National Cancer Institute
CARCINOGENESIS
Technical Report Series
No. 183
1979

BIOASSAY OF DIBUTYLTIN DIACETATE FOR POSSIBLE CARCINOGENICITY

CAS No. 1067-33-0

NCI-CG-TR-183

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

BIOASSAY OF

DIBUTYLTIN DIACETATE

FOR POSSIBLE CARCINOGENICITY

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

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

DHEW Publication No. (NIH) 79-1739

REPORT ON THE BIOASSAY OF DIBUTYLTIN DIACETATE
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 dibutyltin diacetate 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 dibutyltin diacetate was conducted by Litton Bionetics, Inc., Kensington, Maryland, 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. N. P. Page (1,2), Dr. E. K. Weisburger (1) and Dr. J. H. Weisburger (1,3). The principal investigators for the contract were Dr. F. M. Garner (4) and Dr. B. M. Ulland (4,5). Mr. S. Johnson (4) was the coprincipal investigator for the contract. Animal treatment and observation were supervised by Mr. R. Cypher (4), Mr. D. S. Howard (4) and Mr. H. D. Thornett (4); Mr. H. Paulin (4) analyzed dosed feed mixtures. Ms. J. Blalock (4) was responsible for data collection and assembly.

Histopathologic examinations were performed by Dr. N. J. Wosu (4) at Litton Bionetics, Inc., the pathology narratives were written by Dr. N. J. Wosu (4), and the diagnoses included in this report represent the interpretation of this pathologist. Histopathology findings and reports were reviewed by Dr. R. L. Schueler (6).

Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute (7); the statistical analysis was performed by Mr. R. M. Helfand (8) and Dr J. P. Dirkse, III (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 (8) under the direction of the NCI. Those responsible for this report at METREK are the project coordinator, Dr. L. W. Thomas (8), task leader Ms. P. Walker (8), senior biologist Mr. M. Morse (8), biochemist Mr. S. C. Drill (8), chemist Dr. N. Zimmerman (8), and technical editor Ms. P. A. Miller (8). 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. R. A. Griesemer (1), Dr. T. E. Hamm (1), Dr. W. V. Hartwell (1), Dr. M. H. Levitt (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), Dr. A. R. Patel (1), Dr. S. F. Stinson (1), Dr. J. M. Ward (1), and Dr. C. E. Whitmire (1).

---

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

2. Now with the U.S. Environmental Protection Agency, 401 M Street S.W., Washington, D.C.

3. Now with the Naylor Dana Institute for Disease Prevention, American Health Foundation, Hammon House Road, Valhalla, New York.

4. Litton Bionetics, Inc., 5516 Nicholson Lane, Kensington, Maryland.

5. Now with Hazleton Laboratories America, Inc., 9200 Leesburg Turnpike, Vienna, Virginia.

6. Tracor Jitco, Inc., 1776 East Jefferson Street, Rockville, Maryland.

7. EG&G Mason Research Institute, 1530 East Jefferson Street, Rockville, Maryland.

8. The MITRE Corporation, METREK Division, 1820 Dolley Madison Boulevard, McLean, Virginia.

9. Consultant to The MITRE Corporation, currently a professor in the Department of Statistics at The George Washington University, 2100 Eye Street, N.W., Washington, D.C.

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

SUMMARY

A bioassay for the possible carcinogenicity of dibutyltin diacetate was conducted using Fischer 344 rats and B6C3F1 mice. Dibutyltin diacetate was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. Twenty animals of each sex and species were placed on test as controls. The high and low time-weighted average dietary concentrations of dibutyltin diacetate were, respectively, 133 and 66.5 ppm for rats and 152 and 76 ppm for mice. The compound was administered for 78 weeks to rats and mice, followed by a period of no compound administration of 26 weeks for rats and 14 weeks for mice.

There were significant positive associations between the concentrations of dibutyltin diacetate administered and mortality in male rats and female mice. There were no significant positive associations between the concentrations administered and mortality in female rats or male mice. Adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. Mean body weight depression, relative to controls, was observed in male mice and significantly accelerated mortality, relative to controls, was observed in male rats and female mice, indicating that the concentrations of dibutyltin diacetate administered to these animals may have approximated the maximum tolerated concentration. Since no mean body weight depression, no significantly accelerated mortality, and no other signs of toxicity were associated with administration of dibutyltin diacetate to female rats, it is possible that these animals may have been able to tolerate a higher dietary concentration.

There were no neoplasms occurring in statistically significant higher incidences in dosed rats or mice when compared to their respective controls. However, there was an accidental loss of tissues from high dose female rats which precluded an evaluation of carcinogenicity in this group of animals. There was a significant positive association between the concentrations administered and the incidences of hepatocellular adenomas in female mice; however, the Fisher exact comparisons were not significant using the Bonferroni criterion. Liver neoplasms (i.e., a combination of adenomas and carcinomas) were also observed in male mice; however, the occurrence was not statistically significant.

Under the conditions of this bioassay, there was no conclusive evidence for the carcinogenicity of dibutyltin diacetate in male Fischer 344 rats or B6C3F1 mice of either sex. The loss of tissues taken from high dose female rats in this bioassay precluded an evaluation of the carcinogenicity of dibutyltin diacetate to female Fischer 344 rats.

TABLE OF CONTENTS

LIST OF ILLUSTRATIONS

LIST OF TABLES

LIST OF TABLES (Concluded)

I. INTRODUCTION

Dibutyltin diacetate (Figure 1) (NCI No. CO2028), a widely used catalyst for polymerization reactions, was selected for bioassay by the National Cancer Institute in an effort to screen a number of organo-metallic compounds for carcinogenicity.

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is bis(acetyloxy)dibutylstannae.* It is also called diacetoxydibutylstannae, diacetoxybutyltin, and dibutyl tin diacetate.

Dibutyltin diacetate is used as a catalyst for a wide variety of polymerization reactions (Benkeser and Gilman, 1952; Hawley, 1977). It is also used as a stabilizer for chlorinated organic compounds, such as polyvinyl chloride (Benkeser and Gilman, 1952; Hawley, 1977).

Specific production data for dibutyltin diacetate are not available; however, this compound is produced in commercial quantities (in excess of 1000 pounds or $1000 in value annually) by three U.S. companies (Stanford Research Institute, 1977).

The potential for exposure to dibutyltin diacetate is greatest for workers in the chemical and polymer manufacturing industries.

*The CAS registry number is 1067-33-0.

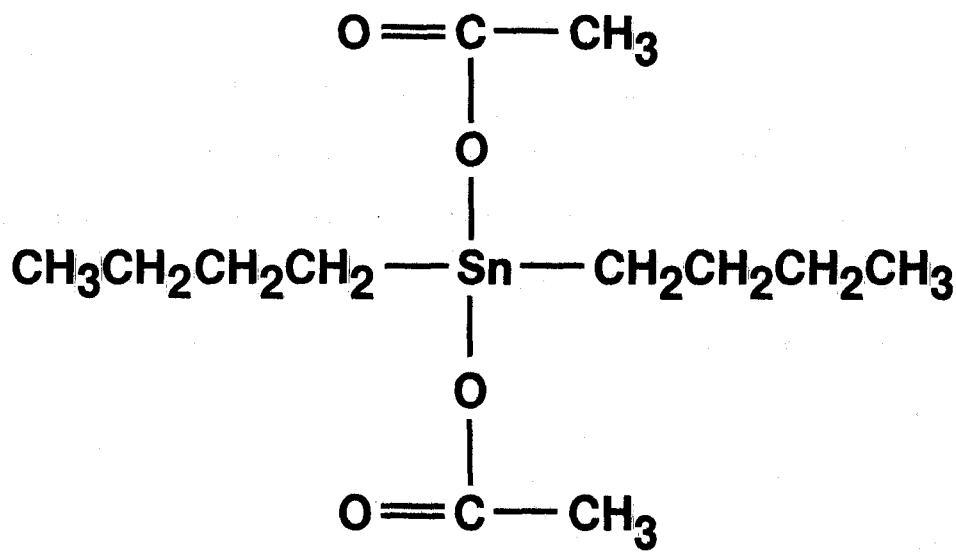


FIGURE 1
CHEMICAL STRUCTURE OF DIBUTYLTIN DIACETATE

II. MATERIALS AND METHODS

A. Chemicals

A commercially available grade of dibutyltin diacetate was purchased from Cincinnati Milacron Chemicals, Inc., Reading, Ohio. Chemical analysis was performed by Litton Bionetics, Inc., Kensington, Maryland. Thin-layer chromatography was performed utilizing two solvent systems (i.e., n-butanol:acetic acid and dioxane:benzene:acetic acid). Each plate, visualized with visible and ultraviolet light, iodine vapor, 0.01 percent dithizone in $CHCl_3$, saturated diphenyl carbazone in ethanol, and 25 percent ammonium hydroxide, revealed only one spot. The results of infrared and nuclear magnetic resonance analyses were consistent with those reported in the literature for dibutyltin diacetate (Sadtler Standard Spectra).

Throughout this report, the term dibutyltin diacetate is used to represent this 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). Dibutyltin diacetate was administered to the dosed animals as a component of the diet.

An aliquot of the test chemical was blended with a small amount of the feed using a mortar and pestle. Once visual homogeneity was attained, the mixture was placed in a 6 kg capacity Patterson-Kelley

standard model twin-shell stainless steel V-blender along with the remainder of the feed to be prepared. After 20 minutes of blending, the mixtures were placed in double plastic bags and stored in the dark at 4°C. The mixture was prepared once weekly.

Dosed feed preparations containing 100 and 250 ppm of dibutyltin diacetate were analyzed spectrophotometrically. The mean result on the day of preparation was 113 percent of theoretical (ranging from 104 to 129 percent). After 10 days at ambient room temperature, the mean result was 97 percent of theoretical (ranging from 92 to 102 percent).

C. Animals

The two animal species, Fischer 344 rats and B6C3F1 mice, used in the carcinogenicity bioassay were obtained through contracts of the Division of Cancer Treatment, National Cancer Institute. Rats were supplied by Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts, and Laboratory Supply Company, Inc., Indianapolis, Indiana. Mice were supplied by Charles River Breeding Laboratories, Inc.

Rats and mice, approximately 4 weeks old when received, were examined and any obviously ill or runted animals were killed. The remaining animals were quarantined for 2 weeks prior to initiation of test. Animals which did not manifest clinical signs of disease were placed on test at this time. Animals were assigned to groups

and distributed among cages so that the average body weight per cage was approximately equal for a given species and sex.

D. Animal Maintenance

Animals were housed by species in rooms maintained at 22° to 26°C and 45 to 55 percent relative humidity. Incoming outside air was filtered through HEPA filters (Flanders Filters, McLean, Virginia) at a rate of 12 to 15 complete changes of room air per hour. Fluorescent lighting was provided 8 hours per day (9:00 a.m. to 5:00 p.m.).

Rats were housed four per cage by sex and mice were housed five per cage by sex. Throughout the study dosed and control animals of both species were housed in polycarbonate cages (Lab Products, Inc., Garfield, New Jersey) suspended from aluminum racks. Racks were fitted with a continuous piece of stainless steel mesh over which a sheet of filter paper was firmly secured. Filter paper was changed at 2-week intervals, when the racks were sanitized. Clean cages and hardwood chip bedding (Ab-sorb-dri®, Wilner Wood Products Company, Norway, Maine) were provided twice weekly.

Acidulated water (pH 2.5) was supplied to animals in water bottles which were changed and washed twice weekly. Sipper tubes were washed at weekly intervals. During the period of chemical administration, dosed and control animals received treated or untreated Wayne Lab-Blox® meal as appropriate. The feed was supplied in hanging stainless steel hoppers which were refilled three times per week

and sanitized weekly. Food and water were available ad libitum for both species.

All dosed and control rats were housed in a room with other rats receiving diets containing* 1-phenyl-2-thiourea (103-85-5); amitrole (61-82-5); zinc acetate (557-34-6); and copper acetate (4180-12-5).

All dosed and control mice were housed in a room with mice receiving diets containing Michler's ketone (90-94-8); 4,4'-methylene-bis(N,N-dimethyl)benzenamine (101-61-1); p-chloroaniline (106-47-8); 5-chloro-o-toluidine (95-79-4); N-phenyl-p-phenylenediamine hydrochloride (2198-59-6); 1-phenyl-2-thiourea (103-85-5); trimethylthiourea (2489-77-2); 2-nitro-p-phenylenediamine (5307-14-2); and 3-chloro-p-toluidine (95-74-9).

E. Selection of Initial Concentrations

To establish the concentrations of dibutyltin diacetate for administration to dosed animals in the chronic studies, subchronic toxicity tests were conducted with both rats and mice. Rats were distributed among six groups, each consisting of five males and five females. Dibutyltin diacetate was incorporated into the basal laboratory diet and supplied ad libitum to five of the six rat groups in concentrations of 70, 100, 145, 215 and 315 ppm. The remaining rat group served as a control group, receiving only the basal laboratory diet.

*CAS registry numbers are given in parentheses.

Mice were distributed among ten groups, each consisting of five males and five females. Dibutyltin diacetate was incorporated into the basal laboratory diet and supplied ad libitum to eight of the ten mouse groups in concentrations of 17, 25, 37, 55, 80, 255, 375 and 650 ppm. The two remaining mouse groups served as control groups, receiving only the basal laboratory diet.

The dosed dietary preparations were administered for a period of 4 weeks, followed by a 2-week observation period during which all animals were fed the basal laboratory diet. Individual body weights were recorded twice weekly throughout the study. Upon termination of the study all survivors were sacrificed and necropsied.

The following table indicates the mean body weight gain, relative to controls, and survival observed in each of the rat groups at the end of the subchronic test.

RAT SUBCHRONIC STUDY RESULTS

	Mean Body Weight Gain (%)*		Survival**	
ppm	Males	Females	Males	Females
315	-74	-30	5/5	5/5
215	- 2	-14	5/5	5/5
145	- 9	- 6	5/5	5/5
100	-32	- 4	5/5	5/5
70	+ 8	+ 1	5/5	5/5
0	--	--	5/5	5/5

*+ is indicative of mean body weight gain greater than that of controls.
- is indicative of mean body weight gain less than that of controls.

**Number of animals observed/number of animals originally in group.

No other clinical abnormalities attributed to administration of the compound were observed. The high concentration selected for administration to dosed male and female rats in the chronic bioassay was 250 ppm.

The following table indicates the mean body weight gain, relative to controls, survival and incidence of rough hair and arched backs observed in each of the mouse groups at the end of the subchronic test.

MOUSE SUBCHRONIC STUDY RESULTS

	Mean Body Weight Gain (%)*		Survival**		Observation of Rough Hair and Arched Backs**	
ppm	Males	Females	Males	Females	Males	Females
650	-10	+12	5/5	5/5	5/5	5/5
375	- 8	+ 1	5/5	5/5	5/5	5/5
255	- 1	+ 6	5/5	5/5	0/5	0/5
80	+ 4	- 6	5/5	5/5	0/5	0/5
55	- 3	0	5/5	5/5	0/5	0/5
37	0	- 7	5/5	5/5	0/5	0/5
25	+ 3	-10	5/5	5/5	0/5	0/5
17	+ 3	-14	5/5	5/5	0/5	0/5
0	--	--	5/5	5/5	0/5	0/5

The high concentration selected for administration to dosed mice in the chronic bioasay was 200 ppm.

F. Experimental Design

The experimental design parameters for the chronic study (species, sex, group size, concentrations administered, and duration of

*+ is indicative of mean body weight gain greater than that of controls.
- is indicative of mean body weight gain less than that of controls.

**Number of animals observed/number of animals originally in group.

treated and untreated observation periods) are summarized in Tables 1 and 2.

All rats were approximately 6 weeks old at the time the test was initiated and were placed on test on the same day. The dietary concentrations of dibutyltin diacetate initially administered to rats were 250 and 125 ppm. Throughout this report those rats initially receiving the former concentration are referred to as the high dose groups and those initially receiving the latter concentration are referred to as the low dose groups. In week 6 the high and low concentrations of dibutyltin diacetate administered to rats were decreased to 125 and 62.5 ppm, respectively, and these dosages were maintained for the remainder of the dosing period. Dosed rats were supplied with feed containing dibutyltin diacetate for 78 weeks followed by a 26-week observation period.

All mice were approximately 6 weeks old at the time the test was initiated and were placed on test on the same day. The dietary concentrations of dibutyltin diacetate initially administered to mice were 200 and 100 ppm. Throughout this report those mice initially receiving the former concentration are referred to as the high dose groups and those initially receiving the latter concentration are referred to as the low dose groups. In week 4 the high and low doses were changed to 150 and 75 ppm, respectively, and these dosages were maintained for the remainder of the dosing period. Dosed mice were

TABLE 1

DESIGN SUMMARY FOR FISCHER 344 RATS
DIBUTYLTIN DIACETATE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	DIBUTYLTIN DIACETATE CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE CONCENTRATION[b]
MALE					
CONTROL	20	0	0	104	
LOW DOSE	50	125	5		66.5
		62.5	73		
		0		26	
HIGH DOSE	50	250	5		133
		125	73		
		0		26	
FEMALE					
CONTROL	20[c]	0	0	104	
LOW DOSE	50	125	5		66.5
		62.5	73		
		0		26	
HIGH DOSE	50	250	5		133
		125	73		
		0		26	

[a]Concentrations given in parts per million.

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

[c]One of these animals was determined to be a male subsequent to test initiation.

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
DIBUTYLTIN DIACETATE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	DIBUTYLTIN DIACETATE CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE CONCENTRATION[b]
MALE					
CONTROL	20	0	0	92	
LOW DOSE	50	100	3		76
		75	75		
		0		14	
HIGH DOSE	50	200	3		152
		150	75		
		0		14	
FEMALE					
CONTROL	20	0	0	92	
LOW DOSE	50	100	3		76
		75	75		
		0		14	
HIGH DOSE	50	200	3		152
		150	75		
		0		14	

[a]Concentrations given in parts per million.

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

supplied with feed containing dibutyltin diacetate for 78 weeks followed by a 14-week observation period.

G. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment and body weights were recorded once a week for the first 6 weeks, every 2 weeks for the next 12 weeks, and at monthly intervals thereafter. All animals were inspected twice daily. Food consumption data were collected at monthly intervals from 20 percent of the animals in each group.

All moribund animals or animals that developed large, palpable masses that jeopardized their health were killed. A necropsy was performed on each animal regardless of whether it died, was killed when moribund, or was killed at the end of the bioassay. The animals were euthanized using carbon dioxide, and were immediately necropsied. Gross and microscopic examinations were performed on all major tissues, organs, and gross lesions taken from killed animals and, whenever possible, from animals found dead.

Tissues were preserved in a 10 percent neutral buffered formalin solution, embedded in paraffin, sectioned, and stained with hematoxylin and eosin prior to microscopic examination.

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, brain, 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 recorded in each group at the time that the test was initiated.

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 apparent in male rats throughout the bioassay. The mean body weight among high dose female rats was depressed, in relation to controls, throughout most of the bioassay (Figure 2).

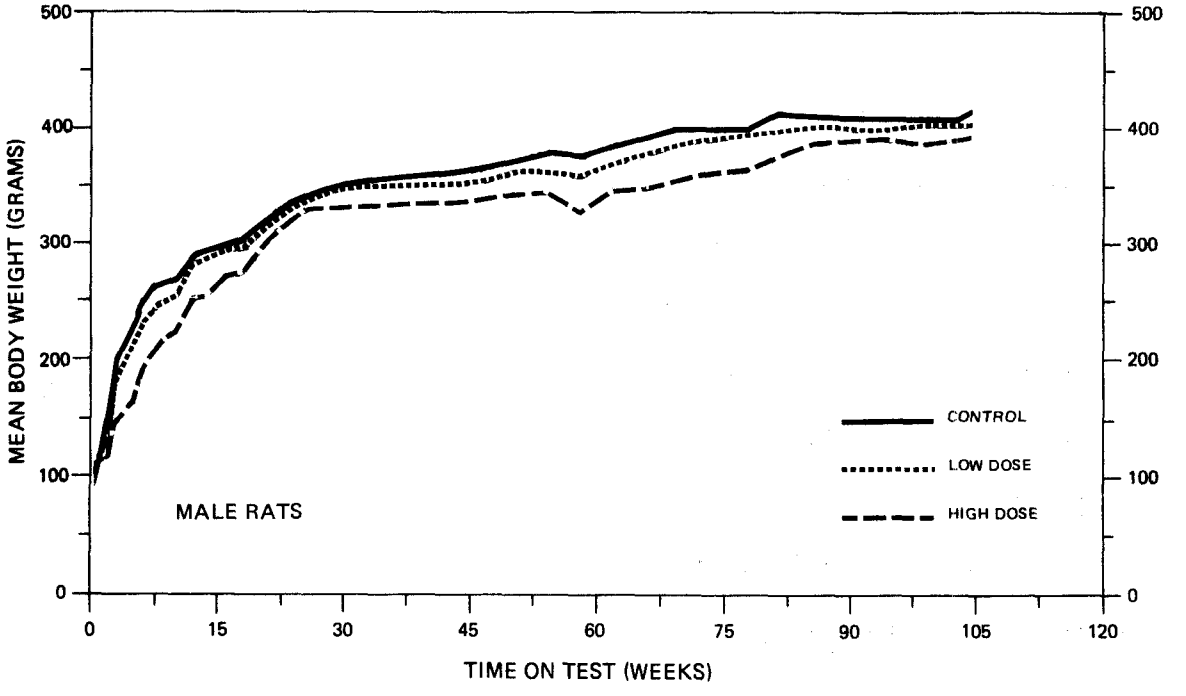
No other clinical signs were recorded.

B. Survival

The estimated probabilities of survival for male and female rats in the control and dibutyltin diacetate-dosed groups are shown in Figure 3. The Tarone test for association between dosage and mortality was significant for males ($P < 0.001$) but not for females.

There were adequate numbers of male rats at risk from late-developing tumors as 52 percent (26/50) of the high dose, 78 percent (39/50) of the low dose, and 85 percent (17/20) of the controls survived on test until the termination of the study.

For females, with 64 percent (32/50) of the high dose, 84 percent (42/50) of the low dose, and 74 percent (14/19) of the controls surviving on test until the termination of the study, there were adequate numbers at risk from late-developing tumors. However, the majority of the tissues taken from 17 of the 50 high dose females were lost at necropsy.



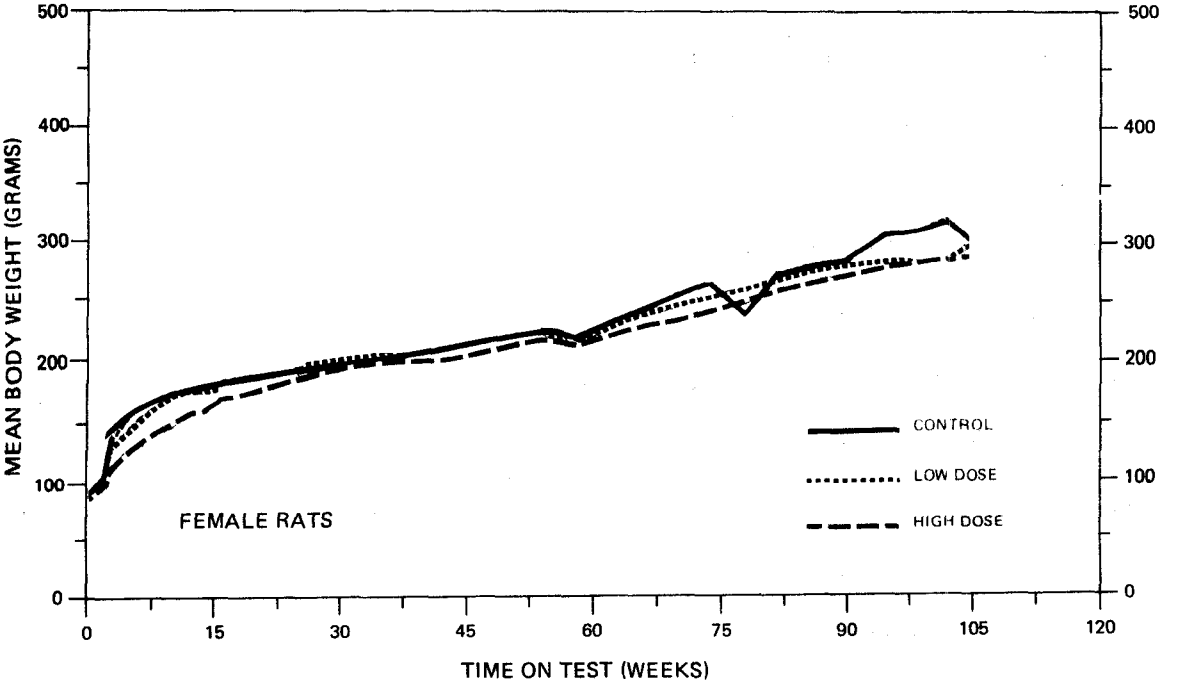
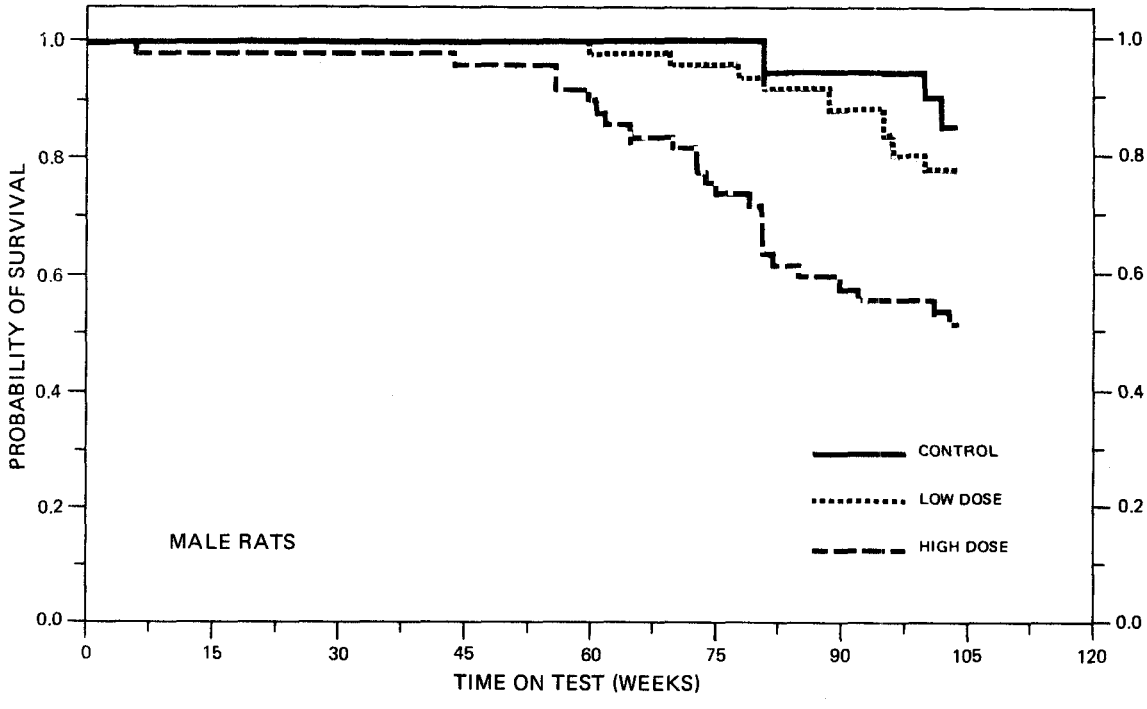


FIGURE 2
GROWTH CURVES FOR DIBUTYLTIN DIACETATE CHRONIC STUDY RATS



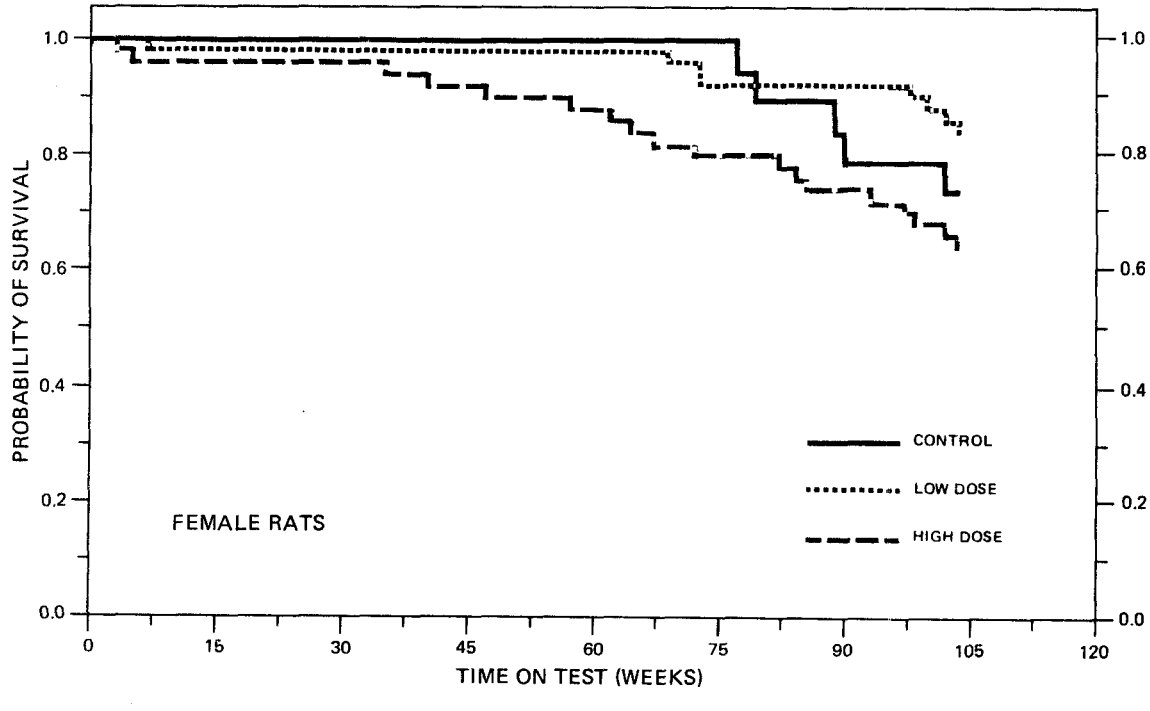


FIGURE 3
SURVIVAL COMPARISONS OF DIBUTYLTIN DIACETATE CHRONIC STUDY RATS

C. Pathology

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

With the exception of the neoplasms of the testis, pituitary glands (both predictably high for this age and strain of rats) and of the uterus, tumor incidence was generally low and the distribution was similar to controls. Histologically proven neoplasms of the uterus appeared to be almost exclusive to the low dose group as indicated below:

UTERUS	Control	Low Dose	High Dose
Number of Animals with Tissues Examined Histopathologically	(19)	(49)	(33)
Adenocarcinoma NOS	0	3(6%)	0
Leiomyoma	0	1(2%)	0
Endometrial Stromal Polyp	0	6(12%)	2(6%)
Hemangioma	1(5%)	0	0

However, the low incidence of these neoplasms among high dose females may be misleading, as the tissues taken from 17 of the 50 high dose females were lost due to an error in processing at necropsy. Uterine tumors were recorded for 5 of the 17 high dose females on the basis of gross observation.

Of the tumors examined microscopically, most were endometrial stromal polyps. These were variable in size and each projected into

and occluded the lumen of the uterus. In a low dose rat a uterine leiomyoma was recognized. It was small and well-delineated from the rest of the myometrium and comprised of slightly pleomorphic spindle cells with cytoplasm which stained more eosinophilic than the surrounding stroma and cells. In the same animal other areas of the uterus were thrown into multiple polypoid projections within which were numerous inflamed and variably dilated endometrial glands containing degenerative neutrophils or erythrocytes.

The adenocarcinomas included a well-differentiated papillary type, a well-differentiated glandular form and a massive and destructive tumor with a scirrhous anaplastic pattern. The latter extended through the myometrium to the serosa as markedly irregular and haphazardly arranged acini and cords of atypical epithelial cells. In addition to eliciting intense desmoplasia, it contained several confluent random foci of necrosis and suppurative inflammation. Vascular destruction resulted in formation of large blood-filled cysts. Pulmonary metastasis was also present.

The nonneoplastic changes of the uterus included endometrial, glandular, cystic or polypoid hyperplasia, suppurative inflammation and combinations thereof, and was observed mostly among low dose rats, much less frequently among high dose rats and in none of the controls.

Bile duct calculi were observed only in dosed male and female rats.

The carcinogenicity of dibutyltin diacetate was not clearly defined by the pathology results obtained in this study. The evidence suggests that the compound may induce inflammatory, hyperplastic and neoplastic changes of the uterus in female Fischer 344 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 is included for every type of malignant tumor in either sex where at least two such tumors were observed in at least one of the control or dibutyltin diacetate-dosed groups and where such tumors were observed in at least 5 percent of the group. Due to the number of early deaths observed among high dose female rats, the analyses for females have been based solely upon those females surviving at least 52 weeks, or in the event that the tumor of interest was observed earlier, at least as long as the time at which the first tumor of interest was observed.

None of the statistical tests for any site in rats of either sex indicated a significant positive association between chemical administration and tumor incidence. It should be noted, however, that the majority of the tissues taken from 17 of the 50 high dose female rats were lost before microscopic examination and as a result were not available for inclusion in the statistical analysis.

In male rats the Cochran-Armitage test and the departure from linear trend test indicated the possibility of a negative association

TABLE 3

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibroma[b]	2/20(0.10)	0/50(0.00)	0/50(0.00)
P Values[c]	P = 0.024(N)	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.042	---	---
Relative Risk (Control)[d]	---	0.000	0.000
Lower Limit	---	0.000	0.000
Upper Limit	---	1.345	1.345
Weeks to First Observed Tumor	104	---	---
Pituitary: Chromophobe Adenoma[b]	1/19(0.05)	2/38(0.05)	2/40(0.05)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.000	0.950
Lower Limit	---	0.057	0.054
Upper Limit	---	57.431	54.640
Weeks to First Observed Tumor	81	104	104
Adrenal: Pheochromocytoma[b]	2/20(0.10)	7/41(0.17)	1/47(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.707	0.213
Lower Limit	---	0.371	0.004
Upper Limit	---	15.887	3.909
Weeks to First Observed Tumor	100	81	104

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Pancreatic Islets: Islet-Cell Adenoma[b]	0/19(0.00)	2/40(0.05)	0/49(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.146	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	104	---
Testis: Interstitial-Cell Tumor[b]	20/20(1.00)	32/41(0.78)	28/50(0.56)
P Values[c]	P < 0.001(N)	P = 0.020(N)	P < 0.001(N)
Relative Risk (Control)[d]	---	0.780	0.560
Lower Limit	---	0.000	0.000
Upper Limit	---	1.818	---
Weeks to First Observed Tumor	81	89	75
Brain: Glioma NOS or Meningioma[b]	0/20(0.00)	4/41(0.10)	0/50(0.00)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.011	---	---
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.471	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	78	---

TABLE 3 (CONCLUDED)

[a]Treated groups received time-weighted average doses of 66.5 or 133 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 $P < 0.05$; 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 $P < 0.05$; 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 $P < 0.05$.

TABLE 4

TIME-ADJUSTED ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE RATS TREATED WITH DIBUTYLTIN DIACETATE[a,e]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Pituitary: Chromophobe Adenoma[b]	9/18(0.50)	12/42(0.29)	9/25(0.36)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.571	0.720
Lower Limit	---	0.290	0.335
Upper Limit	---	1.291	1.643
Weeks to First Observed Tumor	102	98	84
Mammary Gland: Fibroadenoma[b]	2/19(0.11)	2/49(0.04)	1/45(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.388	0.211
Lower Limit	---	0.031	0.004
Upper Limit	---	5.108	3.870
Weeks to First Observed Tumor	102	104	104
Uterus: Adenocarcinoma NOS[b]	0/19(0.00)	3/49(0.06)	0/28(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.243	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	104	---

TABLE 4 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Uterus and Cervix Uteri: Endometrial Stromal Polyp[b]	0/19(0.00)	7/49(0.14)	2/28(0.07)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.787	0.209
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	69	98

[a]Treated groups received time-weighted average doses of 66.5 or 133 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 $P < 0.05$; 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 $P < 0.05$; 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]These analyses were based solely upon animals surviving at least 52 weeks.

between dose and the incidence of fibromas of the subcutaneous tissue. Both the Cochran-Armitage and Fisher exact tests indicated a significant negative association between dose and the incidence of interstitial-cell tumors of the testis.

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 dibutyltin diacetate that could not be established under the conditions of this test.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

No dose-related mean body weight depression was apparent in male mice although the high dose males did weigh less than the controls throughout the bioassay. In female mice slight dose-related mean body weight depression was observed after week 60 (Figure 4). 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.

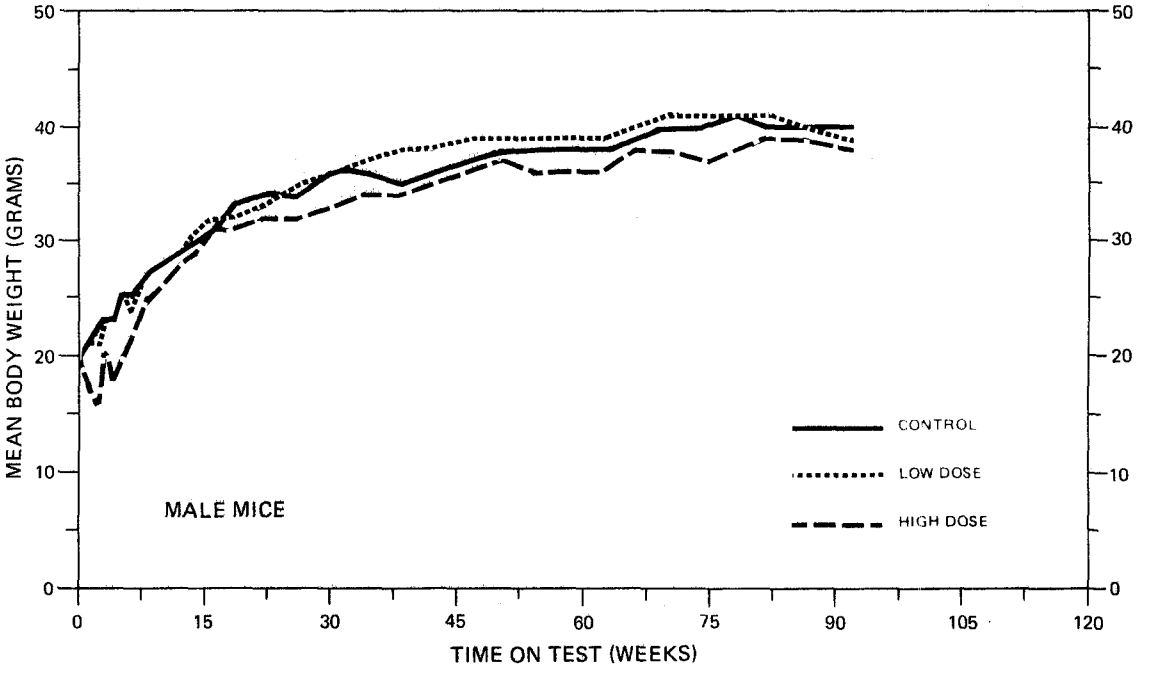
No other clinical signs were recorded.

B. Survival

The estimated probabilities of survival for male and female mice in the control and dibutyltin diacetate-dosed groups are shown in Figure 5. The Tarone test for association between dosage and mortality was significant for female mice ($P < 0.001$) but not for male mice.

There were adequate numbers of male mice at risk from late-developing tumors, as 86 percent (43/50) of the high dose, 96 percent (48/50) of the low dose and 95 percent (19/20) of the controls survived on test until the termination of the study. One high dose male was missing in week 32.

Although one high dose female was missing in week 47, there were adequate numbers of female mice at risk from late-developing tumors.



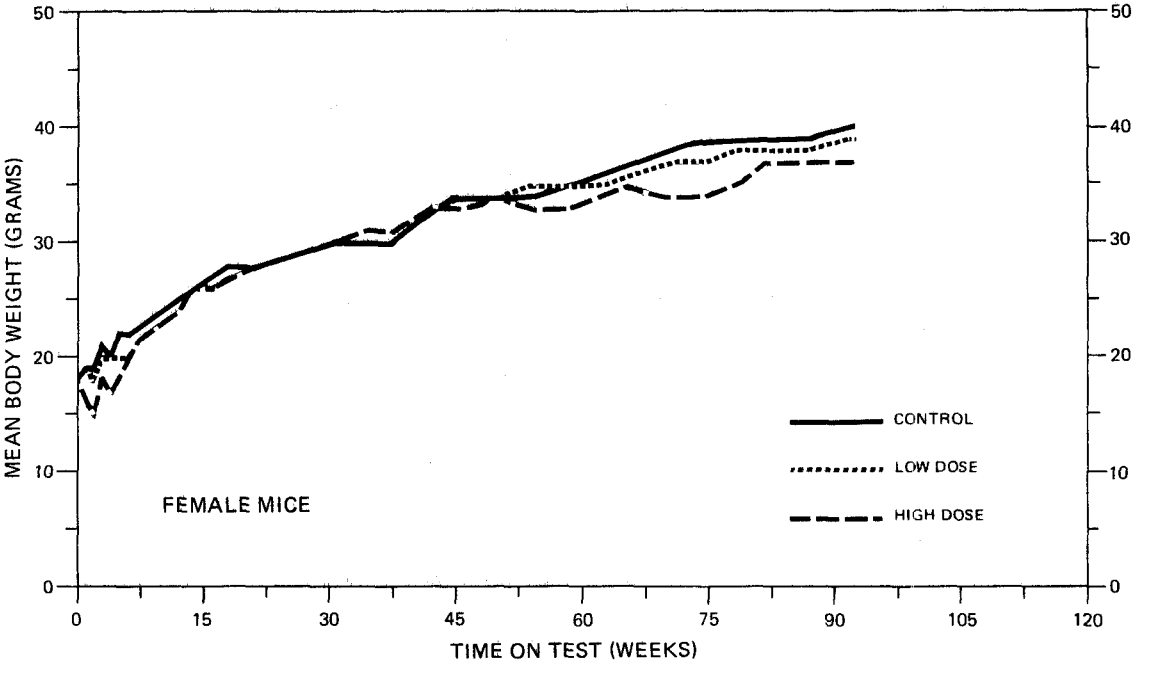
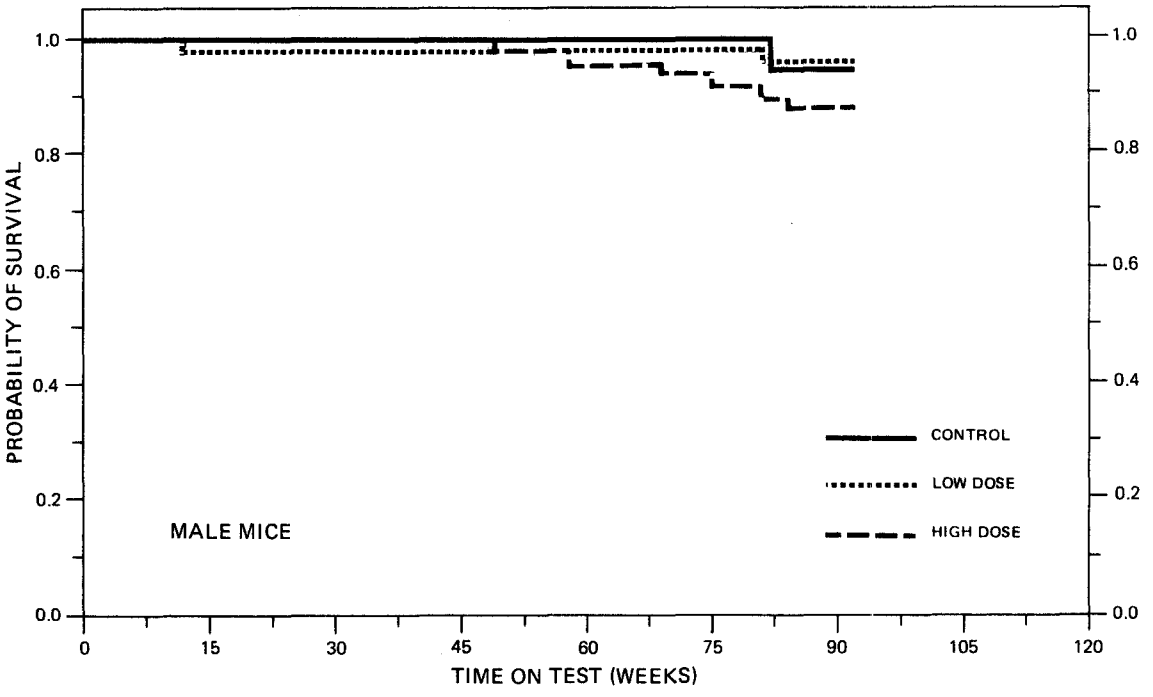


FIGURE 4
GROWTH CURVES FOR DIBUTYLTIN DIACETATE CHRONIC STUDY MICE



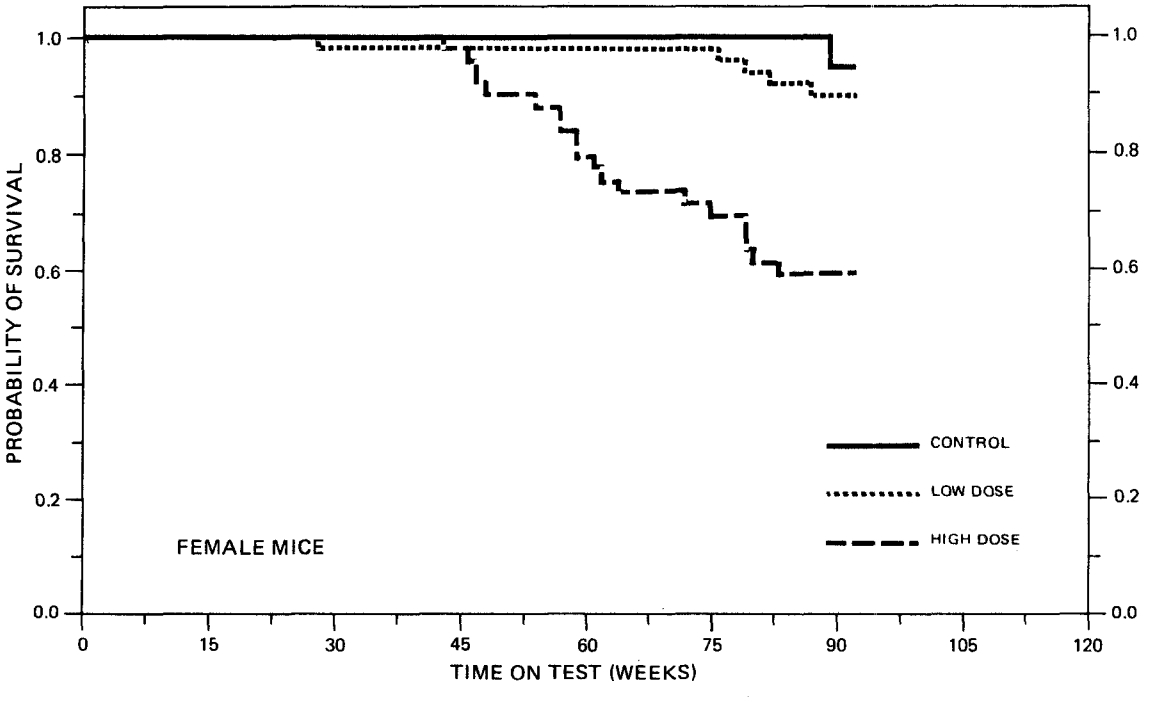


FIGURE 5
SURVIVAL COMPARISONS OF DIBUTYLTIN DIACETATE CHRONIC STUDY MICE

Fifty-eight percent (29/50) of the high dose, 90 percent (45/50) of the low dose and 95 percent (19/20) of the controls survived on test until the termination of the study.

C. Pathology

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

There was an increased incidence of hepatic neoplasms in high dose mice when compared to controls. Among males the incidence of hepatocellular adenomas was 2/19 (11 percent) in controls, 9/49 (18 percent) in the low dose and 13/49 (27 percent) in the high dose. Four hepatocellular carcinomas were observed, two in low dose males and two in high dose males. Each of these metastasized to the lung except for one in the high dose group. In females all hepatic tumors were adenomas, and occurred in 1/20 (5 percent) controls, 4/48 (8 percent) low dose and 12/47 (26 percent) high dose mice. The occurrence of neoplasms in other organs was not attributed to the administration of dibutyltin diacetate.

Inflammatory and hyperplastic lesions occurred randomly and involved multiple organs from all groups with the same incidence and severity expected for this age of B6C3F1 mice. However, degenerative and necrotizing changes especially of the liver were by far more frequent in the high dose animals, much fewer in low dose animals and absent from controls.

Based on this pathology examination, increased incidences of hepatocellular adenomas in dosed female and male B6C3F1 mice appeared to be associated with compound administration, under the conditions of this bioassay.

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 is included for every type of malignant tumor in either sex where at least two such tumors were observed in at least one of the control or dibutyltin diacetate-dosed groups and where such tumors were observed in at least 5 percent of the group. Due to the number of early deaths observed among high dose female mice, the analyses for female mice have been based solely on those females surviving at least 52 weeks, or in the event that the tumor of interest was observed earlier, at least as long as the time at which the first tumor of interest was observed.

In female mice the Cochran-Armitage test indicated a significant ($P = 0.006$) positive association between dosage and the incidence of hepatocellular adenomas (i.e., 5 percent [1/20] in the control, 9 percent [4/47] in the low dose, and 28 percent [12/43] in the high dose group). However, the Fisher exact test comparing high dose to control had a probability level of $P = 0.033$, a marginal result which was not significant under the Bonferroni criterion.

TABLE 5

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Carcinoma[b]	1/19(0.05)	5/49(0.10)	2/48(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.939	0.792
Lower Limit	---	0.243	0.045
Upper Limit	---	89.722	45.751
Weeks to First Observed Tumor	92	92	69
Lung: Alveolar/Bronchiolar Carcinoma or Alveolar/Bronchiolar Adenoma[b]	2/19(0.11)	8/49(0.16)	2/48(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.551	0.396
Lower Limit	---	0.355	0.031
Upper Limit	---	14.223	5.211
Weeks to First Observed Tumor	92	92	69
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	1/20(0.05)	3/50(0.06)	0/49(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.200	0.000
Lower Limit	---	0.106	0.000
Upper Limit	---	61.724	7.624
Weeks to First Observed Tumor	92	81	---

TABLE 5 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma or Hepatocellular Adenoma[b]	2/19(0.11)	11/49(0.22)	15/49(0.31)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.133	2.908
Lower Limit	---	0.538	0.786
Upper Limit	---	18.728	24.676
Weeks to First Observed Tumor	92	92	92

[a]Treated groups received time-weighted average doses of 76 or 152 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 $P < 0.05$; 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 $P < 0.05$; 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.

TABLE 6

TIME-ADJUSTED ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE MICE TREATED WITH DIBUTYLTIN DIACETATE[a,e]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Carcinoma or Alveolar/Bronchiolar Adenoma[b]	2/20(0.10)	4/46(0.09)	0/43(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.870	0.000
Lower Limit	---	0.139	0.000
Upper Limit	---	9.144	1.558
Weeks to First Observed Tumor	92	92	---
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	1/20(0.05)	4/47(0.09)	1/43(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.702	0.465
Lower Limit	---	0.186	0.006
Upper Limit	---	81.978	35.689
Weeks to First Observed Tumor	89	82	92
Liver: Hepatocellular Adenoma[b]	1/20(0.05)	4/47(0.09)	12/43(0.28)
P Values[c]	P = 0.006	N.S.	P = 0.033
Relative Risk (Control)[d]	---	1.702	5.581
Lower Limit	---	0.186	0.937
Upper Limit	---	81.978	231.207
Weeks to First Observed Tumor	92	92	72

TABLE 6 (CONCLUDED)

[a]Treated groups received time-weighted average doses of 76 or 152 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 $P < 0.05$; 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 $P < 0.05$; 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]These analyses were based solely upon animals surviving at least 52 weeks.

None of the statistical tests for male mice indicated a significant positive association between dosage and increased incidence at any site. However, in males the incidences of a combination of hepatocellular adenomas or hepatocellular carcinomas were 11 percent (2/19) for the control versus 22 percent (11/49) and 31 percent (15/49) in the low and high dose groups, respectively.

To provide additional insight into the possible carcinogenicity of this compound, 95 percent confidence intervals on thhe 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 5 and 6, 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 mice by dibutyltin diacetate that could not be established under the conditions of this test.

V. DISCUSSION

There were significant positive associations between the concentrations of dibutyltin diacetate administered and mortality in male rats and female mice. There were no significant positive associations between the concentrations administered and mortality in female rats or male mice. However, adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. Mean body weight depression, relative to controls, was observed in male mice and significantly accelerated mortality, relative to controls, was observed in male rats and female mice, indicating that the concentrations of dibutyltin diacetate administered to these animals may have approximated the maximum tolerated concentration. Since no mean body weight depression, no significantly accelerated mortality, and no other signs of toxicity were associated with administration of dibutyltin diacetate to female rats, it is possible that these animals may have been able to tolerate a higher dietary concentration.

None of the statistical tests for any site in rats of either sex or in male mice indicated a significant positive association between compound administration and tumor incidence. It must be noted, however, that the majority of the tissues taken from 17 of the 50 high dose female rats were lost after necropsy and were, therefore, unavailable for microscopic examination and statistical analysis.

An increase in uterine neoplasms was observed among low dose female rats. This, coupled with the gross observation of 5 uterine tumors among the tissues that were lost, indicates that the loss of the tissues from these 17 high dose female rats may have been a critical factor in the inability to determine a possible carcinogenic effect in female rats.

There was a significant positive association between the concentrations administered and the incidences of hepatocellular adenomas in female mice; however, the Fisher exact comparisons were not significant using the Bonferroni criterion. Liver neoplasms, a combination of adenomas and carcinomas, were also observed in male mice; however, the occurrence was not statistically significant.

Under the conditions of this bioassay, there was no conclusive evidence for the carcinogenicity of dibutyltin diacetate in male Fischer 344 rats or B6C3F1 mice of either sex. The loss, prior to microscopic examinationA of tissues taken from high dose female rats in this bioassay precluded an evaluation of the carcinogenicity of dibutyltin diacetate to female Fischer 344 rats.

VI. BIBLIOGRAPHY

Armitage, P., Statistical Methods in Medical Research, Chapter 14. J. Wiley & Sons, New York, 1971.

Benkeser, R.A. and H. Gilman, "Organometallic Compounds." Encyclopedia of Chemical Technology, Volume 9. R.E. Kirk and D.F. Othmer, editors. The Interscience Encyclopedia, Inc., New York, 1952.

Berenblum, I., editor, Carcinogenicity Testing. International Union Against Cancer, Technical Report Series, Vol. 2. International Union Against Cancer, Geneva, 1969.

Chemical Abstracts Service. The Chemical Abstracts Service (CAS) Ninth Collective Index, Volumes 76-85, 1972-1976. American Chemical Society, Washington, D.C., 1977.

Cox, D.R., Analysis of Binary Data, Chapters 4 and 5. Methuen and Co., Ltd., London, 1970.

Cox, D.R., "Regression Models and Life-Tables." Journal of the Royal Statistical Society, Series "B" 34:187-220, 1972.

Gart, J.J., "The Comparison of Proportions: A Review of Significance Tests, Confidence Limits, and Adjustments for Stratification." International Statistical Institute Review 39:148-169, 1971.

Hawley, G.G., The Condensed Chemical Dictionary, 9th edition. Van Nostrand Reinhold Company, New York, 1977.

Kaplan, E.L., and P. Meier, "Nonparametric Estimation from Incomplete Observations." Journal of the American Statistical Association 53:457-481, 1958.

Linhart, M.S., J.A. Cooper, R.L. Martin, N.P. Page, and J.A. Peters, "Carcinogenesis Bioassay Data System." Computers and Biomedical Research 7:230-248, 1974.

Miller, R.G., Simultaneous Statistical Inference. McGraw-Hill Book Co., New York, 1966.

Sadtler Standard Spectra. Sadtler Research Laboratories, Philadelphia, Pennsylvania.

Saffiotti, U., R. Montesano, A.R. Sellakumar, F. Cefis, and D.G. Kaufman, "Respiratory Tract Carcinogenesis in Hamsters Induced by Different Numbers of Administration of Benzo (a) Pyrene and Ferric Oxide." Cancer Research 32:1073-1079, 1972.

Stanford Research Institute, 1977 Directory of Chemical Producers, U.S.A. Menlo Park, California, 1977.

Tarone, R.E., "Tests for Trend in Life-Table Analysis." Biometrika 62:679-682, 1975.

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

October 25, 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, and State health officials. 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 Dibutyltin Diacetate for carcinogenicity.

The reviewer for the report on the bioassay of Dibutyltin Diacetate agreed with the conclusion that, under the conditions of test, there was no statistical evidence for the carcinogenicity of the compound in rats or mice. The loss of female rat tissues precluded a complete evaluation of uterine neoplasms from the high dose treatment group. The reviewer said that the increased incidence of these neoplasms in low dose treated female rats suggested that the loss of the tissues from the high dose group could have affected the significance of the study.

There was no objection to a recommendation that the report be accepted as written.

Clearinghouse Members Present

Arnold L. Brown (Chairman), University of Wisconsin Medical School
Joseph Highland, Environmental Defense Fund
William Lijinsky, Frederick Cancer Research Center
Henry Pitot, University of Wisconsin Medical Center
Verne A. Ray, Pfizer Medical Research Laboratory
Kenneth Wilcox, Michigan State Health Department

---

* 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.

☆U.S. GOVERNMENT PRINTING OFFICE: 1978-281-217/3306

APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH DIBUTYLTIN DIACETATE

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

	CONTROL (UNTR) 11-1065	LOW DOSE 11-1063	HIGH DOSE 11-1061
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	42	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
KERATOACANTHOMA			1 (2%)
*SUBCUT TISSUE	(20)	(50)	(50)
FIBROMA	2 (10%)		
FIBROSARCOMA		1 (2%)	
HEMANGIOSARCOMA		1 (2%)	
OSTEOSARCOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(20)	(42)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (5%)		1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)
OSTEOSARCOMA, METASTATIC	1 (5%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
LEUKEMIA,NOS			1 (2%)
LYMPHOCYTIC LEUKEMIA	1 (5%)		
ERYTHROCYTIC LEUKEMIA			1 (2%)
GRANULOCYTIC LEUKEMIA		1 (2%)	
MONOCYTIC LEUKEMIA		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(42)	(50)
NEOPLASTIC NODULE		1 (2%)	

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

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 11-1065	LOW DOSE 11-1063	HIGH DOSE 11-1061
HEPATOCELLULAR CARCINOMA		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(20)	(41)	(49)
TRANSITIONAL-CELL CARCINOMA			1 (2%)
#URINARY BLADDER	(17)	(35)	(36)
TRANSITIONAL-CELL CARCINOMA			1 (3%)
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(38)	(40)
CHROMOPHOBE ADENOMA	1 (5%)	2 (5%)	2 (5%)
#ADRENAL	(20)	(41)	(47)
PHEOCHROMOCYTOMA	2 (10%)	7 (17%)	1 (2%)
#THYROID	(17)	(36)	(37)
FOLLICULAR-CELL ADENOMA			1 (3%)
FOLLICULAR-CELL CARCINOMA		1 (3%)	
C-CELL CARCINOMA	1 (6%)	2 (6%)	
#PANCREATIC ISLETS	(19)	(40)	(49)
ISLET-CELL ADENOMA		2 (5%)	
REPRODUCTIVE SYSTEM			
#TESTIS	(20)	(41)	(50)
INTERSTITIAL-CELL TUMOR	20 (100%)	32 (78%)	28 (56%)
NERVOUS SYSTEM			
#BRAIN	(20)	(41)	(50)
GLIOMA, NOS		3 (7%)	
MENINGIOMA		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			

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

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 11-1065	LOW DOSE 11-1063	HIGH DOSE 11-1061
MUSCULOSKELETAL SYSTEM			
*BONE	(20)	(50)	(50)
OSTEOSARCOMA	1 (5%)		
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(50)	(50)
LIPOMA		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	1	8	20
MORIBUND SACRIFICE	2	3	4
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	17	39	26
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1 (CONCLUDED)

	CONTROL (UNTR) 11-1065	LOW DOSE 11-1063	HIGH DOSE 11-1061
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	20	37	31
TOTAL PRIMARY TUMORS	29	57	40
TOTAL ANIMALS WITH BENIGN TUMORS	20	33	30
TOTAL BENIGN TUMORS	26	44	34
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	12	5
TOTAL MALIGNANT TUMORS	3	12	6
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		
TOTAL SECONDARY TUMORS	1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	
TOTAL UNCERTAIN TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

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

	CONTROL (UNTR) 11-1066	LOW DOSE 11-1064	HIGH DOSE 11-1062
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	19	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	50	33
INTEGUMENTARY SYSTEM			
*SKIN	(19)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (5%)		
RESPIRATORY SYSTEM			
#LUNG	(19)	(50)	(33)
ADENOCARCINOMA, NOS, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(19)	(50)	(50)
ERYTHROCYTIC LEUKEMIA		1 (2%)	1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(13)	(40)	(21)
LEIOMYOSARCOMA		1 (3%)	
#LIVER	(19)	(49)	(33)
NEOPLASTIC NODULE		1 (2%)	1 (3%)
URINARY SYSTEM			
#KIDNEY	(19)	(49)	(33)
TRANSITIONAL-CELL CARCINOMA		1 (2%)	

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

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 11-1066	LOW DOSE 11-1064	HIGH DOSE 11-1062
ENDOCRINE SYSTEM			
#PITUITARY	(18)	(42)	(29)
CHROMOPHOBE ADENOMA	9 (50%)	12 (29%)	9 (31%)
#ADRENAL	(19)	(50)	(33)
PHEOCHROMOCYTOMA	1 (5%)		
#THYROID	(17)	(42)	(23)
C-CELL CARCINOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(19)	(50)	(50)
ADENOCARCINOMA, NOS	1 (5%)		
CYSTADENOMA, NOS		2 (4%)	
FIBROADENOMA	2 (11%)	2 (4%)	1 (2%)
#UTERUS	(19)	(49)	(33)
ADENOCARCINOMA, NOS		3 (6%)	
LEIOMYOMA		1 (2%)	
ENDOMETRIAL STROMAL POLYP		6 (12%)	2 (6%)
HEMANGIOMA	1 (5%)		
#CERVIX UTERI	(19)	(49)	(33)
ENDOMETRIAL STROMAL POLYP		1 (2%)	
#OVARY	(19)	(49)	(32)
SARCOMA, NOS		1 (2%)	
NERVOUS SYSTEM			
#CEREBRUM	(19)	(50)	(33)
GLIOMA, NOS	1 (5%)		
#BRAIN	(19)	(50)	(33)
GLIOMA, NOS		1 (2%)	
EPENDYMOMA		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			

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

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 11-1066	LOW DOSE 11-1064	HIGH DOSE 11-1062
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(19)	(50)	(50)
SARCOMA, NOS		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	1	6	16
MORIBUND SACRIFICE	4	2	2
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	14	42	32
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2 (CONCLUDED)

	CONTROL (UNTR) 11-1066	LOW DOSE 11-1064	HIGH DOSE 11-1062
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	12	26	13
TOTAL PRIMARY TUMORS	16	36	14
TOTAL ANIMALS WITH BENIGN TUMORS	10	19	11
TOTAL BENIGN TUMORS	13	24	12
TOTAL ANIMALS WITH MALIGNANT TUMORS	3	11	1
TOTAL MALIGNANT TUMORS	3	11	1
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	
TOTAL SECONDARY TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	1
TOTAL UNCERTAIN TUMORS		1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH DIBUTYLTIN DIACETATE

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

	CONTROL (UNTR) 22-2065	LOW DOSE 22-2063	HIGH DOSE 22-2061
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	20	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	49
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(19)	(49)	(48)
HEPATOCELLULAR CARCINOMA, METAST		2 (4%)	1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (5%)	3 (6%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (5%)	5 (10%)	2 (4%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(49)
MALIGNANT LYMPHOMA, NOS	1 (5%)	1 (2%)	
LEUKEMIA,NOS		2 (4%)	
#SPLEEN	(17)	(42)	(46)
HEMANGIOSARCOMA		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(19)	(49)	(49)
HEPATOCELLULAR ADENOMA	2 (11%)	9 (18%)	13 (27%)
HEPATOCELLULAR CARCINOMA		2 (4%)	2 (4%)
#SMALL INTESTINE	(19)	(47)	(49)
SARCOMA, NOS	1 (5%)		

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

TABLE B1 (CONTINUED)

	CONTROL (UNTR) 22-2065	LOW DOSE 22-2063	HIGH DOSE 22-2061
HEMANGIOMA	1 (5%)		
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
#TESTIS	(19)	(48)	(48)
EMBRYONAL CARCINOMA		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

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

TABLE B1 (CONCLUDED)

	CONTROL (UNTR) 22-2065	LOW DOSE 22-2063	HIGH DOSE 22-2061
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	1	2	5
MORIBUND SACRIFICE			1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	19	48	43
ANIMAL MISSING			1
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	6	19	16
TOTAL PRIMARY TUMORS	7	24	17
TOTAL ANIMALS WITH BENIGN TUMORS	4	11	13
TOTAL BENIGN TUMORS	4	12	13
TOTAL ANIMALS WITH MALIGNANT TUMORS	2	10	4
TOTAL MALIGNANT TUMORS	3	12	4
TOTAL ANIMALS WITH SECONDARY TUMORS#		2	1
TOTAL SECONDARY TUMORS		2	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 DIBUTYLTIN DIACETATE

	CONTROL (UNTR) 22-2066	LOW DOSE 22-2064	HIGH DOSE 22-2062
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	20	48	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	48	48
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(20)	(47)	(48)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (5%)	3 (6%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (5%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(48)	(48)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
LEUKEMIA,NOS	1 (5%)	3 (6%)	
#SPLEEN	(16)	(47)	(43)
MALIGNANT LYMPHOMA, NOS			1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(48)	(47)
HEPATOCELLULAR ADENOMA	1 (5%)	4 (8%)	12 (26%)
URINARY SYSTEM			
NONE			

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

TABLE B2 (CONTINUED)

	CONTROL (UNTR) 22-2066	LOW DOSE 22-2064	HIGH DOSE 22-2062
ENDOCRINE SYSTEM			
#THYROID	(17)	(36)	(29)
FOLLICULAR-CELL CARCINOMA		1 (3%)	
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	1	5	17
MORIBUND SACRIFICE			3
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	19	45	29
ANIMAL MISSING			1

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2 (CONCLUDED)

	CONTROL (UNTR) 22-2066	LOW DOSE 22-2064	HIGH DOSE 22-2062
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	3	12	13
TOTAL PRIMARY TUMORS	4	13	13
TOTAL ANIMALS WITH BENIGN TUMORS	2	6	12
TOTAL BENIGN TUMORS	2	7	12
TOTAL ANIMALS WITH MALIGNANT TUMORS	2	6	1
TOTAL MALIGNANT TUMORS	2	6	1
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 DIBUTYLTIN DIACETATE

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

	CONTROL (UNTR) 11-1065	LOW DOSE 11-1063	HIGH DOSE 11-1061
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	42	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG/BRONCHIOLE	(20)	(42)	(50)
INFLAMMATION, SUPPURATIVE		2 (5%)	
#LUNG	(20)	(42)	(50)
INFLAMMATION, INTERSTITIAL			1 (2%)
ABSCESS, NOS		3 (7%)	
PNEUMONIA, CHRONIC MURINE	3 (15%)	19 (45%)	28 (56%)
INFLAMMATION, CHRONIC			1 (2%)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
CALCIFICATION, METASTATIC			1 (2%)
HYPERKERATOSIS			1 (2%)
#LUNG/ALVEOLI	(20)	(42)	(50)
BASOPHILIC CYTO CHANGE		1 (2%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(18)	(36)	(30)
MYELOSCLEROSIS	1 (6%)		
#SPLEEN	(20)	(41)	(49)
HYPERPLASIA, RETICULUM CELL		1 (2%)	
HYPOPLASIA, LYMPHOID			1 (2%)
#LYMPH NODE	(18)	(35)	(34)
LYMPHANGIECTASIS			1 (3%)
#MANDIBULAR L. NODE	(18)	(35)	(34)
PLASMA-CELL INFILTRATE	1 (6%)	1 (3%)	

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 11-1065	LOW DOSE 11-1063	HIGH DOSE 11-1061
#MEDIASTINAL L.NODE	(18)	(35)	(34)
CYST, NOS			1 (3%)
#MESENTERIC L. NODE	(18)	(35)	(34)
CYST, NOS			1 (3%)
HYPERPLASIA, RETICULUM CELL	1 (6%)		1 (3%)
HYPERPLASIA, LYMPHOID	1 (6%)		
CIRCULATORY SYSTEM			
#HEART	(20)	(40)	(48)
MINERALIZATION			1 (2%)
CALCIFICATION, METASTATIC			1 (2%)
#AURICULAR APPENDAGE	(20)	(40)	(48)
THROMBOSIS, NOS	1 (5%)		
#MYOCARDIUM	(20)	(40)	(48)
INFLAMMATION ACTIVE CHRONIC			1 (2%)
FIBROSIS		2 (5%)	3 (6%)
FIBROSIS, DIFFUSE		1 (3%)	
DEGENERATION, NOS	7 (35%)	15 (38%)	18 (38%)
DIGESTIVE SYSTEM			
#LIVER	(20)	(42)	(50)
INFLAMMATION, NECROTIZING		1 (2%)	1 (2%)
INFLAMMATION, ACUTE NECROTIZING			1 (2%)
ABSCESS, NOS			2 (4%)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
NECROSIS, NOS			1 (2%)
NECROSIS, FOCAL		2 (5%)	3 (6%)
NECROSIS, COAGULATIVE			1 (2%)
INFARCT, NOS			1 (2%)
METAMORPHOSIS FATTY	1 (5%)		1 (2%)
BASOPHILIC CYTO CHANGE	2 (10%)	5 (12%)	6 (12%)
FOCAL CELLULAR CHANGE	1 (5%)		
ANGIECTASIS	1 (5%)		
#LIVER/CENTRILOBULAR	(20)	(42)	(50)
NECROSIS, NOS	1 (5%)		1 (2%)
#LIVER/PERIPORTAL	(20)	(42)	(50)
INFLAMMATION, CHRONIC			1 (2%)

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 11-1065	LOW DOSE 11-1063	HIGH DOSE 11-1061
FIBROSIS			1 (2%)
#BILE DUCT	(20)	(42)	(50)
CALCULUS, NOS			10 (20%)
DILATATION, NOS			2 (4%)
INFLAMMATION, NOS			2 (4%)
INFLAMMATION, VESICULAR			1 (2%)
#PANCREAS	(19)	(40)	(49)
DILATATION/DUCTS			1 (2%)
FIBROSIS			1 (2%)
FIBROSIS, FOCAL		1 (3%)	1 (2%)
FIBROSIS, DIFFUSE		1 (3%)	
ATROPHY, NOS			1 (2%)
#PANCREATIC ACINUS	(19)	(40)	(49)
ATROPHY, NOS	1 (5%)		
#ESOPHAGUS	(20)	(41)	(48)
HYPERKERATOSIS			1 (2%)
#STOMACH	(19)	(41)	(49)
CALCIFICATION, METASTATIC		1 (2%)	1 (2%)
#SMALL INTESTINE	(19)	(41)	(49)
HYPERPLASIA, LYMPHOID	1 (5%)	1 (2%)	2 (4%)
#ILEUM	(19)	(41)	(49)
HYPERPLASIA, LYMPHOID	1 (5%)		
#COLON	(19)	(41)	(48)
NEMATODIASIS	10 (53%)	15 (37%)	9 (19%)
URINARY SYSTEM			
#KIDNEY	(20)	(41)	(49)
PYELONEPHRITIS, NOS		1 (2%)	
ABSCESS, NOS			1 (2%)
INFLAMMATION, CHRONIC	16 (80%)	35 (85%)	38 (78%)
CALCIFICATION, NOS			1 (2%)
#KIDNEY/CORTEX	(20)	(41)	(49)
CYST, NOS			1 (2%)
#KIDNEY/TUBULE	(20)	(41)	(49)
BASOPHILIC CYTO CHANGE	2 (10%)	2 (5%)	1 (2%)

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 11-1065	LOW DOSE 11-1063	HIGH DOSE 11-1061
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(38)	(40)
CYST, NOS	1 (5%)		
#ADRENAL	(20)	(41)	(47)
HEMORRHAGIC CYST	1 (5%)		
#ADRENAL CORTEX	(20)	(41)	(47)
HYPERPLASIA, FOCAL	1 (5%)		
#ADRENAL MEDULLA	(20)	(41)	(47)
HYPERPLASIA, NOS	1 (5%)	6 (15%)	5 (11%)
#THYROID	(17)	(36)	(37)
ATROPHY, NOS		1 (3%)	
HYPERPLASIA, C-CELL	2 (12%)	2 (6%)	1 (3%)
HYPERPLASIA, FOLLICULAR-CELL			1 (3%)
#PARATHYROID	(8)	(15)	(25)
HYPERPLASIA, NOS		1 (7%)	1 (4%)
#PANCREATIC ISLETS	(19)	(40)	(49)
HYPERPLASIA, NOS			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
DILATATION/DUCTS		2 (4%)	
*PREPUTIAL GLAND	(20)	(50)	(50)
ABSCESS, NOS			1 (2%)
#PROSTATE	(19)	(40)	(45)
INFLAMMATION, ACUTE			1 (2%)
*SEMINAL VESICLE	(20)	(50)	(50)
INFLAMMATION, SUPPURATIVE		2 (4%)	
ABSCESS, NOS		1 (2%)	
NERVOUS SYSTEM			
#BRAIN/MENINGES	(20)	(41)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)

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

TABLE C1 (CONCLUDED)

	CONTROL (UNTR) 11-1065	LOW DOSE 11-1063	HIGH DOSE 11-1061
*CHOROID PLEXUS	(20)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
#BRAIN	(20)	(41)	(50)
ABSCESS, NOS			1 (2%)
#CEREBRAL CORTEX	(20)	(41)	(50)
ATROPHY, NOS			1 (2%)
*OPTIC NERVE	(20)	(50)	(50)
ABSCESS, NOS			1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*ABDOMINAL MUSCLE	(20)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
BODY CAVITIES			
*PLEURA	(20)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
*EPICARDIUM	(20)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(50)	(50)
PIGMENTATION, NOS	2 (10%)	3 (6%)	5 (10%)
SPECIAL MORPHOLOGY SUMMARY			
NECROPSY PERF/NO HISTO PERFORMED		8	

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 DIBUTYLTIN DIACETATE

	CONTROL (UNTR) 11-1066	LOW DOSE 11-1064	HIGH DOSE 11-1062
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	19	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	50	33
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(19)	(50)	(33)
BRONCHIECTASIS			1 (3%)
#LUNG	(19)	(50)	(33)
BRONCHOPNEUMONIA, NOS			1 (3%)
INFLAMMATION, INTERSTITIAL	1 (5%)		
PNEUMONIA, ASPIRATION			1 (3%)
BRONCHOPNEUMONIA NECROTIZING		1 (2%)	
PNEUMONIA, CHRONIC MURINE	7 (37%)	18 (36%)	6 (18%)
GRANULOMA, NOS		1 (2%)	
CALCIFICATION, METASTATIC			1 (3%)
BRONCHIOLIZATION		1 (2%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(19)	(47)	(32)
LEUKEMOID REACTION		1 (2%)	
HYPOPLASIA, LYMPHOID			1 (3%)
#MANDIBULAR L. NODE	(15)	(38)	(19)
LYMPHANGIECTASIS		1 (3%)	
HYPERPLASIA, PLASMA CELL	1 (7%)		
HYPERPLASIA, LYMPHOID	1 (7%)		
#MESENTERIC L. NODE	(15)	(38)	(19)
CYST, NOS	1 (7%)		
INFLAMMATION, CHRONIC		1 (3%)	

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

**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 11-1066	LOW DOSE 11-1064	HIGH DOSE 11-1062
HYPERPLASIA, RETICULUM CELL		1 (3%)	
#THYMUS		(1)	
LYMPHANGIECTASIS		1 (100%)	
HEMOSIDEROSIS		1 (100%)	
CIRCULATORY SYSTEM			
#HEART	(19)	(49)	(33)
CALCIFICATION, METASTATIC			1 (3%)
#MYOCARDIUM	(19)	(49)	(33)
DEGENERATION, NOS	13 (68%)	17 (35%)	14 (42%)
DIGESTIVE SYSTEM			
#LIVER	(19)	(49)	(33)
INFLAMMATION, NECROTIZING		1 (2%)	
ABSCESS, NOS			2 (6%)
FIBROSIS			1 (3%)
NECROSIS, FOCAL			1 (3%)
METAMORPHOSIS FATTY	2 (11%)	1 (2%)	1 (3%)
BASOPHILIC CYTO CHANGE	9 (47%)	17 (35%)	10 (30%)
FOCAL CELLULAR CHANGE		2 (4%)	
EOSINOPHILIC CYTO CHANGE		1 (2%)	
GLYCOGENIC CELL		1 (2%)	
#LIVER/CENTRILOBULAR	(19)	(49)	(33)
INFLAMMATION, NECROTIZING			1 (3%)
#LIVER/PERIPORTAL	(19)	(49)	(33)
INFLAMMATION, CHRONIC SUPPURATIV			1 (3%)
#LIVER/HEPATOCYTES	(19)	(49)	(33)
NECROSIS, NOS			1 (3%)
#BILE DUCT	(19)	(49)	(33)
CALCULUS, NOS		1 (2%)	3 (9%)
DILATATION, NOS			2 (6%)
INFLAMMATION, NOS		1 (2%)	1 (3%)
INFLAMMATION, SUPPURATIVE			1 (3%)
INFLAMMATION, CHRONIC		1 (2%)	
FIBROSIS		1 (2%)	

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 11-1066	LOW DOSE 11-1064	HIGH DOSE 11-1062
#PANCREAS	(17)	(47)	(28)
FIBROSIS, FOCAL			1 (4%)
#PANCREATIC ACINUS	(17)	(47)	(28)
ATROPHY, NOS		1 (2%)	1 (4%)
#STOMACH	(19)	(50)	(33)
ULCER, FOCAL			1 (3%)
#SMALL INTESTINE	(19)	(49)	(33)
HYPERPLASIA, LYMPHOID		1 (2%)	
#COLON	(19)	(50)	(32)
NEMATODIASIS	5 (26%)	19 (38%)	7 (22%)
URINARY SYSTEM			
#KIDNEY	(19)	(49)	(33)
INFLAMMATION, CHRONIC	11 (58%)	28 (57%)	21 (64%)
NEPHROPATHY			1 (3%)
CALCINOSIS, NOS			1 (3%)
#KIDNEY/TUBULE	(19)	(49)	(33)
BASOPHILIC CYTO CHANGE		1 (2%)	1 (3%)
#URINARY BLADDER	(12)	(34)	(24)
CALCULUS, NOS		1 (3%)	
#U. BLADDER/MUCOSA	(12)	(34)	(24)
HYPERPLASIA, NOS		1 (3%)	
ENDOCRINE SYSTEM			
#PITUITARY	(18)	(42)	(29)
CYST, NOS		1 (2%)	2 (7%)
HEMORRHAGIC CYST		1 (2%)	
#ADRENAL	(19)	(50)	(33)
HEMORRHAGIC CYST		2 (4%)	
METAMORPHOSIS FATTY		1 (2%)	
#ADRENAL CORTEX	(19)	(50)	(33)
LIPOIDOSIS		1 (2%)	

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 11-1066	LOW DOSE 11-1064	HIGH DOSE 11-1062
HYPERPLASIA, NODULAR		2 (4%)	
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, FOCAL		1 (2%)	
#ADRENAL MEDULLA	(19)	(50)	(33)
HYPERPLASIA, NOS	4 (21%)	6 (12%)	7 (21%)
#THYROID	(17)	(42)	(23)
ULTIMOBRANCHIAL CYST		1 (2%)	
PIGMENTATION, NOS		1 (2%)	
HYPERPLASIA, C-CELL	2 (12%)	7 (17%)	4 (17%)
#PARATHYROID	(11)	(27)	(15)
HYPERPLASIA, NOS			1 (7%)
#PANCREATIC ISLETS	(17)	(47)	(28)
HYPERPLASIA, NOS	1 (6%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(19)	(50)	(50)
CYST, NOS		1 (2%)	
ADENOSIS		1 (2%)	
LACTATION	1 (5%)	1 (2%)	
#UTERUS	(19)	(49)	(33)
STEATITIS	1 (5%)		
INFLAMMATION, SUPPURATIVE		1 (2%)	
PYOMETRA		2 (4%)	1 (3%)
#CERVIX UTERI	(19)	(49)	(33)
INFLAMMATION, SUPPURATIVE		1 (2%)	
HYPERPLASIA, NOS		2 (4%)	
#UTERUS/ENDOMETRIUM	(19)	(49)	(33)
CYST, NOS		1 (2%)	
INFLAMMATION, SUPPURATIVE		5 (10%)	1 (3%)
INFLAMMATION, ACUTE			1 (3%)
HYPERPLASIA, CYSTIC		3 (6%)	
POLYPOID HYPERPLASIA		1 (2%)	
#OVARY	(19)	(49)	(32)
CYST, NOS	2 (11%)	5 (10%)	2 (6%)
FOLLICULAR CYST, NOS		1 (2%)	1 (3%)

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 11-1066	LOW DOSE 11-1064	HIGH DOSE 11-1062
PAROVARIAN CYST		2 (4%)	
NERVOUS SYSTEM			
#BRAIN	(19)	(50)	(33)
HYDROCEPHALUS, NOS		1 (2%)	
ATROPHY, NOS	2 (11%)		2 (6%)
#BRAIN/THALAMUS	(19)	(50)	(33)
ATROPHY, NOS		1 (2%)	2 (6%)
#PONS	(19)	(50)	(33)
ATROPHY, NOS		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(19)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
BODY CAVITIES			
*PERITONEUM	(19)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)
*PLEURA	(19)	(50)	(50)
INFLAMMATION WITH FIBROSIS		1 (2%)	
METAPLASIA, OSSEOUS		1 (2%)	
*PERICARDIUM	(19)	(50)	(50)
GRANULOMA, NOS		1 (2%)	
*MESENTERY	(19)	(50)	(50)
STEATITIS		1 (2%)	
LL OTHER SYSTEMS			
*MULTIPLE ORGANS	(19)	(50)	(50)
PIGMENTATION, NOS	2 (11%)	6 (12%)	4 (8%)

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

TABLE C2 (CONCLUDED)

	CONTROL (UNTR) 11-1066	LOW DOSE 11-1064	HIGH DOSE 11-1062
SPECIAL MORPHOLOGY SUMMARY			
NECROPSY PERF/NO HISTO PERFORMED			17
AUTO/NECROPSY/HISTO PERF	1		

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE TREATED WITH DIBUTYLTIN DIACETATE

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

	CONTROL (UNTR) 22-2065	LOW DOSE 22-2063	HIGH DOSE 22-2061
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	20	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	49
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(19)	(49)	(48)
BRONCHOPNEUMONIA, NOS		1 (2%)	
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, INTERSTITIAL		1 (2%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(17)	(42)	(46)
THROMBOSIS, NOS		1 (2%)	
INFARCT, NOS		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
CIRCULATORY SYSTEM			
#HEART/ATRIUM	(18)	(46)	(46)
THROMBOSIS, NOS		1 (2%)	
#HEART/VENTRICLE	(18)	(46)	(46)
THROMBOSIS, NOS		1 (2%)	
#MYOCARDIUM	(18)	(46)	(46)
DEGENERATION, NOS			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(19)	(49)	(49)
MINERALIZATION			1 (2%)

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

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 22-2065	LOW DOSE 22-2063	HIGH DOSE 22-2061
INFLAMMATION, ACUTE FOCAL	3 (16%)	3 (6%)	5 (10%)
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)
ABSCESS, NOS			2 (4%)
INFLAMMATION, CHRONIC	1 (5%)		
NECROSIS, FOCAL			1 (2%)
INFARCT, NOS	1 (5%)		1 (2%)
HYPERPLASIA, NODULAR			2 (4%)
#LIVER/PERIPORTAL	(19)	(49)	(49)
FIBROSIS			2 (4%)
*GALLBLADDER	(20)	(50)	(49)
INFLAMMATION, NOS			1 (2%)
#BILE DUCT	(19)	(49)	(49)
DILATATION, NOS			1 (2%)
CYST, NOS		1 (2%)	
INFLAMMATION, NOS			1 (2%)
INFLAMMATION ACUTE AND CHRONIC			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
#PANCREATIC DUCT	(19)	(45)	(47)
SCAR			1 (2%)
#SMALL INTESTINE	(19)	(47)	(49)
INFLAMMATION, GRANULOMATOUS	1 (5%)		
#PEYERS PATCH	(19)	(47)	(49)
HYPERPLASIA, NOS	1 (5%)	1 (2%)	
HYPERPLASIA, LYMPHOID			1 (2%)
#COLON	(18)	(44)	(47)
NEMATODIASIS	4 (22%)	3 (7%)	13 (28%)
URINARY SYSTEM			
#KIDNEY	(20)	(49)	(49)
MINERALIZATION			1 (2%)
HYDRONEPHROSIS			1 (2%)
PYELONEPHRITIS, NOS			1 (2%)
INFLAMMATION, FOCAL		1 (2%)	
INFLAMMATION, CHRONIC	7 (35%)	5 (10%)	3 (6%)
INFARCT, HEALED			1 (2%)
#KIDNEY/MEDULLA	(20)	(49)	(49)
CALCIFICATION, NOS			1 (2%)

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

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 22-2065	LOW DOSE 22-2063	HIGH DOSE 22-2061
ENDOCRINE SYSTEM			
#ADRENAL	(7)	(41)	(29)
HYPERPLASIA, NODULAR		1 (2%)	
#THYROID	(15)	(43)	(39)
CYSTIC FOLLICLES		1 (2%)	1 (3%)
HYPERPLASIA, C-CELL			1 (3%)
HYPERPLASIA, FOLLICULAR-CELL		1 (2%)	1 (3%)
REPRODUCTIVE SYSTEM			
#TESTIS	(19)	(48)	(48)
INFLAMMATION, INTERSTITIAL			1 (2%)
INFLAMMATION, ACUTE		1 (2%)	
DEGENERATION, NOS		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(19)	(50)	(48)
HYDROCEPHALUS, NOS		1 (2%)	
INFLAMMATION, NOS			1 (2%)
NECROSIS, FOCAL			1 (2%)
HYPERPLASIA, LYMPHOID		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(20)	(50)	(49)
INFLAMMATION, SUPPURATIVE			1 (2%)
ALL OTHER SYSTEMS			
NONE			

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

TABLE D1 (CONCLUDED)

	CONTROL (UNTR) 22-2065	LOW DOSE 22-2063	HIGH DOSE 22-2061
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	6	20	11
ANIMAL MISSING/NO NECROPSY			1
AUTO/NECROPSY/HISTO PERF		1	

\# 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 DIBUTYLTIN DIACETATE

	CONTROL (UNTR) 22-2066	LOW DOSE 22-2064	HIGH DOSE 22-2062
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	20	48	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	48	48
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(20)	(47)	(48)
INFLAMMATION, INTERSTITIAL			3 (6%)
PNEUMONIA, CHRONIC MURINE		1 (2%)	3 (6%)
NECROSIS, FOCAL			2 (4%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(16)	(47)	(43)
HYPERPLASIA, LYMPHOID	2 (13%)		2 (5%)
#LYMPH NODE	(14)	(40)	(28)
HEMORRHAGIC CYST		1 (3%)	
#BRONCHIAL LYMPH NODE	(14)	(40)	(28)
SCAR			1 (4%)
CIRCULATORY SYSTEM			
#HEART	(17)	(46)	(46)
DEGENERATION, NOS		1 (2%)	1 (2%)
#MYOCARDIUM	(17)	(46)	(46)
INFLAMMATION, NECROTIZING			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(20)	(48)	(47)
INFLAMMATION, ACUTE FOCAL	4 (20%)	11 (23%)	4 (9%)

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

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 22-2066	LOW DOSE 22-2064	HIGH DOSE 22-2062
ABSCESS, NOS			1 (2%)
NECROSIS, NOS			1 (2%)
NECROSIS, FOCAL			5 (11%)
NECROSIS, DIFFUSE			1 (2%)
INFARCT, NOS			4 (9%)
#LIVER/PERIPORTAL	(20)	(48)	(47)
NECROSIS, COAGULATIVE			1 (2%)
*GALLBLADDER	(20)	(48)	(48)
CALCULUS, NOS			1 (2%)
HYPERPLASIA, EPITHELIAL			1 (2%)
#BILE DUCT	(20)	(48)	(47)
DISTENTION			1 (2%)
CYST, NOS			1 (2%)
MULTIPLE CYSTS		1 (2%)	
INFLAMMATION, NOS			2 (4%)
INFLAMMATION, ACUTE		1 (2%)	
ABSCESS, NOS			1 (2%)
HYPERPLASIA, NOS			1 (2%)
#PANCREAS	(18)	(47)	(41)
CYSTIC DUCTS			1 (2%)
INFLAMMATION ACUTE AND CHRONIC			1 (2%)
AMYLOIDOSIS			1 (2%)
#SMALL INTESTINE	(20)	(48)	(46)
ABSCESS, NOS		1 (2%)	
#PEYERS PATCH	(20)	(48)	(46)
HYPERPLASIA, LYMPHOID			1 (2%)
#COLON	(17)	(46)	(41)
NEMATODIASIS	1 (6%)	3 (7%)	4 (10%)
URINARY SYSTEM			
#KIDNEY	(20)	(48)	(48)
PYELONEPHRITIS, NOS			1 (2%)
INFLAMMATION, CHRONIC	5 (25%)	11 (23%)	8 (17%)
ADHESION, NOS			1 (2%)
NEPHROPATHY			1 (2%)
NECROSIS, NOS			1 (2%)

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

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 22-2066	LOW DOSE 22-2064	HIGH DOSE 22-2062
INFARCT, NOS			2 (4%)
HYPERPLASIA, LYMPHOID			1 (2%)
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
#UTERUS/ENDOMETRIUM	(20)	(47)	(37)
INFLAMMATION, SUPPURATIVE	1 (5%)		
#OVARY	(20)	(47)	(33)
CYST, NOS	1 (5%)	4 (9%)	4 (12%)
FOLLICULAR CYST, NOS		2 (4%)	1 (3%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(20)	(48)	(48)
STEATITIS		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	9	14	8

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

TABLE D2 (CONCLUDED)

	CONTROL (UNTR) 22-2066	LOW DOSE 22-2064	HIGH DOSE 22-2062
ANIMAL MISSING/NO NECROPSY			1
AUTO/NECROPSY/HISTO PERF		1	2
AUTOLYSIS/NO NECROPSY		2	1

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

DHEW Publication No. (NIH) 79-1739