2 (4%)	2 (5%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE B2 (CONTINUED)

	CONTROL (UNTR) 02-F061	CONTROL (VEH) 02-F051	LOW DOSE 02-F054	HIGH DOSE 02-F055
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(20)	(20)	(50)	(46)
SQUAMOUS CELL CARCINOMA, METASTA			24 (48%)	13 (28%)
HEPATOCELLULAR CARCINOMA				1 (2%)
*GALLBLADDER	(20)	(20)	(50)	(47)
SQUAMOUS CELL CARCINOMA, METASTA			4 (8%)	1 (2%)
#PANCREAS	(19)	(20)	(50)	(46)
CARCINOMA, NOS, METASTATIC	1 (5%)			
SQUAMOUS CELL CARCINOMA, METASTA			27 (54%)	14 (30%)
#ESOPHAGUS	(20)		(1)	
SQUAMOUS CELL CARCINOMA, METASTA			1 (100%)	
#STOMACH	(20)	(20)	(50)	(48)
SQUAMOUS CELL CARCINOMA			50 (100%)	47 (98%)
#SMALL INTESTINE	(20)	(20)	(42)	(46)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(50)	(46)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	1 (2%)
#URINARY BLADDER	(18)	(19)	(47)	(46)
SQUAMOUS CELL CARCINOMA, METASTA			2 (4%)	2 (4%)
ENDOCRINE SYSTEM				
#ADRENAL	(19)	(19)	(47)	(42)
SQUAMOUS CELL CARCINOMA, METASTA			12 (26%)	9 (21%)
#THYROID	(20)	(20)	(49)	(45)
FOLLICULAR-CELL CARCINOMA	1 (5%)			

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

TABLE B2 (CONTINUED)

	CONTROL(UNTR) 02-F061	CONTROL(VEH) 02-F051	LOW DOSE 02-F054	HIGH DOSE 02-F055
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(20)	(20)	(50)	(47)
SQUAMOUS CELL CARCINOMA, METASTA			4 (8%)	
ADENOCARCINOMA, NOS				2 (4%)
#UTERUS	(20)	(20)	(45)	(45)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	2 (4%)
ENDOMETRIAL STROMAL POLYP	1 (5%)			
#OVARY/OVIDUCT	(20)	(20)	(45)	(45)
SQUAMOUS CELL CARCINOMA, METASTA			3 (7%)	5 (11%)
#OVARY	(20)	(20)	(43)	(44)
CARCINOMA,NOS	1 (5%)			
SQUAMOUS CELL CARCINOMA, METASTA			10 (23%)	5 (11%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*MUSCLE HIP/THIGH	(20)	(20)	(50)	(47)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				

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

TABLE B2 (CONCLUDED)

	CONTROL(UNTR) 02-F061	CONTROL(VEH) 02-F051	LOW DOSE 02-F054	HIGH DOSE 02-F055
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	1	2	41	28
MORIBUND SACRIFICE				2
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	19	18	9	19
ANIMAL MISSING				1
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	6		50	47
TOTAL PRIMARY TUMORS	8		51	53
TOTAL ANIMALS WITH BENIGN TUMORS	1			2
TOTAL BENIGN TUMORS	1			2
TOTAL ANIMALS WITH MALIGNANT TUMORS	6		50	47
TOTAL MALIGNANT TUMORS	7		51	51
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		41	30
TOTAL SECONDARY TUMORS	2		141	89
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				

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH DBCP

TABLE C1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS TREATED WITH DBCP

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-051M	LOW DOSE 01-052M	HIGH DOSE 01-053M
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	20	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(20)	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)			
RESPIRATORY SYSTEM				
#LUNG	(20)	(20)	(50)	(50)
EDEMA, NOS			1 (2%)	
INFLAMMATION, NOS				3 (6%)
INFLAMMATION, FOCAL			2 (4%)	5 (10%)
ABSCESS, NOS			1 (2%)	1 (2%)
PNEUMONIA, CHRONIC MURINE	16 (80%)	20 (100%)	35 (70%)	21 (42%)
CALCIUM DEPOSIT	1 (5%)			
HEMATOPOIETIC SYSTEM				
#SPLEEN	(20)	(20)	(50)	(49)
THROMBOSIS, NOS			1 (2%)	
HEMORRHAGIC CYST			1 (2%)	
INFLAMMATION, NOS			2 (4%)	
NECROSIS, NOS				1 (2%)
NECROSIS, FOCAL			1 (2%)	
HYPOPLASIA, NOS				1 (2%)
ATROPHY, NOS				1 (2%)
ANGIECTASIS			1 (2%)	
LEUKEMOID REACTION			1 (2%)	
HEMATOPOIESIS	1 (5%)	1 (5%)	4 (8%)	1 (2%)
#CERVICAL LYMPH NODE	(19)	(20)	(44)	(48)
INFLAMMATION, NOS	1 (5%)			
#THYMUS	(13)	(5)	(8)	(2)
CYST, NOS			1 (13%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-051M	LOW DOSE 01-052M	HIGH DOSE 01-053M
CIRCULATORY SYSTEM				
#HEART	(20)	(20)	(50)	(50)
MINERALIZATION			1 (2%)	1 (2%)
CALCIUM DEPOSIT	1 (5%)			
#MYOCARDIUM	(20)	(20)	(50)	(50)
INFLAMMATION, NOS	2 (10%)	2 (10%)	2 (4%)	3 (6%)
DEGENERATION, NOS	1 (5%)			
#ENDOCARDIUM	(20)	(20)	(50)	(50)
INFLAMMATION, NOS			1 (2%)	
INFLAMMATION PROLIFERATIVE				1 (2%)
FIBROSIS			1 (2%)	
HYPERPLASIA, NOS	1 (5%)			
*AORTA	(20)	(20)	(50)	(50)
MEDIAL CALCIFICATION	2 (10%)			
CALCIFICATION, NOS		1 (5%)		1 (2%)
*MESENTERIC ARTERY	(20)	(20)	(50)	(50)
MEDIAL CALCIFICATION	1 (5%)			
DIGESTIVE SYSTEM				
#LIVER	(20)	(20)	(50)	(50)
CONGESTION, NOS		1 (5%)	1 (2%)	
INFLAMMATION, NOS	1 (5%)		2 (4%)	
DEGENERATION, NOS				1 (2%)
DEGENERATION, HYDROPIC				1 (2%)
NECROSIS, NOS				2 (4%)
NECROSIS, FOCAL			10 (20%)	1 (2%)
METAMORPHOSIS FATTY	2 (10%)	2 (10%)	6 (12%)	2 (4%)
HYPERTROPHY, NOS			3 (6%)	
HYPERPLASIA, NOS			4 (8%)	1 (2%)
HYPERPLASIA, FOCAL			1 (2%)	
ANGIECTASIS	3 (15%)			
HEMATOPOIESIS			1 (2%)	
#LIVER/CENTRILOBULAR	(20)	(20)	(50)	(50)
DEGENERATION, NOS			8 (16%)	
NECROSIS, NOS			1 (2%)	1 (2%)
*BILE DUCT	(20)	(20)	(50)	(50)
INFLAMMATION, NOS			1 (2%)	
INFLAMMATION, CHRONIC				1 (2%)
HYPERPLASIA, NOS	4 (20%)	1 (5%)	2 (4%)	2 (4%)

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-051M	LOW DOSE 01-052M	HIGH DOSE 01-053M
#PANCREAS	(20)	(20)	(50)	(50)
PERIARTERITIS	4 (20%)	1 (5%)	1 (2%)	
ATROPHY, FOCAL		1 (5%)		
#PANCREATIC ACINUS	(20)	(20)	(50)	(50)
ATROPHY, NOS			2 (4%)	
#STOMACH	(20)	(19)	(50)	(50)
MINERALIZATION			2 (4%)	
ULCER, FOCAL		1 (5%)	2 (4%)	4 (8%)
CALCIUM DEPOSIT	2 (10%)			
CALCIFICATION, NOS		1 (5%)		
HYPERKERATOSIS			2 (4%)	3 (6%)
ACANTHOSIS			2 (4%)	3 (6%)
#LARGE INTESTINE	(19)	(20)	(49)	(49)
PARASITISM		1 (5%)		
#COLON	(19)	(20)	(49)	(49)
NEMATODIASIS	1 (5%)			
PARASITISM			1 (2%)	
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(50)	(50)
MINERALIZATION			5 (10%)	
HYDRONEPHROSIS			3 (6%)	
CONGESTION, NOS		1 (5%)	1 (2%)	
HEMORRHAGE				1 (2%)
PYELONEPHRITIS, NOS	1 (5%)		1 (2%)	
INFLAMMATION, CHRONIC	15 (75%)	15 (75%)	26 (52%)	17 (34%)
NEPHROPATHY, TOXIC			50 (100%)	49 (98%)
NEPHROSIS, CHOLEMIC			1 (2%)	
CALCIUM DEPOSIT	1 (5%)			
CALCIFICATION, NOS			1 (2%)	
#URINARY BLADDER	(19)	(19)	(49)	(46)
INFLAMMATION, NOS	1 (5%)		1 (2%)	1 (2%)
INFLAMMATION, CHRONIC				1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY	(20)	(20)	(49)	(48)
CYST, NOS		1 (5%)	1 (2%)	
ANGIECTASIS	1 (5%)			

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-031H	CONTROL (VEH) 01-051H	LOW DOSE 01-052H	HIGH DOSE 01-053H
#ADRENAL	(20)	(20)	(49)	(50)
DEGENERATION, NOS		1 (5%)	12 (24%)	9 (18%)
CYTOLOGIC DEGENERATION		1 (5%)	4 (8%)	
ATROPHY, NOS				1 (2%)
HYPERTROPHY, NOS				1 (2%)
#ADRENAL CORTEX	(20)	(20)	(49)	(50)
DEGENERATION, NOS		2 (10%)	19 (39%)	35 (70%)
HYPERTROPHY, NOS		1 (5%)	1 (2%)	7 (14%)
HYPERTROPHY, FOCAL		1 (5%)		
ANGIECTASIS	1 (5%)			
#THYROID	(19)	(20)	(48)	(49)
ULTIMOBRANCHIAL CYST	2 (11%)			
CYST, NOS			1 (2%)	3 (6%)
HYPERPLASIA, C-CELL	1 (5%)	1 (5%)		1 (2%)
HYPERPLASIA, FOLLICULAR-CELL	1 (5%)	2 (10%)	1 (2%)	2 (4%)
#PARATHYROID	(3)	(1)		
HYPERPLASIA, NOS	2 (67%)	1 (100%)		
REPRODUCTIVE SYSTEM				
#PROSTATE	(20)	(16)	(39)	(12)
INFLAMMATION, NOS	5 (25%)	1 (6%)	1 (3%)	1 (8%)
INFLAMMATION, SUPPURATIVE			1 (3%)	
ATROPHY, NOS			1 (3%)	1 (8%)
*SEMINAL VESICLE	(20)	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)			
ATROPHY, NOS			1 (2%)	2 (4%)
#TESTIS	(20)	(19)	(50)	(49)
GRANULOMA, SPERMATIC	1 (5%)			
ATROPHY, NOS	11 (55%)	4 (21%)	38 (76%)	47 (96%)
*EPIDIDYMIS	(20)	(20)	(50)	(50)
NECROSIS, FOCAL				1 (2%)
NECROSIS, FAT	1 (5%)	1 (5%)		
ATROPHY, NOS	3 (15%)			
NERVOUS SYSTEM				
#BRAIN/MENINGES	(20)	(20)	(50)	(50)
INFLAMMATION, NOS				1 (2%)

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-051M	LOW DOSE 01-052M	HIGH DOSE 01-053M
*BRAIN	(20)	(20)	(50)	(50)
HYDROCEPHALUS, INTERNAL			1 (2%)	
INFLAMMATION, NOS				1 (2%)
SPECIAL SENSE ORGANS				
*EYE/LACRIMAL GLAND	(20)	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)			
*HARDERIAN GLAND	(20)	(20)	(50)	(50)
INFLAMMATION, NOS		1 (5%)		
MUSCULOSKELETAL SYSTEM				
*SKELETAL MUSCLE	(20)	(20)	(50)	(50)
MINERALIZATION			1 (2%)	
DEGENERATION, NOS			1 (2%)	
BODY CAVITIES				
*ABDOMINAL CAVITY	(20)	(20)	(50)	(50)
THROMBOSIS, NOS			1 (2%)	
*PERITONEUM	(20)	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)			
*PLEURA	(20)	(20)	(50)	(50)
INFLAMMATION, NOS				1 (2%)
*PERICARDIUM	(20)	(20)	(50)	(50)
INFLAMMATION, NOS	2 (10%)			2 (4%)
INFLAMMATION, SUPPURATIVE			1 (2%)	
*EPICARDIUM	(20)	(20)	(50)	(50)
INFLAMMATION, NOS		3 (15%)	1 (2%)	
*MESENTERY	(20)	(20)	(50)	(50)
PERIARTERITIS	4 (20%)			
ALL OTHER SYSTEMS				
NONE				

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

TABLE C1 (CONCLUDED)

	CONTROL(UNTR) 01-031M	CONTROL(VEH) 01-051M	LOW DOSE 01-052M	HIGH DOSE 01-053M
SPECIAL MORPHOLOGY SUMMARY				
NONE				

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

TABLE C2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS TREATED WITH DBCP

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-051F	LOW DOSE 01-054F	HIGH DOSE 01-055F
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	20	50	50
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(20)	(20)	(50)	(50)
ABSCESS, NOS			1 (2%)	
RESPIRATORY SYSTEM				
#LUNG	(20)	(20)	(42)	(44)
INFLAMMATION, NOS				4 (9%)
INFLAMMATION, FOCAL			1 (2%)	1 (2%)
ABSCESS, NOS		3 (15%)		1 (2%)
PNEUMONIA, CHRONIC MURINE	18 (90%)	16 (80%)	34 (81%)	30 (68%)
FIBROSIS				1 (2%)
METAPLASIA, SQUAMOUS				1 (2%)
HEMATOPOIETIC SYSTEM				
#SPLEEN	(20)	(20)	(42)	(44)
THROMBUS, ORGANIZED				1 (2%)
HEMATOPOIESIS			15 (36%)	13 (30%)
#MESENTERIC L. NODE	(20)	(18)	(23)	(43)
ATROPHY, NOS				1 (2%)
CIRCULATORY SYSTEM				
#HEART	(20)	(20)	(42)	(44)
MINERALIZATION			1 (2%)	
#MYOCARDIUM	(20)	(20)	(42)	(44)
INFLAMMATION, NOS				1 (2%)
FIBROSIS	1 (5%)			
#ENDOCARDIUM	(20)	(20)	(42)	(44)
INFLAMMATION, NOS				1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-051F	LOW DOSE 01-054F	HIGH DOSE 01-055F
*AORTA	(20)	(20)	(50)	(50)
MEDIAL CALCIFICATION	1 (5%)			
DIGESTIVE SYSTEM				
#LIVER	(20)	(20)	(42)	(44)
INFLAMMATION, NOS			2 (5%)	3 (7%)
INFLAMMATION, NECROTIZING				1 (2%)
NECROSIS, NOS			1 (2%)	4 (9%)
METAMORPHOSIS FATTY	1 (5%)		8 (19%)	2 (5%)
HYPERTROPHY, NOS				2 (5%)
HYPERPLASIA, NOS		1 (5%)		
ANGIECTASIS		1 (5%)	1 (2%)	
HEMATOPOIESIS			1 (2%)	1 (2%)
#LIVER/CENTRILOBULAR	(20)	(20)	(42)	(44)
FIBROSIS				1 (2%)
NECROSIS, NOS	1 (5%)		4 (10%)	2 (5%)
METAMORPHOSIS FATTY				1 (2%)
#LIVER/HEPATOCYTES	(20)	(20)	(42)	(44)
INFLAMMATION, NOS				1 (2%)
*BILE DUCT	(20)	(20)	(50)	(50)
HYPERPLASIA, NOS			1 (2%)	5 (10%)
#PANCREAS	(20)	(19)	(42)	(44)
FIBROSIS			1 (2%)	
NECROSIS, FAT			1 (2%)	
ATROPHY, NOS				1 (2%)
#STOMACH	(20)	(20)	(50)	(49)
INFLAMMATION, NOS	1 (5%)			
ULCER, NOS			1 (2%)	
ULCER, FOCAL		1 (5%)	1 (2%)	3 (6%)
HYPERKERATOSIS	1 (5%)		4 (8%)	10 (20%)
ACANTHOSIS	1 (5%)		5 (10%)	10 (20%)
#LARGE INTESTINE	(19)	(19)	(42)	(44)
PARASITISM		2 (11%)	1 (2%)	

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-051F	LOW DOSE 01-054F	HIGH DOSE 01-055F
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(42)	(44)
MINERALIZATION			1 (2%)	
INFLAMMATION, FOCAL				1 (2%)
INFLAMMATION, CHRONIC	9 (45%)	9 (45%)	9 (21%)	9 (20%)
NEPHROPATHY, TOXIC			42 (100%)	44 (100%)
CALCIUM DEPOSIT	1 (5%)			
ENDOCRINE SYSTEM				
#PITUITARY	(19)	(20)	(40)	(41)
CYST, NOS		1 (5%)		
HYPERPLASIA, CHROMOPHOBE-CELL		1 (5%)		
#ADRENAL	(20)	(20)	(40)	(44)
DEGENERATION, NOS		1 (5%)		9 (20%)
ATROPHY, NOS			1 (3%)	
HYPERTROPHY, NOS				1 (2%)
ANGIECTASIS		1 (5%)	1 (3%)	
HEMATOPOIESIS			3 (8%)	
#ADRENAL CORTEX	(20)	(20)	(40)	(44)
DEGENERATION, NOS		1 (5%)	33 (83%)	31 (70%)
HYPERTROPHY, NOS		1 (5%)		
ANGIECTASIS	3 (15%)			
#THYROID	(20)	(20)	(39)	(44)
HYPERPLASIA, C-CELL	4 (20%)	1 (5%)		1 (2%)
#PARATHYROID	(1)			
HYPERPLASIA, NOS	1 (100%)			
REPRODUCTIVE SYSTEM				
#UTERUS	(20)	(20)	(39)	(43)
HYDROMETRA	4 (20%)	2 (10%)	3 (8%)	3 (7%)
#UTERUS/ENDOMETRIUM	(20)	(20)	(39)	(43)
INFLAMMATION, NOS	1 (5%)	1 (5%)		
HYPERPLASIA, CYSTIC	1 (5%)			
#OVARY	(20)	(20)	(39)	(43)
FOLLICULAR CYST, NOS				1 (2%)

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

TABLE C2 (CONCLUDED)

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-051F	LOW DOSE 01-054F	HIGH DOSE 01-055F
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EYE	(20)	(20)	(50)	(50)
CATARACT		1 (5%)		
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*PLEURA	(20)	(20)	(50)	(50)
INFLAMMATION, NOS		1 (5%)		
*PERICARDIUM	(20)	(20)	(50)	(50)
INFLAMMATION, NOS		3 (15%)	3 (6%)	5 (10%)
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED			4	3

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE TREATED WITH DBCP

TABLE D1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE TREATED WITH DBCP

	CONTROL (UNTR) 02-M061	CONTROL (VEH) 02-M051	LOW DOSE 02-M052	HIGH DOSE 02-M053
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	19	20	47	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	20	45	50
INTEGUMENTARY SYSTEM				
*SKIN	(19)	(20)	(47)	(50)
INFLAMMATION, NOS				1 (2%)
CALCIUM DEPOSIT			1 (2%)	
*SUBCUT TISSUE	(19)	(20)	(47)	(50)
ABSCESS, NOS	2 (11%)		1 (2%)	
RESPIRATORY SYSTEM				
#LUNG	(18)	(20)	(46)	(48)
EDEMA, NOS	1 (6%)			
INFLAMMATION, NOS	1 (6%)			
INFLAMMATION, SUPPURATIVE	1 (6%)			
PNEUMONIA, CHRONIC MURINE	1 (6%)		3 (7%)	3 (6%)
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(17)	(2)	(45)	(48)
NECROSIS, NOS	1 (6%)			
#SPLEEN	(19)	(20)	(45)	(47)
INFLAMMATION, NOS			1 (2%)	
AMYLOIDOSIS	12 (63%)		4 (9%)	
ATROPHY, NOS	2 (11%)			
HEMATOPOIESIS			15 (33%)	4 (9%)
CIRCULATORY SYSTEM				
#HEART	(19)	(20)	(46)	(48)
ABSCESS, NOS	1 (5%)			
CALCIFICATION, NOS	3 (16%)			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 02-M061	CONTROL (VEH) 02-M051	LOW DOSE 02-M052	HIGH DOSE 02-M053
#MYOCARDIUM	(19)	(20)	(46)	(48)
INFLAMMATION, SUPPURATIVE	1 (5%)			
DEGENERATION, NOS	1 (5%)		1 (2%)	
DIGESTIVE SYSTEM				
#LIVER	(19)	(20)	(46)	(48)
THROMBUS, ORGANIZED	1 (5%)			
INFLAMMATION, NOS			3 (7%)	5 (10%)
NECROSIS, FOCAL	1 (5%)			
AMYLOIDOSIS	12 (63%)		1 (2%)	
METAMORPHOSIS FATTY				1 (2%)
CALCIFICATION, NOS	1 (5%)			
HYPERPLASIA, NODULAR			2 (4%)	2 (4%)
LEUKEMOID REACTION			1 (2%)	
HEMATOPOIESIS			1 (2%)	
#LIVER/CENTRILOBULAR	(19)	(20)	(46)	(48)
DEGENERATION, NOS	3 (16%)			
NECROSIS, NOS	1 (5%)			
#BILE DUCT	(19)	(20)	(47)	(50)
DILATATION, NOS				1 (2%)
#PANCREAS	(19)	(19)	(45)	(48)
AMYLOIDOSIS	6 (32%)			
#ESOPHAGUS	(18)		(3)	(7)
INFLAMMATION, NOS				2 (29%)
#STOMACH	(20)	(20)	(46)	(49)
INFLAMMATION, FOCAL	1 (5%)			
CALCIFICATION, NOS	3 (15%)			
#SMALL INTESTINE	(18)	(19)	(44)	(47)
NEMATODIASIS	1 (6%)			
#LARGE INTESTINE	(19)	(19)	(46)	(47)
NEMATODIASIS	1 (5%)			
*RECTUM	(19)	(20)	(47)	(50)
PROLAPSE				1 (2%)

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

TABLE D1 (CONTINUED)

	CONTROL(UNTR) 02-M061	CONTROL(VEH) 02-M051	LOW DOSE 02-M052	HIGH DOSE 02-M053
URINARY SYSTEM				
#KIDNEY	(19)	(20)	(46)	(48)
PYELONEPHRITIS SUPPURATIVE	1 (5%)			
INFLAMMATION, CHRONIC	15 (79%)	2 (10%)		
NEPHROPATHY, TOXIC			11 (24%)	45 (94%)
AMYLOIDOSIS	6 (32%)		1 (2%)	
CALCIFICATION, NOS	1 (5%)			
LEUKEMOID REACTION			1 (2%)	
#URINARY BLADDER	(17)	(19)	(46)	(47)
INFLAMMATION, FOCAL	1 (6%)			
ENDOCRINE SYSTEM				
#ADRENAL	(19)	(20)	(42)	(49)
AMYLOIDOSIS	2 (11%)			
ANGIECTASIS	1 (5%)			
REPRODUCTIVE SYSTEM				
*PREPUTIAL GLAND	(19)	(20)	(47)	(50)
ABSCESS, NOS		1 (5%)		
#TESTIS	(19)	(20)	(45)	(48)
GRANULOMA, SPERMATIC	1 (5%)			
ATROPHY, NOS				1 (2%)
NERVOUS SYSTEM				
#BRAIN	(18)	(20)	(46)	(48)
CALCIFICATION, NOS	1 (6%)			
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*MUSCLE HIP/THIGH	(19)	(20)	(47)	(50)
CALCIUM DEPOSIT			1 (2%)	

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

TABLE D1 (CONCLUDED)

	CONTROL(UNTR) 02-M061	CONTROL(VEH) 02-M051	LOW DOSE 02-M052	HIGH DOSE 02-M053
BODY CAVITIES				
*PERITONEUM	(19)	(20)	(47)	(50)
INFLAMMATION, NOS				1 (2%)
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED		14	2	
AUTO/NECROPSY/HISTO PERF		1		
AUTO/NECROPSY/NO HISTO			2	
AUTOLYSIS/NO NECROPSY	1		3	

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

TABLE D2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE TREATED WITH DBCP

	CONTROL (UNTR) 02-F061	CONTROL (VEH) 02-F051	LOW DOSE 02-F054	HIGH DOSE 02-F055
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS MISSING				1
ANIMALS NECROPSIED	20	20	50	47
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	20	50	47
INTEGUMENTARY SYSTEM				
*SKIN	(20)	(20)	(50)	(47)
INFLAMMATION, CHRONIC	1 (5%)			
RESPIRATORY SYSTEM				
#LUNG	(20)	(20)	(50)	(46)
PNEUMONIA, CHRONIC MURINE	11 (55%)		2 (4%)	
HYPERPLASIA, FOCAL			1 (2%)	
HYPERPLASIA, LYMPHOID	1 (5%)			
HEMATOPOIETIC SYSTEM				
#SPLEEN	(20)	(20)	(50)	(46)
HEMATOPOIESIS			3 (6%)	3 (7%)
#MESENTERIC L. NODE	(20)	(19)	(46)	(39)
ANGIECTASIS	1 (5%)			
#THYMUS	(20)	(20)	(50)	(46)
HYPERPLASIA, LYMPHOID	1 (5%)			
CIRCULATORY SYSTEM				
#MYOCARDIUM	(20)	(20)	(50)	(46)
INFLAMMATION, NOS	1 (5%)			
DIGESTIVE SYSTEM				
#LIVER	(20)	(20)	(50)	(46)
INFLAMMATION, NOS			2 (4%)	3 (7%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 02-F061	CONTROL (VEH) 02-F051	LOW DOSE 02-F054	HIGH DOSE 02-F055
#LIVER/CENTRILOBULAR	(20)	(20)	(50)	(46)
DEGENERATION, NOS	2 (10%)			
NECROSIS, NOS	1 (5%)			
*BILE DUCT	(20)	(20)	(50)	(47)
INFLAMMATION, NOS	1 (5%)			
INFLAMMATION, FOCAL	1 (5%)			
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(50)	(46)
PYELONEPHRITIS, NOS			3 (6%)	
INFLAMMATION, CHRONIC	13 (65%)			
NEPHROPATHY, TOXIC			14 (28%)	43 (93%)
#URINARY BLADDER	(18)	(19)	(47)	(46)
INFLAMMATION, FOCAL	4 (22%)			
ENDOCRINE SYSTEM				
#ADRENAL	(19)	(19)	(47)	(42)
INFLAMMATION, NOS			1 (2%)	
REPRODUCTIVE SYSTEM				
#UTERUS	(20)	(20)	(45)	(45)
HYDROMETRA		4 (20%)	3 (7%)	2 (4%)
#UTERUS/ENDOMETRIUM	(20)	(20)	(45)	(45)
HYPERPLASIA, CYSTIC	17 (85%)	3 (15%)	2 (4%)	
#OVARY	(20)	(20)	(43)	(44)
CYST, NOS		3 (15%)		
PAROVARIAN CYST	4 (20%)			
INFLAMMATION, NOS	1 (5%)			
ANGIECTASIS	1 (5%)			
NERVOUS SYSTEM				
*BRAIN/MENINGES	(20)	(20)	(50)	(46)
INFLAMMATION, FOCAL	1 (5%)			

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

TABLE D2 (CONCLUDED)

	CONTROL(UNTR) 02-F061	CONTROL(VEH) 02-F051	LOW DOSE 02-F054	HIGH DOSE 02-F055
*SPINAL CORD	(20)	(20)	(50)	(47)
CYST, NOS	1 (5%)			
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*SKELETAL MUSCLE	(20)	(20)	(50)	(47)
INFLAMMATION, FOCAL	1 (5%)			
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED		12		
ANIMAL MISSING/NO NECROPSY				1
AUTOLYSIS/NO NECROPSY				2

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

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