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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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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 CHLOROBENZILATE
FOR POSSIBLE CARCINOGENICITY

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

FOREWORD: This report presents the results of the bioassay of chlorobenzilate conducted for the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), National Institutes of Health, Bethesda, Maryland. This is one of a series of experiments designed to determine whether selected chemicals have the capacity to produce cancer in animals. Negative results, in which the test animals do not have a significantly greater incidence of cancer than control animals, do not necessarily mean the test chemical is not a carcinogen because the experiments are conducted under a limited set of circumstances. Positive results demonstrate that the test chemical is carcinogenic for animals under the conditions of the test and indicate a potential risk to man. The actual determination of the risk to man from animal carcinogens requires a wider analysis.

CONTRIBUTORS: This bioassay of chlorobenzilate 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 Testing 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) and the analytical results were reviewed by Dr. N. Zimmerman (6); the technical supervisor of animal treatment and observation was Ms. K. J. Petrovics (3).

Histopathologic examinations were performed by Dr. R. H. Habermann (3) and Dr. B. M. Ulland (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. Histopathology findings and reports were reviewed by Dr. R. L. Schueler (7).

Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute (8); the statistical analysis was performed by Mr. W. W. Belew (6,9) using

methods selected for the Carcinogenesis Testing Program by Dr. J. J. Gart (10).

This report was prepared at METREK, a Division of The MITRE Corporation (6) under the direction of the NCI. Those responsible for this report at METREK are the project coordinator, Dr. L. W. Thomas (6), task leader Dr. M. R. Kornreich (6,11), senior biologist Ms. P. Walker (6), biochemist Dr. B. Fuller (6), and technical editor Ms. P. A. Miller (6). The final report was reviewed by members of the participating organizations.

The following other scientists at the National Cancer Institute were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. K. C. Chu (1), Dr. C. Cueto, Jr. (1), Dr. J. F. Douglas (1), Dr. D. G. Goodman (1,11), Dr. R. A. Griesemer (1), Dr. M. H. Levitt (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), Dr. R. A. Squire (1,12), Dr. S. F. Stinson (1), Dr. J. M. Ward (1), and Dr. C. E. Whitmire (1).

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SUMMARY

A bioassay of technical-grade chlorobenzilate for possible carcinogenicity was conducted using Osborne-Mendel rats and B6C3F1 mice. Chlorobenzilate was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. Chlorobenzilate was administered for 78 weeks followed by an observation period of 12 or 13 additional weeks in mice and 32 or 33 additional weeks in rats.

The time-weighted average dietary concentrations of chlorobenzilate were 2995 and 1600 ppm for high and low dose male rats, respectively, and 2229 and 1175 ppm for high and low dose female rats. Mice received time-weighted average high and low dietary concentrations of 7846 and 4231 ppm, respectively, for males and 5908 and 3200 ppm, respectively, for females.

Survival in both species was high (over 68 percent of the high dose rats and over 82 percent of the high dose mice survived on test until the end of the study). Dose-related mean body weight depression, observed in both species, indicated that the maximum dose for optimal bioassay sensitivity was used in the high dose groups.

An increased incidence of hepatocellular carcinomas was observed in dosed mice, i.e., 4/19 (21 percent) in control males, 32/48 (67 percent) in low dose males, 22/45 (49 percent) in high dose males, 0/20 in control females, 11/49 (22 percent) in low dose females, and 13/50 (26 percent) in high dose females.

There was a statistically significant positive association between the administration of chlorobenzilate and the appearance of cortical adenoma of the adrenal gland in low dose male and high dose female rats. Although suggestive, the findings of a low incidence of benign adrenal tumors was not considered sufficient evidence to establish the carcinogenicity of chlorobenzilate for the Osborne-Mendel rat.

Under the conditions of this bioassay, orally administered chlorobenzilate was carcinogenic in male and female B6C3F1 mice, causing an increased incidence of hepatocellular carcinomas. The results do not, however, provide sufficient evidence for the carcinogenicity of chlorobenzilate in Osborne-Mendel rats.

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I. INTRODUCTION

Chlorobenzilate (Figure 1) (NCI No. C00408) was one of a group of agricultural pesticides that scientists at the National Cancer Institute (NCI) selected for inclusion in the Carcinogenesis Testing Program. In a study by Innes et al. (1969) evidence emerged suggesting that the incidence of hepatomas was significantly elevated in male mice upon oral administration of chlorobenzilate. In addition, the widespread use of chlorobenzilate and the resulting human exposure emphasized the need for carcinogenicity testing.

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is 4,4'-dichlorobenzilic acid, ethyl ester.* It is a carbinol compound and is also called ethyl 4,4'-dichlorobenzilate.

Introduced in 1952 for use as a selective acaricide, chlorobenzilate had an annual domestic production of approximately 36 million pounds in 1974 (Fowler and Mahan, 1976). Essentially most of the chlorobenzilate that enters the environment is through its dispersion as a pesticide. Ninety percent of chlorobenzilate usage in 1971 was for mite control on citrus crops (Stanford Research Institute, 1975). Additionally, it is effective against mites in orchards, vineyards, tea plantations, field crops, and ornamental plants. Since bees are not severely affected by chlorobenzilate, it is also used to control

*The CAS registry number is 510-15-6.

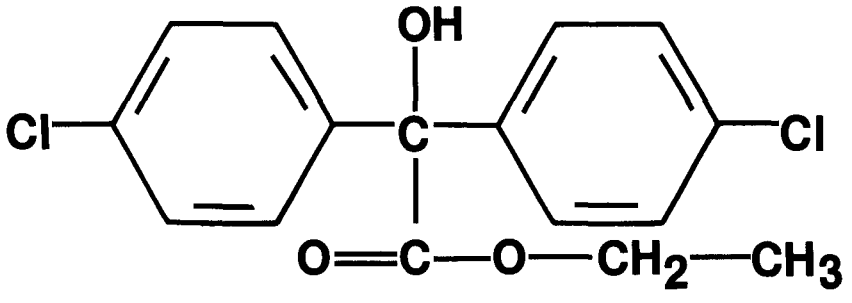


FIGURE 1
CHEMICAL STRUCTURE OF CHLOROBENZILATE

the tracheal mite of this insect (Bartsch et al., 1971). The greatest potential for exposure to chlorobenzilate appears to be among persons associated with its production, formulation, and agricultural application. No chlorobenzilate was detected in food in the United States in total diet studies carried out in 1966 by the U.S. Food and Drug Administration (Bartsch et al., 1971) or reported in recent analyses of food composites (Johnson and Manske, 1976). Residue levels found on fruits, citrus, grapes, tea, and vegetables were all below the tolerance levels set by the U.S. Environmental Protection Agency (Bartsch et al., 1971).

II. MATERIALS AND METHODS

A. Chemicals

A single batch of technical-grade chlorobenzilate was purchased by Hazleton Laboratories America, Inc., Vienna, Virginia, from Geigy Agricultural Chemicals. The compound was tested by Hazleton Laboratories for purity at the start of the bioassay, at an intermediate stage, and again during the final year of the feeding study. The final analysis was conducted prior to termination of the bioassay.

The technical-grade chlorobenzilate was analyzed twice within the first 12 months of the bioassay by gas-liquid chromatography using both total-area analysis and the internal standard method. An FDA manufacturer's standard for chlorobenzilate (99.9 percent) was used as the internal standard. Total-area analysis results showed a major peak of 97 and 99 percent of chlorobenzilate for the first and second assays, respectively. Comparisons of the technical-grade chlorobenzilate with the internal standard revealed that the technical-grade compound contained 95 and 98 percent chlorobenzilate based on the first and second assays, respectively.

The chemical purity of chlorobenzilate was assayed for a third time 22 months after the feeding study was initiated. Total-area analysis indicated a peak area of 97 percent. The internal standard assay, performed to corroborate this analysis indicated a relative peak area of 90 percent.

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

B. Dietary Preparation

The basal laboratory diet for both dosed and control animals consisted of Wayne Lab-Blox® meal (Allied Mills, Inc., Chicago, Illinois) plus 2 percent Duke's® corn oil (S. F. Sauer Company, Richmond, Virginia) by weight. Fresh mixtures of chlorobenzilate in corn oil were prepared each week and stored in the dark. The chlorobenzilate mixtures were incorporated into the appropriate amount of laboratory diet in a twin-shell blender fitted with an accelerator bar.

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, 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 dosed 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 to 15 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 ten in solid-bottom, polypropylene cages equipped with filter tops. Sanitized cages with fresh bedding (Sanichips®, Pinewood Sawdust Company, Moonachie, New Jersey) 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, while fresh heat-sterilized glass water bottles and sipper tubes were provided three times a week. Food (Wayne Lab-Blox® meal) and water were available ad libitum.

Dosed rats were housed in the same room with other rats receiving diets containing* sulfallate (95-06-7); DDT (50-29-3); and TDE (72-54-8).

*CAS registry numbers are given in paretheses.

Control rats were housed in a room with other rats receiving diets containing trifluralin (1582-09-8); dioxathion (78-34-2); dicofol (115-32-2); nitrofen (1836-75-5); endosulfan (115-29-7); and mexacarbate (315-18-4).

All mice used in the chlorobenzilate study, including controls, were housed in the same room as other mice receiving diets containing trifluralin (1582-09-8); dioxathion (78-34-2); sulfallate (95-06-7); DDT (50-29-3); methoxychlor (72-43-5); DDE (72-55-9); TDE (72-54-8); dicofol (115-32-2); pentachloronitrobenzene (82-68-8); clonitralid (1420-04-8); acetylaminofluorene (53-96-3); nitrofen (1836-75-5); endosulfan (115-29-7); mexacarbate (315-18-4); amitrole (61-82-5); and safrole (94-59-7).

E. Selection of Initial Concentrations

In order to establish the maximum tolerated concentrations of chlorobenzilate for administration to dosed animals in the chronic studies, subchronic toxicity tests were conducted with both rats and mice. Animals of each species were distributed among six groups, each consisting of five males and five females. Chlorobenzilate was premixed with a small amount of corn oil. This mixture was then incorporated into the laboratory diet and fed ad libitum to five of the six rat groups and five of the six mouse groups in concentrations of 1780, 3160, 5620, 10,000, and 17,800 ppm. The sixth group of each species served as a control group, receiving only the mixture of corn oil and laboratory meal. The dosed dietary preparations were administered

for a period of 6 weeks, followed by a 2-week observation period during which all animals were fed the basal laboratory diet.

A dosage inducing no mortality and resulting in a depression in mean body weight of approximately 20 percent relative to controls was to be selected as the high dose for administration in the chronic bioassay. When weight gain criteria were not applicable, mortality data alone were utilized.

All male and female rats receiving 10,000 ppm chlorobenzilate or less survived the entire 8-week study. The depressions in mean body weight in males receiving concentrations of 3160 and 5620 ppm were 14 and 38 percent, respectively. In females receiving concentrations of 1780 and 3160 ppm the depressions in mean body weight were 18 and 22 percent, respectively. The high concentrations selected for administration to rats in the chronic study were 3200 and 2350 ppm for males and females, respectively.

In the male mice four deaths were observed in the group receiving 3160 ppm but no other deaths, except one male at 17,800 ppm, were recorded. All female mice survived the 8-week study, except two in the group receiving 10,000 ppm. Mean body weight gain, expressed as a percentage of the weight gained by the controls, was 108 and 50 percent in the males dosed with 10,000 and 17,800 ppm, respectively. In the females, the body weight gains were 82 and 45 percent at concentrations of 5620 and 10,000 ppm, respectively. The high concentrations selected for administration to mice in the chronic study were 12,000 and 6400 ppm for males and females, respectively.

F. Experimental Design

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

The dosed and control rats were all approximately 6 weeks old at the time they were placed on test. However, the control rats had a median birth date approximately 2 weeks earlier than the dosed rats and were placed on test approximately 2 weeks before the dosed rats. The concentrations of chlorobenzilate initially administered to males were 3200 and 1600 ppm. Throughout this report those male rats receiving the former concentration are referred to as the high dose group and those receiving the latter concentration are referred to as the low dose group. For females, the initial concentrations of chlorobenzilate were 2350 and 1175 ppm. Throughout this report those female rats receiving the former concentration are referred to as the high dose group and those receiving the latter concentration are referred to as the low dose group. The basal diet for all groups contained 2 percent corn oil. In week 58 of the study, administration of chlorobenzilate to the high dose male rats ceased for 1 week, due to toxicity of the compound, and was then followed by 4 weeks of feeding at the previous concentration of 3200 ppm. This pattern of cyclic administration continued for the remainder of the dosing period. This same method of total intake reduction and the same rationale were employed for the high dose female rats beginning with week 63.

TABLE 1

DESIGN SUMMARY FOR OSBORNE-MENDEL RATS
CHLOROBENZILATE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	CHLORO-BENZILATE CONCENTRATION[a]	OBSERVATION PERIOD		TIME-WEIGHTED AVERAGE CONCENTRATION OVER A 78-WEEK PERIOD[b]
			TREATED (WEEKS)	UNTREATED (WEEKS)	
MALE					
CONTROL	50	0		111	0
LOW DOSE	50	1600	78		1600
		0		32	
HIGH DOSE	50	3200	57		2995
		3200[c]	16	5	
		0		32	
FEMALE					
CONTROL	50	0		111	0
LOW DOSE	50	1175	78		1175
		0		33	
HIGH DOSE	50	2350	62		2229
		2350[c]	12	4	
		0		33	

[a] Concentrations in parts per million.

[b] Time-weighted average concentration = $\frac{\Sigma(\text{concentration X weeks received})}{78 \text{ weeks}}$

[c] These doses were cyclically administered with a pattern of 1 dose-free week followed by 4 weeks of dosing at the levels indicated.

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
CHLOROBENZILATE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	CHLORO-BENZILATE CONCENTRATION[a]	OBSERVATION PERIOD		TIME-WEIGHTED AVERAGE CONCENTRATION OVER A 78-WEEK PERIOD[b]
			TREATED (WEEKS)	UNTREATED (WEEKS)	
MALE					
CONTROL	20	0		90	0
LOW DOSE	50	6,000	9		4,231
		4,000	69		
		0		12	
HIGH DOSE	50	12,000	9		7,846
		8,000	43		
		8,000[c]	20	6	
		0		12	
FEMALE					
CONTROL	20	0		90	0
LOW DOSE	50	3,200	78		3,200
		0		13	
HIGH DOSE	50	6,400	52		5,908
		6,400[c]	20	6	
		0		13	

[a] Concentrations in parts per million.

[b] Time-weighted average concentration = $\frac{\Sigma(\text{concentration} \times \text{weeks received})}{78 \text{ weeks}}$

[c] These doses were cyclically administered with a pattern of 1 dose-free week followed by 4 weeks of dosing at the levels indicated.

The control and dosed mice were all approximately 6 weeks old on the first day of the test and they all shared the same median birth date. The initial concentrations administered to male mice were 12,000 and 6000 ppm. Throughout this report those male mice receiving the former concentration are referred to as the high dose group and those receiving the latter concentration are referred to as the low dose group. In week 10 of the experiment, when the male mice were 16 weeks old, the high and low concentrations were decreased to 8000 and 4000 ppm, respectively, because a hunched posture was observed in the high dose males. Female mice received initial concentrations of 6400 and 3200 ppm and were maintained at these levels until termination of the experiment. Throughout this report those female mice receiving the former concentration are referred to as the high dose group and those receiving the latter concentration are referred to as the low dose group. In week 53 of the study, administration of chlorobenzilate to the high dose male and female mice ceased for 1 week and was then followed by 4 weeks of dietary administration at the previous concentrations of 8000 and 6400 ppm. The concentrations administered were decreased due to the reappearance of a hunched posture in the dosed animals. This pattern of cyclic administration was continued for the remainder of the dosing period.

G. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment. 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. From the first day, all animals were inspected daily for mortality. 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, and gross lesions taken from sacrificed animals and, whenever possible, from animals found dead.

Tissues 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.

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), pancreas, esophagus, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, testis, prostate, seminal vesicle, brain, muscle, uterus, mammary gland, and ovary.

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.

H. Data Recording and Statistical Analyses

Pertinent data on this experiment have been recorded in an automatic data processing system, the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969). Data tables were generated for verification of data transcription and for statistical review.

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

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be

missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) when testing two groups for equality and used Tarone's (1975) extensions of Cox's methods when 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 when appropriate. 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.

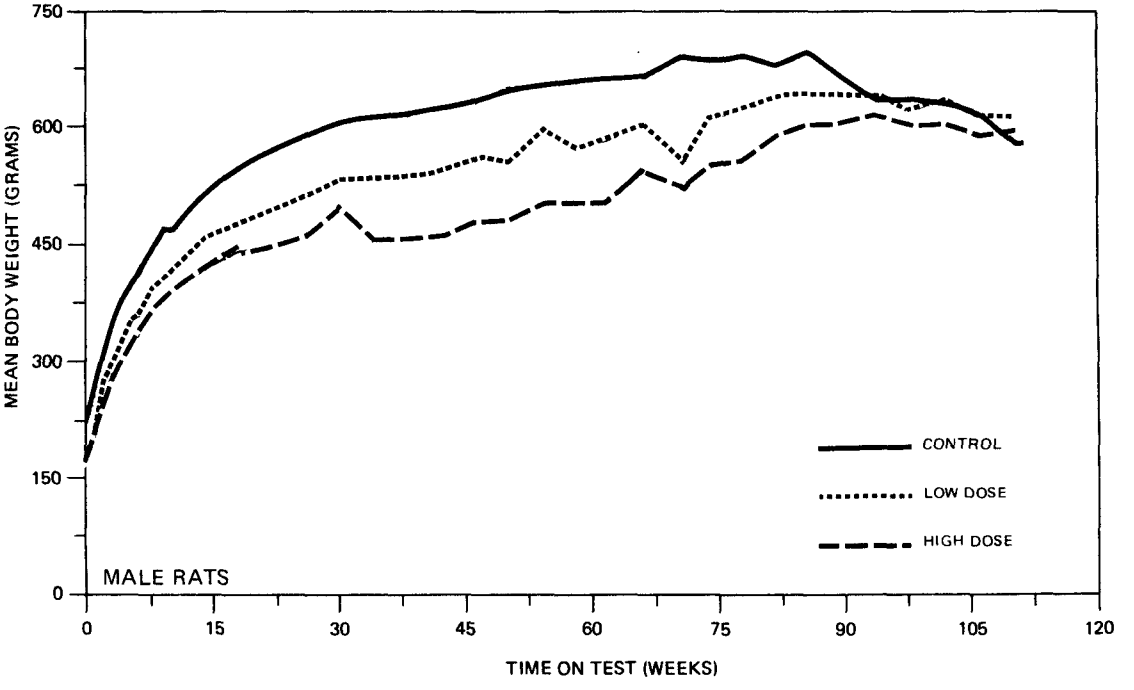
III. CHRONIC TESTING RESULTS: RATS

A. Body Weights and Clinical Observations

Dose-related mean body weight depression was observed in both male and female rats beginning in week 10. This continued until approximately week 90 at which time the control male and female rats exhibited a slight decrease in mean body weight while the dosed groups generally maintained their relative mean body weights (Figure 2). Fluctuations in the growth curve may be due to mortality; as the size of the group diminishes, the mean body weight may be subject to wide variations.

During the first year of the study the appearance and behavior patterns observed among dosed rats were generally comparable to those of the controls, except that by week 8, urine staining of the abdominal fur was noted in a few high dose males. As the study progressed (weeks 9 to 78), abdominal urine stains and a hunched appearance were observed at a slightly greater frequency in the dosed groups than in the controls. Thereafter, these signs were noted at a comparable rate in dosed and control animals. Undersized gonads were observed during the last 6 months of the study in several dosed male rats, an observation subsequently confirmed at necropsy as compound-related testicular atrophy.

Respiratory involvement, characterized by labored respiration, wheezing, and/or nasal discharge was observed at a low incidence in all groups during the study. Incidental signs associated with aging



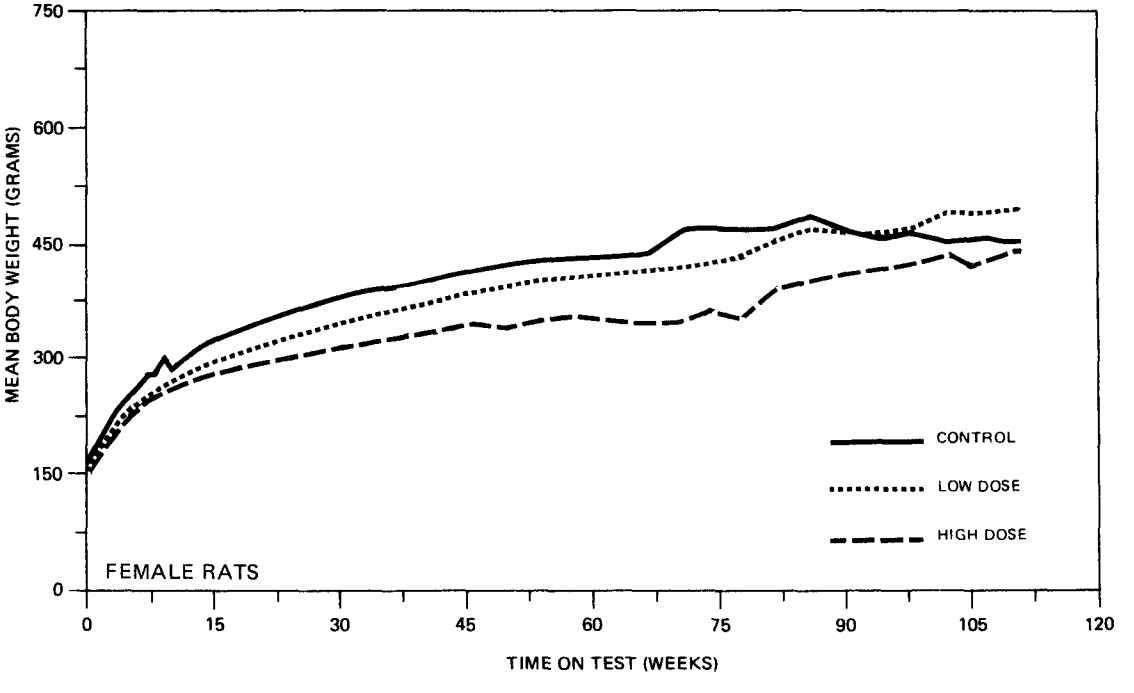


FIGURE 2
GROWTH CURVES FOR CHLOROBENZILATE CHRONIC STUDY RATS

were observed in comparable numbers of dosed and control rats during the last 6 months. These signs included rough fur, eyes that were pale, squinted, cloudy, or showing reddish discharge, sores on the tail or other parts of the body, localized alopecia, swollen areas of the body, palpable nodules, and/or tissue masses. Isolated, apparently incidental, observations noted sporadically during the study in one to five dosed rats included ataxia, tremors, head tilt, circling or loss of equilibrium, and hind-limb paralysis.

B. Survival

The estimated probabilities of survival for male and female rats in the control and chlorobenzilate-dosed groups are shown in Figure 3. In both sexes, the Tarone test indicated no positive association between dose and mortality.

In both sexes there were adequate numbers of rats at risk from late-developing tumors, with 68 percent (34/50) of the high dose males and 72 percent (36/50) of the high dose females surviving on test until the end of the study.

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).

A variety of neoplasms was observed among both dosed and control rats. The types of tumors observed have been encountered previously as spontaneous lesions in the Osborne-Mendel rat, and the incidence

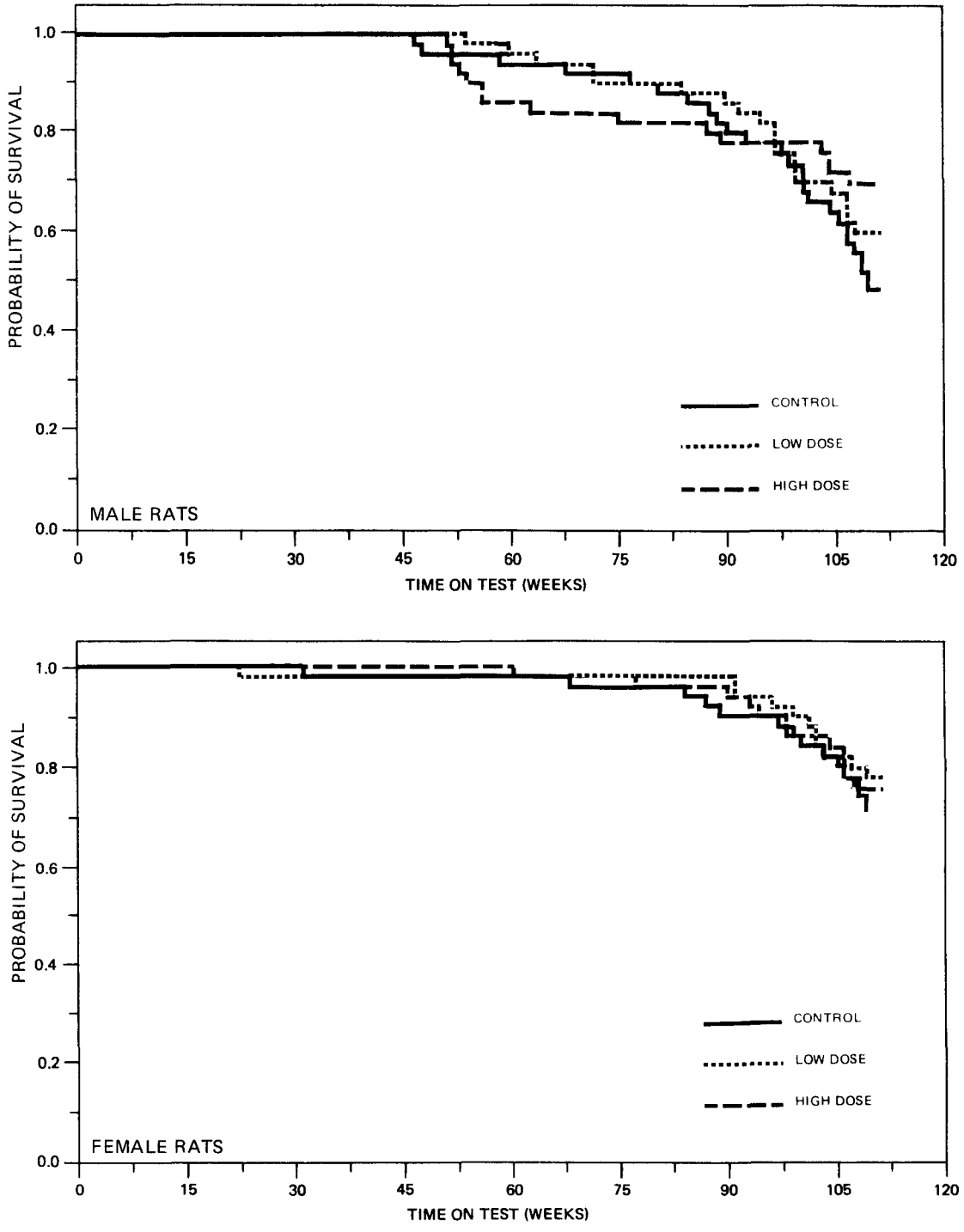


FIGURE 3
SURVIVAL COMPARISONS OF CHLOROBENZILATE CHRONIC STUDY RATS

of tumor types, with the exceptions of malignant lymphomas and adrenal neoplasms, appeared to be unrelated to group or sex.

Malignant lymphomas (histiocytic or lymphocytic types) occurred with somewhat greater frequency in dosed than in control animals. This slightly greater frequency in dosed rats when compared to controls is of doubtful significance, as these tumors do not represent unusual types and have been known to occur spontaneously at these incidences in the Osborne-Mendel rat.

Cortical adenomas and pheochromocytomas of the adrenal gland occurred only in dosed rats. Cortical adenomas were observed in 6/49 (12 percent) low dose males, 3/49 (6 percent) high dose males, 2/47 (4 percent) low dose females, and 5/47 (11 percent) high dose females. Pheochromocytomas were observed in 1/49 (2 percent) low dose males, 1/49 (2 percent) high dose males, 2/47 (4 percent) low dose females and 0/47 high dose females.

A wide variety of nonproliferative lesions of spontaneous disease occurred in both dosed and control rats (see Appendix C). Sections of testicle, however, indicated compound-related testicular atrophy in the dosed male groups. Thirty-one of 49 (63 percent) high dose males and 26/49 (53 percent) low dose males showed significant degrees of testicular atrophy, while in the male control group only 9/44 (20 percent) of the rats were observed with testicular atrophy.

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 CHLOROBENZILATE[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibroma[b]	1/49(0.02)	1/50(0.02)	4/50(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.980	3.920
Lower Limit	---	0.013	0.405
Upper Limit	---	75.404	188.989
Weeks to First Observed Tumor	111	99	110
Circulatory System: Hemangiosarcoma[b]	12/49(0.24)	4/50(0.10)	1/50(0.02)
P Values[c]	P = 0.001(N)	P = 0.049(N)	P = 0.001(N)
Relative Risk (Control)[d]	---	0.327	0.082
Lower Limit	---	0.082	0.002
Upper Limit	---	1.993	0.518
Weeks to First Observed Tumor	68	106	110
Pituitary: Chromophobe Adenoma[b]	4/41(0.10)	7/40(0.18)	4/46(0.09)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.794	0.891
Lower Limit	---	0.499	0.177
Upper Limit	---	7.745	4.499
Weeks to First Observed Tumor	108	92	89

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Adrenal: Cortical Adenoma[b]	0/46(0.00)	6/49(0.12)	3/49(0.06)
P Values[c]	N.S.	P = 0.016	N.S.
Departure from Linear Trend[e]	P = 0.031	---	---
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	1.506	0.566
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	97	110
Thyroid: Follicular-Cell Adenoma or Follicular-Cell Carcinoma[b]	5/48(0.15)	3/49(0.06)	6/49(0.12)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.588	1.176
Lower Limit	---	0.096	0.321
Upper Limit	---	2.846	4.557
Weeks to First Observed Tumor	106	106	110
Hematopoietic System: Malignant Lymphoma[b]	1/49(0.02)	5/50(0.10)	2/50(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	4.900	1.960
Lower Limit	---	0.578	0.105
Upper Limit	---	6.748	113.312
Weeks to First Observed Tumor	107	95	107

TABLE 3 (CONCLUDED)

[a]Treated groups received time-weighted average doses of 1600 or 2995 ppm in feed.

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

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when P is less than 0.05; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]The probability level of the test for departure from linear trend is given beneath the control group when P is less than 0.05.

TABLE 4

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Circulatory System: Hemangiosarcoma[b]	4/50(0.08)	1/49(0.02)	0/50(0.00)
P Values[c]	P = 0.026(N)	N.S.	N.S.
Relative Risk (Control)[d]	---	0.255	0.000
Lower Limit	---	0.005	0.000
Upper Limit	---	2.459	1.079
Weeks to First Observed Tumor	89	111	--
Pituitary: Chromophobe Adenoma[b]	15/50(0.30)	11/45(0.24)	11/45(0.24)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.815	0.815
Lower Limit	---	0.378	0.378
Upper Limit	---	1.688	1.688
Weeks to First Observed Tumor	100	101	90
Adrenal: Cortical Adenoma[b]	0/50(0.00)	2/47(0.04)	5/47(0.11)
P Values[c]	P = 0.014	N.S.	P = 0.024
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.315	1.347
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	103	98

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	5/50(0.10)	3/47(0.06)	2/47(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.638	0.426
Lower Limit	---	0.104	0.042
Upper Limit	---	3.088	2.454
Weeks to First Observed Tumor	111	111	111
Thyroid: Follicular-Cell Adenoma or Follicular-Cell Carcinoma[b]	1/50(0.02)	2/47(0.04)	4/47(0.09)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.128	4.255
Lower Limit	---	0.114	0.444
Upper Limit	---	2.810	204.823
Weeks to First Observed Tumor	111	110	90
Mammary Gland: Fibroadenoma[b]	15/50(0.30)	14/49(0.29)	16/50(0.32)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.952	1.067
Lower Limit	---	0.479	0.558
Upper Limit	---	1.879	2.049
Weeks to First Observed Tumor	87	99	60

TABLE 4 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Uterus: Endometrial Stromal Polyp[b]	4/49(0.08)	1/47(0.02)	4/46(0.09)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.266	1.087
Lower Limit	---	0.005	0.215
Upper Limit	---	2.559	5.505
Weeks to First Observed Tumor	111	111	94
Hematopoietic System: Malignant Lymphoma[b]	1/50(0.02)	0/49(0.00)	3/50(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.000	3.000
Lower Limit	---	0.000	0.250
Upper Limit	---	9.032	154.270
Weeks to First Observed Tumor	111	---	106

[a]Treated groups received time-weighted average doses of 1175 or 2229 ppm in feed.

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

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when P is less than 0.05; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

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

The incidence of cortical adenomas of the adrenal gland was noted in dosed rats of both sexes. For males the Fisher exact test indicated a significantly (P = 0.016) higher incidence of these tumors in the low dose group than in the control group. The comparison between the control and the high dose group, however, was not significant. For female rats the Fisher exact test indicated a significantly higher (P = 0.024) proportion of cortical adenoma of the adrenal gland for the high dose group than for the control group. Additionally, the Cochran-Armitage test for positive dose-related trend was statistically significant (P = 0.014), indicating a positive association between dosage and tumor incidence. In historical control data compiled by this laboratory for the NCI Carcinogenesis Testing Program 3/160 (2 percent) of the male and 2/160 (1 percent) of the female untreated Osborne-Mendel rats had a cortical carcinoma or a cortical adenoma of the adrenal gland; additionally, 2/160 (1 percent) of the female historical untreated controls had an adrenal pheochromocytoma.

Based upon these results there was an association between the administration of chlorobenzilate and the increased incidence of cortical adenoma of the adrenal gland in both male and female rats.

The possibility of a negative association between compound administration and incidence was noted for hemangiosarcoma in both male and female rats.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on the relative risk have been estimated and entered in the tables based upon the observed tumor incidence rates. In many of the intervals shown in Tables 3 and 4, the value one is included; this indicates the absence of statistically significant results. It should also be noted that many of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in rats by chlorobenzilate that could not be established under the conditions of this test.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

Dose-related mean body weight depression was observed in both male and female mice. This effect was relatively consistent throughout the study in females and until week 80 in males. At this time the high dose males gained weight rapidly, and their weight equaled that of the low dose group at termination of the study (Figure 4).

Clinical signs were restricted to a hunched appearance, observed in the high dose males during the first 10 weeks of the study. Following a decrease in concentrations administered to the dosed males in week 11, the incidence decreased markedly until week 54 when approximately 50 percent of all the dosed mice displayed a hunched posture. By week 66 and for the remainder of the study the animals appeared to have recovered, and less than 10 percent were exhibiting this clinical sign.

Signs commonly observed in group-housed laboratory mice were observed in comparable numbers of control and dosed mice with the frequency of observation increasing during the latter part of the study. These signs included sores on the body (particularly in the males), penile, anal, or vulvar irritation with occasional prolapse and/or discharge, bloated appearance or abdominal distension, swollen areas of the body, and alopecia.

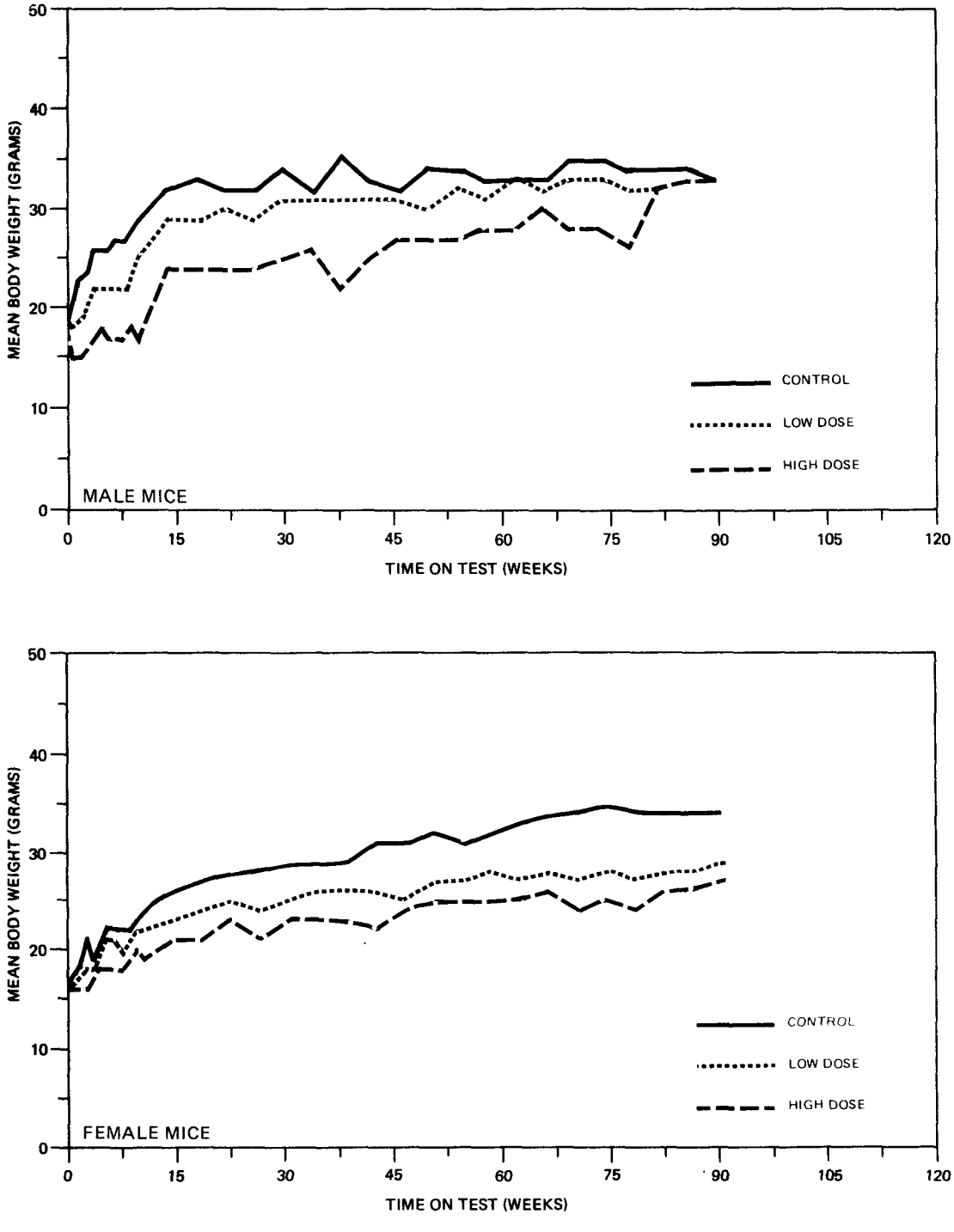


FIGURE 4
GROWTH CURVES FOR CHLOROBENZILATE CHRONIC STUDY MICE

B. Survival

The estimated probabilities of survival for male and female mice in the control and chlorobenzilate-dosed groups are shown in Figure 5. For both sexes, the Tarone test did not show a positive association between dosage and mortality.

In both sexes there were adequate numbers of mice at risk from late-developing tumors with 82 percent (41/50) of the high dose males and 88 percent (44/50) of the high dose females surviving on test until the end of the study.

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).

Hepatocellular carcinomas occurred in 4/19 (21 percent) control males, 32/48 (67 percent) low dose males, 22/45 (49 percent) high dose males, 0/20 control females, 11/49 (22 percent) low dose females, and 13/50 (26 percent) high dose females.

The hepatocellular carcinomas varied greatly in appearance. Some lesions contained well-differentiated hepatic cells that had a relatively uniform arrangement of the cords, whereas others had very anaplastic liver cells with large hyperchromatic nuclei, often with inclusion bodies and with vacuolated, pale cytoplasm. Arrangement of the neoplastic liver cells varied from short stubby cords to nests of hepatic cells and occasionally acinar formation. Mitotic figures

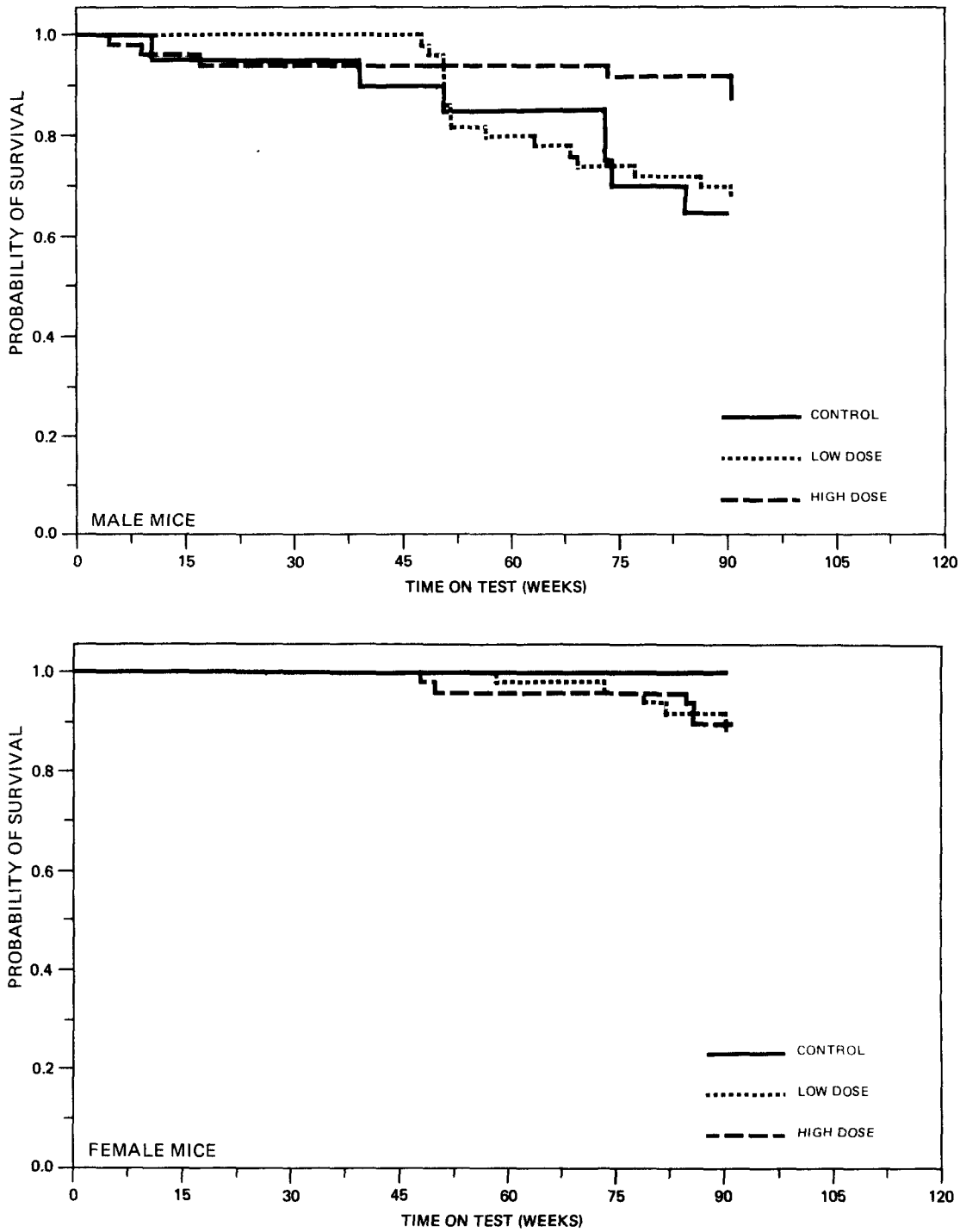


FIGURE 5
SURVIVAL COMPARISONS OF CHLOROBENZILATE CHRONIC STUDY MICE

were often present. Some of the tumors were characterized by discrete areas of highly anaplastic cells. The hepatic neoplasms occurring in the control mice were not different in histologic appearance from those noted in the dosed mice.

Inflammatory, degenerative, and proliferative lesions in control and dosed animals occurred in numbers and kinds similar to those naturally occurring lesions seen in aged laboratory mice. Focal or nodular hyperplasia of the hepatocytes occurred in 1/19 (5 percent) control males, 3/48 (6 percent) low dose males, 2/45 (4 percent) high dose males, 0/20 control females, 5/49 (10 percent) low dose females, and 4/50 (8 percent) high dose females.

Based on the results of this pathologic examination, evidence was provided for the carcinogenicity of chlorobenzilate under the conditions of this bioassay (i.e., it caused an increased incidence of hepatocellular carcinoma) in both dosed 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 chlorobenzilate-dosed groups of either sex is included.

For male mice the Fisher exact test indicated a significantly larger proportion of hepatocellular carcinoma in the low dose group ($P = 0.001$) than in the control. The comparison of high dose to control had a probability level of $P = 0.034$, a marginal result which

TABLE 5

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	4/19(0.21)	32/48(0.67)	22/45(0.49)
P Values[c]	N.S.	P = 0.001	P = 0.034
Departure from Linear Trend[e]	P = 0.002	---	---
Relative Risk (Control)[d]	---	3.167	2.322
Lower Limit	---	1.377	0.956
Upper Limit	---	10.454	8.149
Weeks to First Observed Tumor	84	68	90
Hematopoietic System: Malignant Lymphoma[b]	1/19(0.05)	1/49(0.02)	1/48(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.388	0.396
Lower Limit	---	0.005	0.005
Upper Limit	---	29.845	30.454
Weeks to First Observed Tumor	90	77	90

[a]Treated groups received time-weighted average doses of 4231 or 7846 ppm in feed.

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

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when P is less than 0.05; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]The probability level of the test for departure from linear trend is given beneath the control group when P is less than 0.05.

TABLE 6

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	0/20(0.00)	11/49(0.22)	13/50(0.26)
P Values[c]	P = 0.021	P = 0.016	P = 0.007
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	1.411	1.670
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	90	86
Hematopoietic System: Malignant Lymphoma[b]	3/20(0.15)	7/50(0.14)	0/50(0.00)
P Values[c]	P = 0.011(N)	N.S.	P = 0.021(N)
Relative Risk (Control)[d]	---	0.933	0.000
Lower Limit	---	0.246	0.000
Upper Limit	---	5.215	0.659
Weeks to First Observed Tumor	90	73	---

[a]Treated groups received time-weighted average doses of 3200 or 5908 ppm in feed.

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

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when P is less than 0.05; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

was not significant under the Bonferroni criterion. The results for hepatocellular carcinoma were similar in female mice, as both the low dose group (P = 0.016) and the high dose group (P = 0.007) had significantly higher proportions than the control groups. Additionally, the Cochran-Armitage test indicated a significant (P = 0.021) positive association between dosage and tumor incidence.

Based upon these results there was an association between the chlorobenzilate concentrations administered and the occurrence of hepatocellular carcinomas in both male and female mice. There are no other neoplasms for which the statistical tests were significant.

The possibility of a negative association between compound administration and incidence was noted for malignant lymphomas in the female mice.

V. DISCUSSION

In both species, adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors.

In all groups of dosed mice, hepatocellular carcinomas occurred at significantly higher incidences than in control groups. A significant positive dose-related trend for tumor incidence was observed in female mice, but in male mice hepatocellular carcinomas appeared in a higher proportion of the low dose group. This departure from a positive linear trend in male mice does not necessarily reduce the significance of these findings.

The association of liver tumors in B6C3F1 mice with oral administration of chlorobenzilate in this bioassay is in agreement with results reported by Innes et al. (1969) for male B6C3F1 and B6AKF1 mice. The Innes study, however, reported the incidence of hepatomas, a general term applied to a broad range of liver tumors. In that study, the proportion of chlorobenzilate-dosed male mice of both strains developing hepatomas approached the proportion found in positive controls; hepatomas were not observed, however, in female mice (Innes et al., 1969).

There was a statistically significant association between administration of chlorobenzilate and the appearance of cortical adenomas of the adrenal gland in low dose male and high dose female rats. Cortical adenomas were observed in 0/46 control males, 6/49 (12 percent) low dose males, 3/49 (6 percent) high dose males, 0/50 control

females, 2/47 (4 percent) low dose females, and 5/47 (11 percent) high dose females. Although the incidence of cortical adenomas in control rats in this bioassay was lower than the incidence in historical controls at the same laboratory (3/160 [2 percent] of male Osborne-Mendel rats and 2/160 [1 percent] of female Osborne-Mendel rats), the incidence in rats dosed with chlorobenzilate was elevated relative to the historical controls.

The lack of clearly observable carcinogenic effects in dosed rats does not appear to be due to inadequate dose levels. Dose-related mean body weight depression was observed during the chronic bioassay in both male and female rats. Compound-related testicular atrophy was observed in male rats.

Under the conditions of this bioassay, orally administered chlorobenzilate was carcinogenic in male and female B6C3F1 mice, causing an increased incidence of hepatocellular carcinomas. The results do not, however, provide sufficient evidence for carcinogenicity of chlorobenzilate in Osborne-Mendel rats.

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Review of the Bioassay of Chlorobenzilate* for Carcinogenicity by the Data Evaluation/Risk Assessment Subgroup of the Clearinghouse on Environmental Carcinogens

June 29, 1978

The Clearinghouse on Environmental Carcinogens was established in May, 1976, in compliance with DHEW Committee Regulations and the Provisions of the Federal Advisory Committee Act. The purpose of the Clearinghouse is to advise the Director of the National Cancer Institute (NCI) on its bioassay program to identify and to evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, State health officials, and quasi-public health and research organizations. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in chemistry, biochemistry, biostatistics, toxicology, pathology, and epidemiology. Representatives of various Governmental agencies participate as ad hoc members. The Data Evaluation/Risk Assessment Subgroup of the Clearinghouse is charged with the responsibility of providing a peer review of reports prepared on NCI-sponsored bioassays of chemicals studied for carcinogenicity. It is in this context that the below critique is given on the bioassay of Chlorobenzilate for carcinogenicity.

The reviewer agreed with the conclusion in the report that Chlorobenzilate was carcinogenic in treated mice. The evidence in treated rats was only "suggestive" of a carcinogenic effect. The reviewer was critical of the high dosages administered, which necessitated the intermittant treatment of the animals, and of the small number of control mice. Despite the shortcomings and the demonstration of a carcinogenic response in only one species, he moved that the report on the bioassay of Chlorobenzilate be accepted as written. The motion was approved without objection.

Clearinghouse Members present:

Arnold L. Brown (Chairman), Mayo Clinic
Paul Nettesheim, National Institute of Environmental Health Sciences
Verne Ray, Pfizer Medical Research Laboratory
Verald K. Rowe, Dow Chemical U.S.A.
Michael B. Shimkin, University of California at San Diego
Louise Strong, University of Texas Health Sciences Center

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* Subsequent to this review, changes may have been made in the bioassay report either as a result of the review or other reasons. Thus, certain comments and criticisms reflected in the review may no longer be appropriate.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH CHLOROBENZILATE

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

	CONTROL (VEH) 01-M001	LOW DOSE 01-M004	HIGH DOSE 01-M005
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	49	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(49)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
HEMANGIOPERICYTOMA, MALIGNANT	1 (2%)		
*SUBCUT TISSUE	(49)	(50)	(50)
CARCINOMA,NOS			1 (2%)
SQUAMOUS CELL CARCINOMA			1 (2%)
FIBROMA	1 (2%)	1 (2%)	4 (8%)
FIBROSARCOMA	1 (2%)	2 (4%)	
LIPOMA			2 (4%)
HEMANGIOSARCOMA	4 (8%)	3 (6%)	
ANGIOSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(49)	(50)	(50)
MIXED TUMOR, MALIGNANT	1 (2%)		
HEMANGIOSARCOMA, METASTATIC	2 (4%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(49)	(50)	(50)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)	1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)	1 (2%)
*SUBCUT TISSUE/GROIN	(49)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
#SPLEEN	(47)	(49)	(49)
HEMANGIOSARCOMA	4 (9%)	2 (4%)	1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	

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

TABLE A1 (CONTINUED)

	CONTROL (VEH) 01-M001	LOW DOSE 01-M004	HIGH DOSE 01-M005
CIRCULATORY SYSTEM			
#HEART	(47)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)		
HEMANGIOSARCOMA, METASTATIC	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(49)	(49)	(49)
NEOPLASTIC NODULE		1 (2%)	1 (2%)
HEMANGIOSARCOMA, METASTATIC	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(47)	(49)	(50)
LIPOMA	2 (4%)		
HEMANGIOSARCOMA	1 (2%)		
HAMARTOMA +		1 (2%)	
#URINARY BLADDER	(46)	(49)	(46)
PAPILLOMA, NOS	3 (7%)		
ENDOCRINE SYSTEM			
#PITUITARY	(41)	(40)	(46)
CHROMOPHOBE ADENOMA	4 (10%)	7 (18%)	4 (9%)
#ADRENAL	(46)	(49)	(49)
CORTICAL ADENOMA		6 (12%)	3 (6%)
PHEOCHROMOCYTOMA		1 (2%)	1 (2%)
#THYROID	(48)	(49)	(49)
FOLLICULAR-CELL ADENOMA	3 (6%)	2 (4%)	4 (8%)
FOLLICULAR-CELL CARCINOMA	4 (8%)	1 (2%)	2 (4%)
C-CELL CARCINOMA		1 (2%)	1 (2%)
#PARATHYROID	(46)	(30)	(31)
ADENOMA, NOS	1 (2%)	1 (3%)	
#PANCREATIC ISLETS	(46)	(49)	(49)
ISLET-CELL ADENOMA	1 (2%)	1 (2%)	1 (2%)

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
\+ THIS IS CONSIDERED TO BE A BENIGN FORM OF THE MALIGNANT MIXED TUMOR OF THE KIDNEY AND CONSISTS OF PROLIFERATIVE LIPOCYTES, TUBULAR STRUCTURES, FIBROBLASTS, AND VASCULAR SPACES IN VARYING PROPORTIONS.

TABLE A1 (CONTINUED)

	CONTROL (VEH) 01-M001	LOW DOSE 01-M004	HIGH DOSE 01-M005
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(49)	(50)	(50)
ADENOCARCINOMA, NOS	2 (4%)		
FIBROADENOMA	1 (2%)	1 (2%)	
#PROSTATE	(34)	(43)	(35)
HEMANGIOSARCOMA, METASTATIC	1 (3%)		
*SEMINAL VESICLE	(49)	(50)	(50)
HEMANGIOSARCOMA, METASTATIC	1 (2%)		
NERVOUS SYSTEM			
#BRAIN	(47)	(50)	(50)
GLIOMA, NOS	1 (2%)		
EPENDYMOMA			1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(49)	(50)	(50)
FIBROSARCOMA	1 (2%)		
*MUSCLE OF THORAX	(49)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)		
BODY CAVITIES			
*MEDIASTINUM	(49)	(50)	(50)
FIBROSARCOMA		1 (2%)	
*ABDOMINAL CAVITY	(49)	(50)	(50)
LIPOMA	1 (2%)		
*TUNICA VAGINALIS	(49)	(50)	(50)
MESOTHELIOMA, NOS			1 (2%)

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

TABLE A1 (CONCLUDED)

	CONTROL (VEH) 01-M001	LOW DOSE 01-M004	HIGH DOSE 01-M005
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(49)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	24	20	15
MORIBUND SACRIFICE	2		1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	24	30	34
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	28	31	23
TOTAL PRIMARY TUMORS	41	39	30
TOTAL ANIMALS WITH BENIGN TUMORS	13	20	14
TOTAL BENIGN TUMORS	17	21	19
TOTAL ANIMALS WITH MALIGNANT TUMORS	18	15	9
TOTAL MALIGNANT TUMORS	24	17	9
TOTAL ANIMALS WITH SECONDARY TUMORS#	2		
TOTAL SECONDARY TUMORS	6		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	2
TOTAL UNCERTAIN TUMORS		1	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE A2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH CHLOROBENZILATE

	CONTROL (VEH) 01-F001	LOW DOSE 01-F006	HIGH DOSE C1-F007
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	50	48	48
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(50)	(49)	(50)
BASAL-CELL CARCINOMA	1 (2%)		
FIBROMA	2 (4%)	2 (4%)	
FIBROSARCOMA		1 (2%)	
LIPOMA	1 (2%)		
HEMANGIOSARCOMA	3 (6%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(48)	(48)
ALVEOLAR/BRONCHIOLAR ADENOMA			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(49)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
#SPLEEN	(50)	(47)	(48)
HEMANGIOSARCOMA		1 (2%)	
#CERVICAL LYMPH NODE	(48)	(46)	(43)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)		
#SMALL INTESTINE	(50)	(48)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
CIRCULATORY SYSTEM			
#ENDOCARDIUM	(50)	(48)	(48)
SARCOMA, NOS		1 (2%)	

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

TABLE A2 (CONTINUED)

	CONTROL (VEH) 01-F001	LOW DOSE 01-F006	HIGH DOSE 01-F007
DIGESTIVE SYSTEM			
#LIVER	(50)	(48)	(48)
NEOPLASTIC NODULE	1 (2%)		
HEPATOCELLULAR CARCINOMA			1 (2%)
#DUODENUM	(50)	(48)	(48)
HEMANGIOSARCOMA	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(50)	(48)	(48)
LIPOMA	1 (2%)		
MIXED TUMOR, MALIGNANT	1 (2%)		
HAMARTOMA +	1 (2%)	1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(45)	(45)
CHROMOPHOBE ADENOMA	15 (30%)	11 (24%)	11 (24%)
#ADRENAL	(50)	(47)	(47)
CORTICAL ADENOMA		2 (4%)	5 (11%)
PHEOCHROMOCYTOMA		2 (4%)	
#THYROID	(50)	(47)	(47)
FOLLICULAR-CELL ADENOMA		2 (4%)	3 (6%)
FOLLICULAR-CELL CARCINOMA	1 (2%)		1 (2%)
C-CELL ADENOMA	5 (10%)	2 (4%)	2 (4%)
C-CELL CARCINOMA		1 (2%)	
#PANCREATIC ISLETS	(50)	(48)	(48)
ISLET-CELL ADENOMA		2 (4%)	1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(49)	(50)
CARCINOMA,NOS		1 (2%)	
ADENOMA, NOS		1 (2%)	1 (2%)
ADENOCARCINOMA, NOS			1 (2%)
FIBROADENOMA	15 (30%)	14 (29%)	16 (32%)
#UTERUS	(49)	(47)	(46)
LEIOMYOMA		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 A2 (CONTINUED)

	CONTROL (VEH) 01-F001	LOW DOSE 01-F006	HIGH DOSE 01-F007
ENDOMETRIAL STROMAL POLYP	4 (8%)	1 (2%)	4 (9%)
#UTERUS/ENDOMETRIUM	(49)	(47)	(46)
ENDOMETRIAL STROMAL POLYP		1 (2%)	
#OVARY	(49)	(48)	(46)
CARCINOMA,NOS	1 (2%)		
PAPILLARY CYSTADENOMA, NOS		1 (2%)	
GRANULOSA-CELL TUMOR	1 (2%)		
OSTEOSARCOMA		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(49)	(50)
LIPOMA			1 (2%)
*ABDOMINAL VISCERA	(50)	(49)	(50)
HEMANGIOSARCOMA	1 (2%)		
ALL OTHER SYSTEMS			
NONE			

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

TABLE A2 (CONCLUDED)

	CONTROL (VEH) 01-F001	LOW DOSE 01-F006	HIGH DOSE C1-F007
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	14	9	11
MORIBUND SACRIFICE		2	2
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			1
TERMINAL SACRIFICE	36	38	36
ANIMAL MISSING		1	
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	36	38	34
TOTAL PRIMARY TUMORS	56	49	51
TOTAL ANIMALS WITH BENIGN TUMORS	31	34	32
TOTAL BENIGN TUMORS	44	43	45
TOTAL ANIMALS WITH MALIGNANT TUMORS	9	6	6
TOTAL MALIGNANT TUMORS	10	6	6
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	2		
TOTAL UNCERTAIN TUMORS	2		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH CHLOROBENZILATE

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

	CONTROL (VEH) 02-M006	LOW DOSE 02-M007	HIGH DOSE 02-M008
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	1		1
ANIMALS NECROPSIED	19	49	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	17	47	45
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(19)	(49)	(48)
FIBROSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(19)	(48)	(44)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (5%)	1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(19)	(49)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	1 (2%)
#SPLEEN	(18)	(47)	(44)
HEMANGIOSARCOMA			1 (2%)
#KIDNEY	(19)	(47)	(45)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (5%)		
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(19)	(48)	(45)
HEPATOCELLULAR CARCINOMA	4 (21%)	32 (67%)	22 (49%)
HEMANGIOMA		1 (2%)	
HEMANGIOSARCOMA, METASTATIC			1 (2%)
URINARY SYSTEM			
NONE			

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

TABLE B1 (CONTINUED)

	CONTROL (VEH) 02-M006	LOW DOSE 02-M007	HIGH DOSE 02-M008
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(19)	(49)	(48)
ADENOMA, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	7	15	6
MORIBUND SACRIFICE		1	
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			2
TERMINAL SACRIFICE	12	34	41
ANIMAL MISSING	1		1

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B1 (CONCLUDED)

	CONTROL (VEH) 02-M006	LOW DOSE 02-M007	HIGH DOSE 02-M008
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	5	34	25
TOTAL PRIMARY TUMORS	6	37	25
TOTAL ANIMALS WITH BENIGN TUMORS	1	3	1
TOTAL BENIGN TUMORS	1	3	1
TOTAL ANIMALS WITH MALIGNANT TUMORS	4	33	24
TOTAL MALIGNANT TUMORS	5	34	24
TOTAL ANIMALS WITH SECONDARY TUMORS#			1
TOTAL SECONDARY TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH CHLOROBENZILATE

	CONTROL (VEH) 02-F006	LOW DOSE 02-F009	HIGH DOSE 02-F010
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	49	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(19)	(49)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (11%)	1 (2%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (5%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		6 (12%)	
MALIGNANT LYMPHOMA, MIXED TYPE	2 (10%)		
#SPLEEN	(20)	(49)	(49)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(49)	(50)
HEPATOCELLULAR CARCINOMA		11 (22%)	13 (26%)
#STOMACH	(19)	(49)	(50)
SQUAMOUS CELL CARCINOMA			1 (2%)
URINARY SYSTEM			
NONE			

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

TABLE B2 (CONTINUED)

	CONTROL (VEH) 02-F006	LOW DOSE 02-F009	HIGH DOSE 02-F010
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
#UTERUS	(20)	(49)	(48)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
ENDOMETRIAL STROMAL POLYP		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@		6	4
MORIBUND SACRIFICE			1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			1
TERMINAL SACRIFICE	20	44	44
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2 (CONCLUDED)

	CONTROL (VEH) 02-F006	LOW DOSE 02-F009	HIGH DOSE 02-F010
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	5	18	15
TOTAL PRIMARY TUMORS	5	22	16
TOTAL ANIMALS WITH BENIGN TUMORS	2	3	2
TOTAL BENIGN TUMORS	2	3	2
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	16	14
TOTAL MALIGNANT TUMORS	3	19	14
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
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 CHLOROBENZILATE

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

	CONTROL (VEH) 01-M001	LOW DOSE 01-M004	HIGH DOSE 01-M005
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	49	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(49)	(50)	(50)
EPIDERMAL INCLUSION CYST	1 (2%)		
INFLAMMATION, CHRONIC		1 (2%)	
*SUBCUT TISSUE	(49)	(50)	(50)
ABSCESS, NOS	1 (2%)		
NECROSIS, FAT			1 (2%)
RESPIRATORY SYSTEM			
#TRACHEA	(4)	(50)	(50)
INFLAMMATION, NOS	4 (100%)		
INFLAMMATION, CHRONIC		6 (12%)	1 (2%)
HYPERPLASIA, LYMPHOID		2 (4%)	
#LUNG/BRONCHIOLE	(49)	(50)	(50)
HYPERPLASIA, LYMPHOID		18 (36%)	6 (12%)
#LUNG	(49)	(50)	(50)
HEMORRHAGE		1 (2%)	
LOBAR PNEUMONIA, NOS			1 (2%)
INFLAMMATION, NOS		2 (4%)	9 (18%)
INFLAMMATION, FOCAL		5 (10%)	7 (14%)
PNEUMONIA, ASPIRATION		1 (2%)	1 (2%)
LOBAR PNEUMONIA NECROTIZING			1 (2%)
ABSCESS, NOS			1 (2%)
PNEUMONIA, CHRONIC MURINE	20 (41%)	12 (24%)	1 (2%)
CALCIFICATION, NOS		1 (2%)	
HYPERPLASIA, ALVEOLAR EPITHELIUM			1 (2%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(47)	(49)	(49)
FIBROSIS	1 (2%)		

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

TABLE C1 (CONTINUED)

	CONTROL (VEH) 01-M001	LOW DOSE 01-M004	HIGH DOSE 01-M005
HEMOSIDEROSIS		3 (6%)	1 (2%)
HYPERPLASIA, LYMPHOID		1 (2%)	
HEMATOPOIESIS	1 (2%)	3 (6%)	1 (2%)
#MESENTERIC L. NODE	(45)	(48)	(47)
CYST, NOS	1 (2%)		
FIBROSIS		1 (2%)	
CIRCULATORY SYSTEM			
#HEART/ATRIUM	(47)	(50)	(50)
EMBOLUS, SEPTIC		1 (2%)	
#HEART/VENTRICLE	(47)	(50)	(50)
THROMBOSIS, NOS			1 (2%)
#MYOCARDIUM	(47)	(50)	(50)
INFLAMMATION, NOS	14 (30%)		
INFLAMMATION, FOCAL		1 (2%)	
INFLAMMATION, INTERSTITIAL		1 (2%)	
INFLAMMATION, HEMORRHAGIC		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
FIBROSIS	1 (2%)	5 (10%)	7 (14%)
FIBROSIS, FOCAL		8 (16%)	
DEGENERATION, NOS		1 (2%)	2 (4%)
CALCIFICATION, FOCAL		1 (2%)	1 (2%)
#ENDOCARDIUM	(47)	(50)	(50)
HYPERPLASIA, NOS		2 (4%)	2 (4%)
*ARTERIOLE	(49)	(50)	(50)
HYPERTROPHY, NOS		1 (2%)	
*AORTA	(49)	(50)	(50)
ARTERIOSCLEROSIS, NOS	4 (8%)		
MEDIAL CALCIFICATION		1 (2%)	
CALCIFICATION, NOS		2 (4%)	
*PULMONARY ARTERY	(49)	(50)	(50)
CALCIFICATION, NOS		5 (10%)	1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(49)	(49)	(49)
CYST, NOS	2 (4%)		

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

TABLE C1 (CONTINUED)

	CONTROL (VEH) 01-M001	LOW DOSE 01-M004	HIGH DOSE C1-M005
HEMORRHAGE			1 (2%)
INFLAMMATION, NOS	3 (6%)		
ABSCESS, NOS		1 (2%)	
NECROSIS, NOS			1 (2%)
NECROSIS, FOCAL			1 (2%)
METAMORPHOSIS FATTY	3 (6%)		
FOCAL CELLULAR CHANGE		2 (4%)	1 (2%)
HYPERPLASIA, NOS	5 (10%)		
ANGIECTASIS		2 (4%)	
#LIVER/CENTRILOBULAR	(49)	(49)	(49)
METAMORPHOSIS FATTY		1 (2%)	
*BILE DUCT	(49)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
HYPERPLASIA, NOS	3 (6%)	13 (26%)	7 (14%)
#PANCREAS	(46)	(49)	(49)
INFLAMMATION, ACUTE		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
PERIARTERITIS	5 (11%)	3 (6%)	2 (4%)
ATROPHY, NOS		4 (8%)	3 (6%)
ATROPHY, FOCAL		5 (10%)	1 (2%)
#ESOPHAGUS	(1)	(40)	(44)
INFLAMMATION, NOS	1 (100%)		
#STOMACH	(46)	(50)	(49)
MINERALIZATION		1 (2%)	
HEMORRHAGE		1 (2%)	2 (4%)
INFLAMMATION, NOS	1 (2%)		
INFLAMMATION, CHRONIC		2 (4%)	
ULCER, CHRONIC		1 (2%)	
CALCIFICATION, NOS		1 (2%)	
HYPERKERATOSIS		2 (4%)	3 (6%)
#GASTRIC MUCOSA	(46)	(50)	(49)
HEMORRHAGE			1 (2%)
CALCIFICATION, NOS			1 (2%)
#LARGE INTESTINE	(46)	(48)	(50)
NEMATODIASIS		5 (10%)	6 (12%)
#COLON	(46)	(48)	(50)
INFLAMMATION, NOS	1 (2%)		

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

TABLE C1 (CONTINUED)

	CONTROL (VEH) 01-M001	LOW DOSE 01-M004	HIGH DOSE 01-M005
URINARY SYSTEM			
#KIDNEY	(47)	(49)	(50)
MINERALIZATION		1 (2%)	
PYELONEPHRITIS, NOS	2 (4%)		2 (4%)
PYONEPHROSIS	1 (2%)		
ABSCESS, NOS	1 (2%)		
INFLAMMATION, CHRONIC	37 (79%)	35 (71%)	34 (68%)
#KIDNEY/CORTEX	(47)	(49)	(50)
ABSCESS, NOS		1 (2%)	
#RENAL PAPILLA	(47)	(49)	(50)
CALCIFICATION, NOS		1 (2%)	
#KIDNEY/PELVIS	(47)	(49)	(50)
CALCIUM DEPOSIT			1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)	
#URINARY BLADDER	(46)	(49)	(46)
INFLAMMATION, NOS	1 (2%)		
INFLAMMATION, HEMORRHAGIC		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(41)	(40)	(46)
CYST, NOS	1 (2%)	3 (8%)	2 (4%)
HYPERPLASIA, FOCAL		1 (3%)	
HYPERPLASIA, CHROMOPHOBE-CELL		1 (3%)	1 (2%)
#ADRENAL	(46)	(49)	(49)
ANGIECTASIS	8 (17%)		1 (2%)
#ADRENAL CORTEX	(46)	(49)	(49)
DEGENERATION, NOS		9 (18%)	10 (20%)
NECROSIS, NOS		1 (2%)	
METAMORPHOSIS FATTY		5 (10%)	
#ADRENAL MEDULLA	(46)	(49)	(49)
HYPERPLASIA, NOS		1 (2%)	
#THYROID	(48)	(49)	(49)
CYST, NOS	1 (2%)		
FOLLICULAR CYST, NOS		6 (12%)	3 (6%)

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

TABLE C1 (CONTINUED)

	CONTROL (VEH) 01-M001	LOW DOSE 01-M004	HIGH DOSE 01-M005
HYPERPLASIA, C-CELL	1 (2%)	8 (16%)	5 (10%)
HYPERPLASIA, FOLLICULAR-CELL	4 (8%)	1 (2%)	
#PARATHYROID	(46)	(30)	(31)
HYPERPLASIA, NOS	2 (4%)	2 (7%)	3 (10%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(49)	(50)	(50)
GALACTOCELE	1 (2%)		
CYST, NOS	1 (2%)	1 (2%)	
#PROSTATE	(34)	(43)	(35)
INFLAMMATION, NOS	9 (26%)		
INFLAMMATION, HEMORRHAGIC		1 (2%)	
INFLAMMATION, ACUTE		6 (14%)	4 (11%)
INFLAMMATION, CHRONIC		6 (14%)	3 (9%)
HYPERPLASIA, FOCAL		1 (2%)	
*SEMINAL VESICLE	(49)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		
#TESTIS	(44)	(49)	(49)
EDEMA, NOS		7 (14%)	8 (16%)
GRANULOMA, SPERMATIC		1 (2%)	
PERIARTERITIS		8 (16%)	17 (35%)
DEGENERATION, NOS		3 (6%)	2 (4%)
ATROPHY, NOS	9 (20%)	26 (53%)	31 (63%)
ATROPHY, FOCAL		5 (10%)	
HYPERPLASIA, INTERSTITIAL CELL		1 (2%)	
*EPIDIDYMIS	(49)	(50)	(50)
NECROSIS, FAT			1 (2%)
*SCROTUM	(49)	(50)	(50)
NECROSIS, FAT			1 (2%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(47)	(50)	(50)
GRANULOMA, NOS		1 (2%)	
#CEREBRUM	(47)	(50)	(50)
MALACIA			1 (2%)

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

TABLE C1 (CONCLUDED)

	CONTROL (VEH) 01-M001	LOW DOSE 01-M004	HIGH DOSE 01-M005
SPECIAL SENSE ORGANS			
*EYE	(49)	(50)	(50)
CATARACT		1 (2%)	
PHTHISIS BULBI	1 (2%)		
*EYE/LACRIMAL GLAND	(49)	(50)	(50)
INFLAMMATION, FOCAL		2 (4%)	
*HARDERIAN GLAND	(49)	(50)	(50)
INFLAMMATION, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(49)	(50)	(50)
DEGENERATION, NOS	1 (2%)		
BODY CAVITIES			
*PLEURA	(49)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)
*PERICARDIUM	(49)	(50)	(50)
INFLAMMATION, NOS	5 (10%)		
INFLAMMATION, CHRONIC NECROTIZIN			1 (2%)
*EPICARDIUM	(49)	(50)	(50)
CALCIFICATION, NOS			1 (2%)
*MESENTERY	(49)	(50)	(50)
INFLAMMATION, ACUTE		1 (2%)	
PERIARTERITIS	2 (4%)	1 (2%)	1 (2%)
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
AUTOLYSIS/NO NECROPSY	1		

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

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

	CONTROL (VEH) 01-F001	LOW DOSE 01-F006	HIGH DOSE 01-F007
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	50	48	48
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(50)
INFLAMMATION, NOS	1 (2%)		
*SUBCUT TISSUE	(50)	(49)	(50)
NECROSIS, FAT			1 (2%)
RESPIRATORY SYSTEM			
#TRACHEA	(5)	(47)	(48)
INFLAMMATION, NOS	5 (100%)		
INFLAMMATION, CHRONIC		3 (6%)	4 (8%)
#LUNG/BRONCHIOLE	(50)	(48)	(48)
HYPERPLASIA, LYMPHOID		12 (25%)	9 (19%)
#LUNG	(50)	(48)	(48)
HEMORRHAGE		1 (2%)	
LOBAR PNEUMONIA, NOS			1 (2%)
INFLAMMATION, NOS		7 (15%)	5 (10%)
INFLAMMATION, FOCAL			11 (23%)
INFLAMMATION, MULTIFOCAL		1 (2%)	4 (8%)
INFLAMMATION, DIFFUSE			1 (2%)
PNEUMONIA, CHRONIC MURINE	15 (30%)	2 (4%)	4 (8%)
#LUNG/ALVEOLI	(50)	(48)	(48)
MINERALIZATION		1 (2%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(50)	(47)	(48)
METAMORPHOSIS FATTY	1 (2%)		
#SPLEEN	(50)	(47)	(48)
HEMORRHAGE			1 (2%)

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

TABLE C2 (CONTINUED)

	CONTROL (VEH) 01-F001	LOW DOSE 01-F006	HIGH DOSE 01-F007
HEMOSIDEROSIS		4 (9%)	
HEMATOPOIESIS	5 (10%)	1 (2%)	2 (4%)
CIRCULATORY SYSTEM			
#MYOCARDIUM	(50)	(48)	(48)
MINERALIZATION		2 (4%)	
FIBROSIS		3 (6%)	1 (2%)
FIBROSIS, FOCAL			3 (6%)
DEGENERATION, NOS	2 (4%)		
#ENDOCARDIUM	(50)	(48)	(48)
HYPERPLASIA, NOS	1 (2%)		1 (2%)
*AORTA	(50)	(49)	(50)
MINERALIZATION		1 (2%)	
ARTERIOSCLEROSIS, NOS	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(50)	(48)	(48)
INFLAMMATION, NOS	4 (8%)		
METAMORPHOSIS FATTY	1 (2%)		
FOCAL CELLULAR CHANGE	1 (2%)		2 (4%)
ANGIECTASIS		1 (2%)	
*BILE DUCT	(50)	(49)	(50)
DILATATION, NOS	1 (2%)		
INFLAMMATION, NOS		1 (2%)	
FIBROSIS		3 (6%)	
HYPERPLASIA, NOS	2 (4%)	9 (18%)	12 (24%)
HYPERPLASIA, CYSTIC			1 (2%)
#PANCREAS	(50)	(48)	(48)
ATROPHY, NOS		2 (4%)	2 (4%)
ATROPHY, FOCAL			1 (2%)
#STOMACH	(50)	(48)	(48)
MINERALIZATION		2 (4%)	
HEMORRHAGE			1 (2%)
ULCER, FOCAL	5 (10%)		
INFLAMMATION, CHRONIC			1 (2%)
CALCIUM DEPOSIT	1 (2%)		
#LARGE INTESTINE	(49)	(48)	(46)
NEMATODIASIS		4 (8%)	3 (7%)
PARASITISM	1 (2%)		

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

TABLE C2 (CONTINUED)

	CONTROL (VEH) 01-F001	LOW DOSE 01-F006	HIGH DOSE 01-F007
URINARY SYSTEM			
#KIDNEY	(50)	(48)	(48)
PYELONEPHRITIS, NOS	1 (2%)		
INFLAMMATION, CHRONIC	23 (46%)	15 (31%)	17 (35%)
#RENAL PAPILLA	(50)	(48)	(48)
CALCIFICATION, NOS		17 (35%)	15 (31%)
HYPERPLASIA, EPITHELIAL		1 (2%)	
ANGIECTASIS		1 (2%)	
METAPLASIA, SQUAMOUS		1 (2%)	
#KIDNEY/PELVIS	(50)	(48)	(48)
INFLAMMATION, NOS			1 (2%)
CALCIFICATION, NOS		1 (2%)	
#URINARY BLADDER	(49)	(46)	(42)
METAPLASIA, SQUAMOUS			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(45)	(45)
COLLOID CYST		3 (7%)	
DEGENERATION, NOS		1 (2%)	
HYPERPLASIA, CHROMOPHOBE-CELL		4 (9%)	
ANGIECTASIS	1 (2%)	1 (2%)	1 (2%)
#ADRENAL	(50)	(47)	(47)
THROMBOSIS, NOS		1 (2%)	
ANGIECTASIS	17 (34%)	14 (30%)	11 (23%)
#ADRENAL CORTEX	(50)	(47)	(47)
DEGENERATION, NOS		7 (15%)	7 (15%)
#ADRENAL MEDULLA	(50)	(47)	(47)
HYPERPLASIA, NOS		1 (2%)	
#THYROID	(50)	(47)	(47)
FOLLICULAR CYST, NOS		3 (6%)	4 (9%)
HYPERPLASIA, C-CELL	2 (4%)	4 (9%)	
HYPERPLASIA, FOLLICULAR-CELL	2 (4%)		
#PARATHYROID	(48)	(24)	(24)
HYPERPLASIA, NOS		1 (4%)	

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

TABLE C2 (CONTINUED)

	CONTROL (VEH) 01-F001	LOW DOSE 01-F006	HIGH DOSE C1-F007
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(49)	(50)
HYPERPLASIA, NOS	1 (2%)		
#UTERUS	(49)	(47)	(46)
HYDROMETRA	9 (18%)	1 (2%)	
INFLAMMATION, NOS	2 (4%)		
#UTERUS/ENDOMETRIUM	(49)	(47)	(46)
CYST, NOS		4 (9%)	6 (13%)
HYPERPLASIA, CYSTIC	3 (6%)		
#OVARY	(49)	(48)	(46)
CYST, NOS	2 (4%)		2 (4%)
NERVOUS SYSTEM			
#MEDULLA OBLONGATA	(50)	(48)	(48)
HEMORRHAGE		2 (4%)	
SPECIAL SENSE ORGANS			
*EYE	(50)	(49)	(50)
SYNECHIA, ANTERIOR		1 (2%)	
CATARACT		1 (2%)	
*EYE/RETINA	(50)	(49)	(50)
ATROPHY, NOS		1 (2%)	
*EYE/CONJUNCTIVA	(50)	(49)	(50)
INFLAMMATION, CHRONIC			1 (2%)
*EYE/LACRIMAL GLAND	(50)	(49)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(49)	(50)
NECROSIS, FAT			1 (2%)

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

TABLE C2 (CONCLUDED)

	CONTROL (VEH) 01-F001	LOW DOSE 01-F006	HIGH DOSE 01-F007
*EPICARDIUM	(50)	(49)	(50)
INFLAMMATION, ACUTE			1 (2%)
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1		
ANIMAL MISSING/NO NECROPSY		1	
NECROPSY PERF/NO HISTO PERFORMED			2
AUTO/NECROPSY/NO HISTO		1	

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

APPENDIX D

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

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

	CONTROL (VEH) 02-M006	LOW DOSE 02-M007	HIGH DOSE 02-M008
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	1		1
ANIMALS NECROPSIED	19	49	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	17	47	45
INTEGUMENTARY SYSTEM			
*SKIN	(19)	(49)	(48)
INFLAMMATION, NOS		2 (4%)	
INFLAMMATION, CHRONIC	3 (16%)		
ACANTHOSIS		2 (4%)	
*SUBCUT TISSUE	(19)	(49)	(48)
ABSCESS, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(19)	(48)	(44)
PNEUMONIA, CHRONIC MURINE	3 (16%)	1 (2%)	2 (5%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(18)	(47)	(44)
AMYLOIDOSIS	5 (28%)		
CIRCULATORY SYSTEM			
#MYOCARDIUM	(19)	(47)	(44)
INFLAMMATION, NOS	1 (5%)		
*AORTA	(19)	(49)	(48)
INFLAMMATION, NOS	1 (5%)		
DIGESTIVE SYSTEM			
#LIVER	(19)	(48)	(45)
THROMBUS, ORGANIZED		1 (2%)	

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

TABLE D1 (CONTINUED)

	CONTROL (VEH) 02-M006	LOW DOSE 02-M007	HIGH DOSE 02-M008
INFLAMMATION, NOS		2 (4%)	2 (4%)
FIBROSIS		1 (2%)	
INFARCT, NOS		1 (2%)	
AMYLOIDOSIS	3 (16%)		
HYPERPLASIA, NODULAR		3 (6%)	2 (4%)
HYPERPLASIA, FOCAL	1 (5%)		
*BILE DUCT	(19)	(49)	(48)
HYPERPLASIA, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(19)	(47)	(45)
PYELONEPHRITIS, NOS		1 (2%)	
INFLAMMATION, CHRONIC	6 (32%)		1 (2%)
#KIDNEY/PELVIS	(19)	(47)	(45)
NECROSIS, NOS	1 (5%)		
#URINARY BLADDER	(15)	(44)	(43)
CALCULUS, NOS		1 (2%)	1 (2%)
INFLAMMATION, NOS		2 (5%)	
ENDOCRINE SYSTEM			
#ADRENAL	(16)	(45)	(44)
AMYLOIDOSIS	2 (13%)		
#THYROID	(15)	(41)	(43)
FOLLICULAR CYST, NOS	1 (7%)		
REPRODUCTIVE SYSTEM			
#PROSTATE	(9)	(28)	(23)
INFLAMMATION, NOS		1 (4%)	
#TESTIS	(16)	(47)	(45)
ATROPHY, NOS			1 (2%)
*EPIDIDYMIS	(19)	(49)	(48)
GRANULOMA, SPERMATIC		1 (2%)	
NECROSIS, FAT	1 (5%)		
NERVOUS SYSTEM			
NONE			

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

TABLE D1 (CONCLUDED)

	CONTROL (VEH) 02-M006	LOW DOSE 02-M007	HIGH DOSE 02-M008
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	5	14
ANIMAL MISSING/NO NECROPSY	1		1
NECROPSY PERF/NO HISTO PERFORMED			1
AUTO/NECROPSY/NO HISTO	2	2	2
AUTOLYSIS/NO NECROPSY		1	1

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

	CONTROL (VEH) 02-F006	LOW DOSE 02-F009	HIGH DOSE 02-F010
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	49	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(19)	(49)	(50)
PNEUMONIA, CHRONIC MURINE		3 (6%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(20)	(49)	(49)
HEMATOPOIESIS		2 (4%)	
#MESENTERIC L. NODE	(18)	(46)	(44)
INFLAMMATION, NOS		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(49)	(50)
THROMBUS, ORGANIZED			1 (2%)
INFLAMMATION, NOS			1 (2%)
PELIOSIS HEPATIS			1 (2%)
INFARCT, NOS		1 (2%)	
METAMORPHOSIS FATTY			1 (2%)
HYPERPLASIA, NODULAR		5 (10%)	4 (8%)
ANGIECTASIS			1 (2%)

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

TABLE D2 (CONTINUED)

	CONTROL (VEH) 02-F006	LOW DOSE 02-F009	HIGH DOSE 02-F010
#PANCREAS	(20)	(48)	(49)
DILATATION/DUCTS		1 (2%)	1 (2%)
INFLAMMATION, NOS		1 (2%)	
#STOMACH	(19)	(49)	(50)
INFLAMMATION, NOS			1 (2%)
HYPERKERATOSIS		1 (2%)	
ACANTHOSIS		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(20)	(49)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
AMYLOIDOSIS		1 (2%)	
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
#UTERUS	(20)	(49)	(48)
HYDROMETRA		5 (10%)	3 (6%)
INFLAMMATION, NOS		8 (16%)	1 (2%)
ABSCESS, NOS	1 (5%)		
#UTERUS/ENDOMETRIUM	(20)	(49)	(48)
INFLAMMATION, SUPPURATIVE	2 (10%)		
HYPERPLASIA, CYSTIC	12 (60%)	5 (10%)	6 (13%)
#OVARY/OVIDUCT	(20)	(49)	(48)
INFLAMMATION, NOS		3 (6%)	
#OVARY	(19)	(48)	(48)
CYST, NOS	2 (11%)	4 (8%)	2 (4%)
FOLLICULAR CYST, NOS	4 (21%)	2 (4%)	
INFLAMMATION, NOS		6 (13%)	
ABSCESS, NOS	2 (11%)		
INFLAMMATION, CHRONIC SUPPURATIV	1 (5%)		
NERVOUS SYSTEM			
NONE			

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

TABLE D2 (CONCLUDED)

	CONTROL (VEH) 02-F006	LOW DOSE 02-F009	HIGH DOSE 02-F010
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(20)	(50)	(50)
CYST, NOS		1 (2%)	
INFLAMMATION, NOS		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	4	6	22
AUTO/NECROPSY/NO HISTO		1	

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

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