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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 TRIPHENYLTIN HYDROXIDE
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 triphenyltin hydroxide 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 triphenyltin hydroxide was conducted by Litton Bionetics, Inc., Bethesda, 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. S. M. Garner (4,5) 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. Chemical analysis was performed by Midwest Research Institute (6) and the analytical results were reviewed by Dr. N. Zimmerman (7).

Histopathologic examinations were performed by Drs. B. Cockrell (4), F. M. Garner (4), E. Gorgacz (4), P. Hildebrandt (4), R. Montali (4), C. Montgomery (4), H. Seibold (4), and N. Wosu (4) and reviewed by Dr. A. DePaoli (4) at Litton Bionetics, Inc.; the pathology narratives were written by Dr. A. DePaoli (4), and the diagnoses included in this report represent the interpretation of these pathologists. Histopathology findings and reports were reviewed by Dr. R. L. Schueler (8).

Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute (9); the statistical analysis was performed by Mr. W. W. Belew (7,10) and Mr. R. M. Helfand (7), using methods selected for the Carcinogenesis Testing Program by Dr. J. J. Gart (11).

This report was prepared at METREK, a Division of The MITRE Corporation (7) under the direction of the NCI. Those responsible for this report at METREK are the project coordinator, Dr. L. W. Thomas (7), task leader Ms. P. Walker (7), senior biologist Mr. M. Morse (7), biochemist Mr. S. C. Drill (7), and technical editor Ms. P. A. Miller (7). 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 (1,12), Dr. R. A. Griesemer (1), Dr. M. H. Levitt (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), Dr. R. A. Squire (1,13), Dr. S. F. Stinson (1), Dr. J. M. Ward (1), and Dr. C. E. Whitmire (1).

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SUMMARY

A bioassay of triphenyltin hydroxide for possible carcinogenicity was conducted using Fischer 344 rats and B6C3F1 mice. Triphenyltin hydroxide was administered in the feed, at either of two concentrations, to groups of 50 male and 50 female animals of each species. The high and low concentrations of triphenyltin hydroxide were, respectively, 75 and 37.5 ppm for rats and mice. After a 78-week period of compound administration, there was an additional observation period of 26 weeks for both species. Twenty animals of each sex and species were placed on test as controls.

For male mice, there was a significant positive association between dosage and mortality. In both species, however, adequate numbers of animals survived sufficiently long to be at risk from late-developing tumors. Except for a slight depression of mean body weight gain in male rats and female mice, compound-related mean body weight depression was not observed in either species. In female rats no significant accelerated mortality, retardation of growth, or other signs of toxicity were associated with the dietary administration of triphenyltin hydroxide. Therefore it is possible that the compound was not administered at the maximum tolerated concentrations.

No tumors occurred at a significantly higher incidence in dosed rats or mice than in their controls.

Under the conditions of this bioassay, there was no evidence for the carcinogenicity of triphenyltin hydroxide to Fischer 344 rats or to B6C3F1 mice.

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I. INTRODUCTION

Triphenyltin hydroxide (Figure 1) (NCI No. C00260), an organometalic compound used as a fungicide and antifeeding compound for insect control, was selected for bioassay by the National Cancer Institute because of its use on edible crops and a lack of adequate chronic toxicity data.

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is hydroxytriphenylstannane.* It is also called hydroxytriphenyltin, fentin hydroxide, TPTH, TPTOH, and ENT 2009.

Triphenyltin hydroxide, a nonsystemic fungicide, is effective against many of the fungi which are susceptible to the action of copper fungicides (Martin and Worthing, 1977). Triphenyltin hydroxide is used to control early and late blight on potatoes; leaf spot on sugar beets and peanuts; scab and several diseases on pecans (Farm Chemicals Handbook, 1976); blast diseases of rice; coffee berry disease (Martin and Worthing, 1977); and most of the other important fungus diseases (Spencer, 1973).

Triphenyltin hydroxide can also be used as an antifeeding compound for the control of surface feeding insects (Farm Chemicals Handbook, 1976).

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*The CAS registry number is 76-87-9.

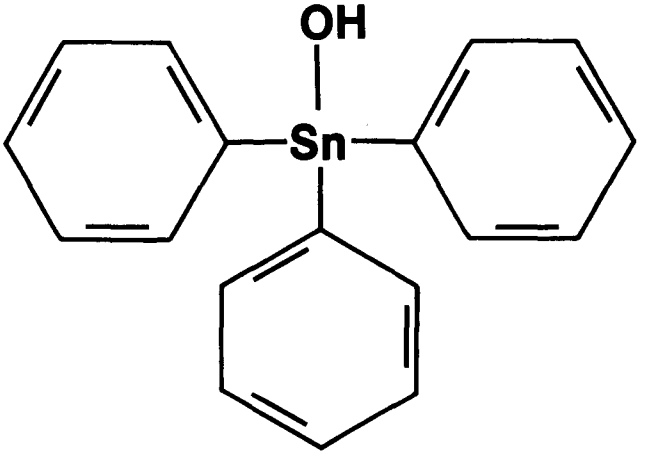


FIGURE 1
CHEMICAL STRUCTURE OF TRIPHENYLTIN HYDROXIDE

Specific production data for triphenyltin hydroxide are not available; however, this compound is produced in commercial quantities (in excess of 1000 pounds or $1000 in value annually) (Stanford Research Institute, 1977).

The potential for exposure to triphenyltin hydroxide is greatest for agricultural workers, but some exposure may also occur in pesticide production facilities. Residents of agricultural communities may be exposed to airborne residues following spraying operations. Exposure may also occur via ingestion of residues in food crops.

Triphenyltin hydroxide was not lethal to germ cells in a dominant lethal study of ICR/Ha Swiss mice following intraperitoneal injections of 1.3 mg/kg to 7 males (8 to 10 weeks old) and 8.5 mg/kg to 9 males, and administration of 11 mg/kg by gavage on 5 successive days to 10 males (Epstein et al., 1972).

II. MATERIALS AND METHODS

A. Chemicals

Triphenyltin hydroxide was purchased from Pfaltz and Bauer Chemical Company. Analysis was performed by Midwest Research Institute. The melting point (121° to 123°) was similar to that reported in the literature (119° to 121°C [Suzuki et al., 1968]). Thin-layer chromatographic plates visualized with ultraviolet light and dithizone showed one spot when an ethyl ether:benzene:acetic acid solvent system was used and two spots when an n-butanol:acetic acid solvent system was used. Elemental analysis was close to the theoretical. Titration of the basic group with hydrochloric acid was 97 to 98 percent of the theoretical. Infrared analysis was not inconsistent with the structure of the compound. Ultraviolet analysis showed λ_{max} at 246, 252, 258, 262, 264 and 268 nm with respective molar extinction coefficients of 552, 759, 954, 782, 794, and 527. Second and third batches were purchased from the same supplier 10 and 14 months later, respectively. Analyses suggested the compounds to be of similar purity.

Throughout this report, the term triphenyltin hydroxide is used to represent this material.

B. Dietary Preparation

The basal laboratory diet for both dosed and control animals consisted of Wayne Lab-Blox® (Allied Mills, Inc., Chicago, Illinois).

Triphenyltin hydroxide was administered to the dosed animals as a component of the diet.

The chemical was removed from its container and a proper amount was blended with an aliquot of the ground 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 37.5 and 75.0 ppm of triphenyltin hydroxide were analyzed spectrophotometrically. The mean result immediately after preparation was 88.1 percent of theoretical (ranging from 81.3 to 98.8 percent), including correction for the analytical method of recovery used. After 7 days at ambient room temperature, the mean result was 57.9 percent of theoretical (ranging from 54.3 to 62.0 percent) including correction for analytical method of recovery used. Data were not corrected for any loss which may have been due to instability of the chemical.

C. Animals

Two animal species, rats and mice, were used in the carcinogenicity bioassay. Fischer 344 rats and B6C3F1 mice were obtained through contracts of the Division of Cancer Treatment, National Cancer Institute. All rats were supplied by A. R. Schmidt, Madison,

Wisconsin. All mice were supplied by Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts.

Rats and mice were approximately 4 weeks old when received. Upon receipt, animals were examined for visible signs of disease or parasites. Obviously ill or runted animals were culled. 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

All animals were housed by species in temperature- and humidity-controlled rooms. The temperature range was 22° to 26°C and the relative humidity was maintained between 45 and 55 percent. Incoming 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.).

All rats were housed four per cage by sex and all mice 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 stainless steel mesh lid 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 bedding were provided twice weekly. Ab-sorb-dri® hardwood chip bedding (Wilner Wood Products Company, Norway, Maine) was used in polycarbonate cages for the entire bioassay.

Acidulated water (pH 2.5) was supplied to animals in water bottles filled by an automated metering device that was checked daily for diluting accuracy. Water bottles were changed twice weekly and 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* diaminozide (1596-84-5) and carbromal (77-65-6); and other rats intubated with β-nitrostyrene (102-96-5).

All dosed and control mice were housed in a room with mice receiving diets containing EDTA trisodium salt (150-38-9); diaminozide (1596-84-5); 3,3'-dimethoxybenzidine-4,4'-diisocyanate (91-93-0); p-quinone dioxime (105-11-3); 4-amino-2-nitrophenol (119-34-6); carbromal (75-65-6); N,N'-diethylthiourea (105-55-5); other mice intubated with lithocholic acid (434-13-9); and mice receiving I.P. injections of methiodal sodium (434-13-9).

*CAS registry numbers are given in parentheses.

E. Selection of Initial Concentrations

In order to establish the maximum tolerated concentrations of triphenyltin hydroxide 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. Triphenyltin hydroxide was incorporated into the basal laboratory diet of five of the six groups of both species in concentrations of 100, 146, 213, 315 and 464 ppm. The sixth group of each species served as a control group, receiving only the basal laboratory diet.

The dosed dietary preparations were administered for a period of 7 weeks, followed by a 1-week observation period during which all animals were fed the untreated basal diet. Individual body weights and food consumption data were recorded twice weekly throughout the study. Upon termination of the observation period, all survivors were sacrificed and necropsied.

All rats died at a dietary concentration of 464 ppm. At the end of the subchronic test, mean body weight gain among male rats receiving a dietary concentration of 100 ppm was 25 percent less than the mean body weight gain of their controls, while female rats receiving the same concentration displayed a mean body weight gain of 10 percent less than their controls.

All mice died at a dietary concentration of 464 ppm. At the end of the subchronic test, mean body weight gain among both male and

female mice receiving a dietary concentration of 100 ppm was 6 percent less than the mean body weight gain of their respective control groups.

The high concentration selected for administration to dosed groups of both species in the chronic bioassay was 75 ppm.

F. Experimental Design

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

All rats and mice were approximately 6 weeks old at the time the test was initiated. All groups of the same species were placed on test simultaneously. The dietary concentrations of triphenyltin hydroxide utilized were 75 and 37.5 ppm. Throughout this report those animal groups receiving the former concentration are referred to as the high dose groups and those receiving the latter concentration are referred to as the low dose groups. Dosed rats and mice were supplied with feed containing triphenyltin hydroxide for 78 weeks followed by a 26-week observation period.

G. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment. From the first day, all animals were inspected twice daily for mortality. Food consumption data were collected at monthly intervals from 20 percent of the animals in each group. Body weights

TABLE 1

DESIGN SUMMARY FOR FISCHER 344 RATS
TRIPHENYLTIN HYDROXIDE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	TRIPHENYLTIN HYDROXIDE CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)
MALE				
CONTROL	20	0	0	104
LOW DOSE	50	37.5	78	
		0		26
HIGH DOSE	50	75	78	
		0		26
FEMALE				
CONTROL	20	0	0	104
LOW DOSE	50	37.5	78	
		0		26
HIGH DOSE	50	75	78	
		0		26

[a]Concentrations given in parts per million.

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
TRIPHENYLTIN HYDROXIDE FEEDING EXPERIMENT

	INITIAL GROUP SIZE	TRIPHENYLTIN HYDROXIDE CONCENTRATION[a]	OBSERVATION PERIOD	
			TREATED (WEEKS)	UNTREATED (WEEKS)
MALE				
CONTROL	20	0	0	104
LOW DOSE	50	37.5	78	
		0		26
HIGH DOSE	50	75	78	
		0		26
FEMALE				
CONTROL	20	0	0	104
LOW DOSE	50	37.5	78	
		0		26
HIGH DOSE	50	75	78	
		0		26

[a]Concentrations given in parts per million.

were recorded once a week for the first 6 weeks, every 2 weeks for the next 10 weeks, and at monthly intervals for the remainder of the bioassay.

All moribund animals or animals that developed large, palpable masses that jeopardized their health were sacrificed. A necropsy was performed on each animal regardless of whether it died, was sacrificed when moribund, or was sacrificed at the end of the bioassay. The animals were euthanized by carbon dioxide asphyxiation, and were immediately necropsied. The histopathologic examination consisted of gross and microscopic examination of all major tissues, organs, and gross lesions taken from sacrificed 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, tunica vaginalis, 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

A very slight dose-related mean body weight depression was evident in male rats after week 40, while no distinct mean body weight depression was associated with compound administration in females (Figure 2).

No abnormal clinical signs were recorded.

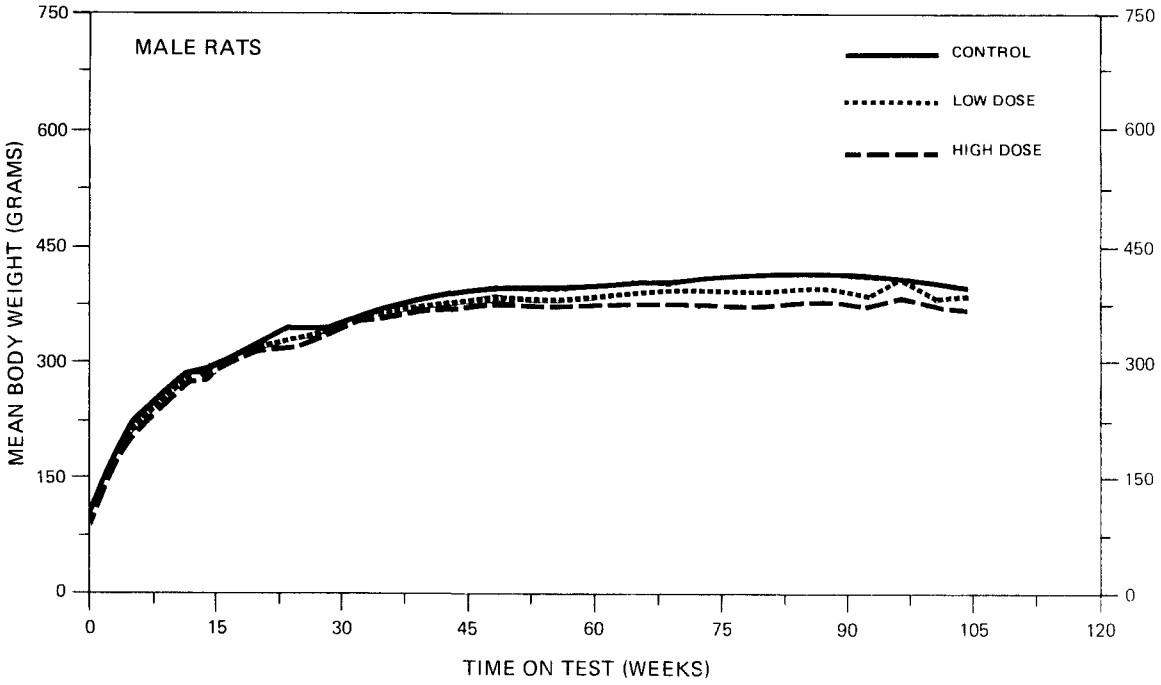
B. Survival

The estimated probabilities of survival for male and female rats in the control and triphenyltin hydroxide-dosed groups are shown in Figure 3. The Tarone test for association between increased dosage and elevated mortality was not significant for either males or females.

For both sexes, there were adequate numbers of rats at risk from late-developing tumors. Eighty-four percent (42/50) of the high dose males, 76 percent (38/50) of the low dose males, and 75 percent (15/20) of the control males survived on test until the conclusion of the study. Ninety percent (45/50) of the high dose females, 80 percent (40/50) of the low dose females, and 90 percent (18/20) of the control females survived on test until the end of the study.

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).



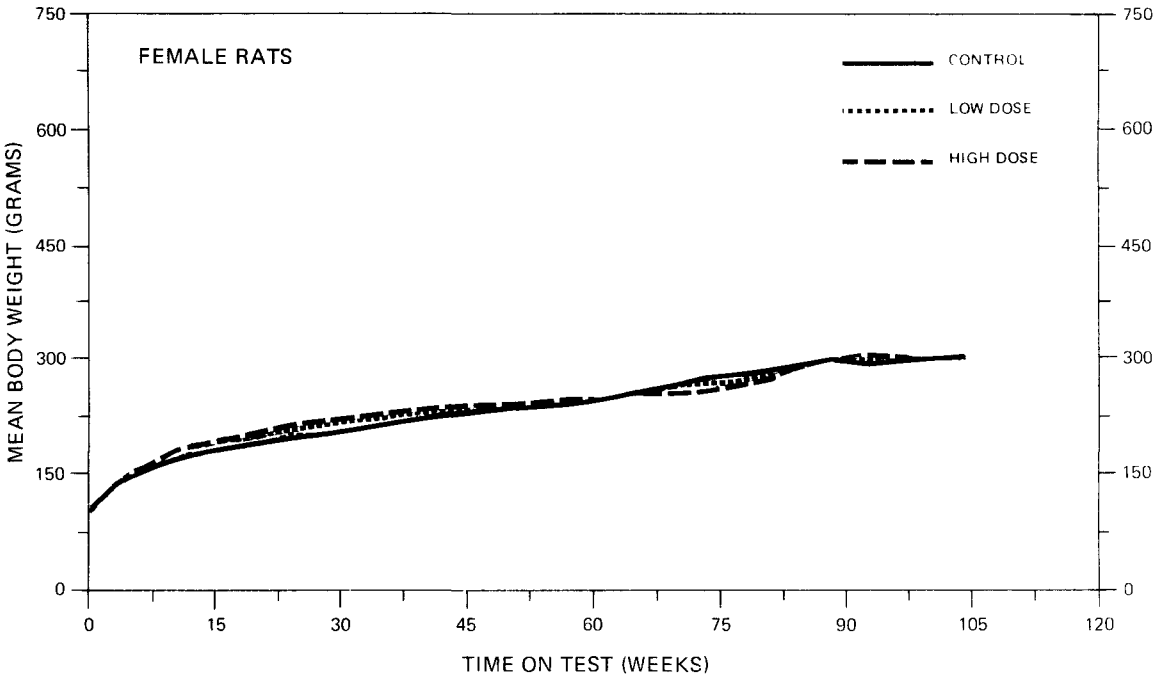


FIGURE 2
GROWTH CURVES FOR TRIPHENYLTIN HYDROXIDE CHRONIC STUDY RATS

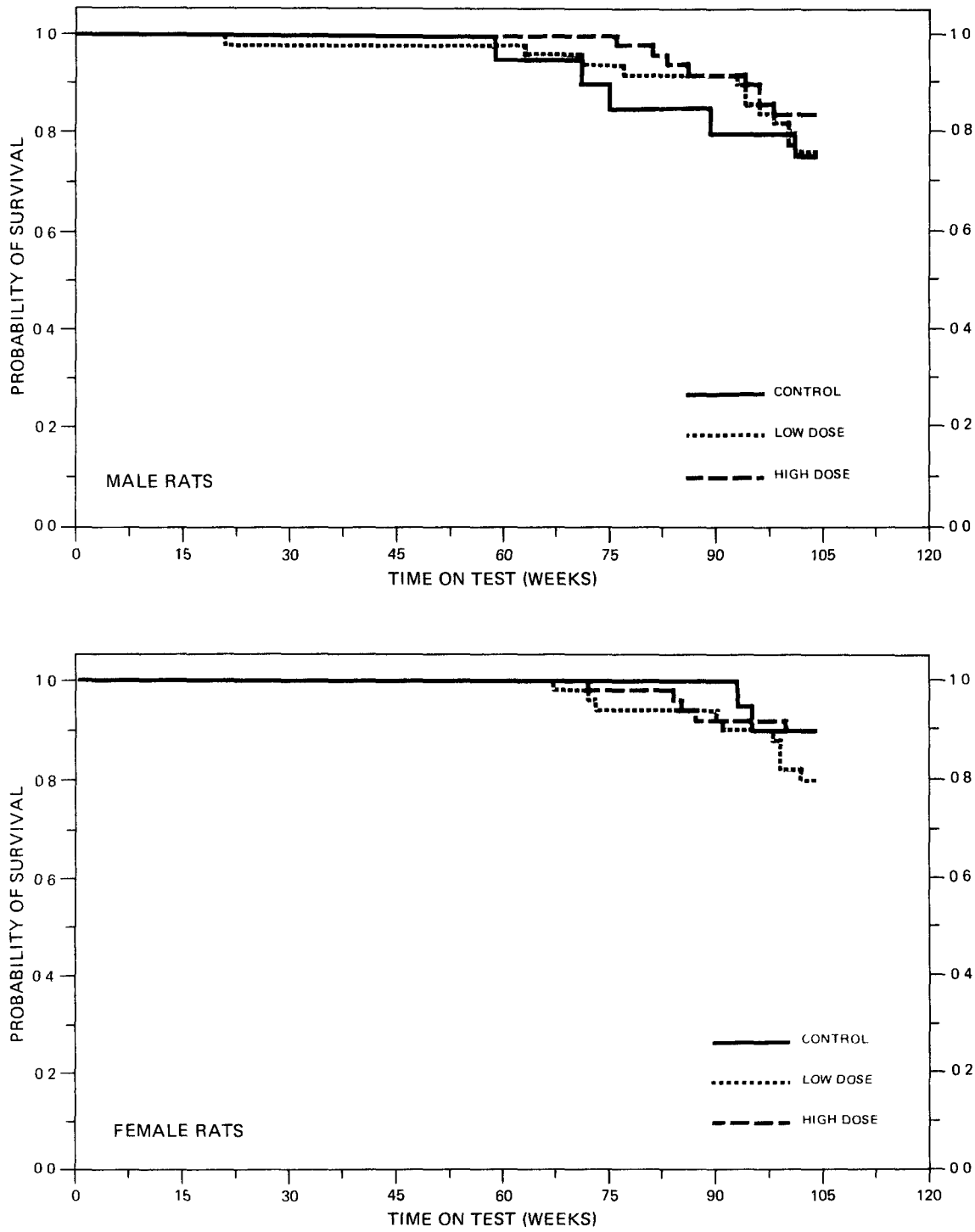


FIGURE 3
SURVIVAL COMPARISONS OF TRIPHENYLTIN HYDROXIDE CHRONIC STUDY RATS

A variety of neoplasms occurred both in the control and dosed groups while other neoplasms occurred only, or with a greater frequency, in dosed rats as compared with controls. These lesions, however, are not uncommon in this strain of rats.

The incidences of inflammatory, degenerative, and proliferative lesions were similar in dosed and control animals, and were consistent with spontaneous lesions found in aged Fischer 344 rats (Appendix C).

The results of this pathologic examination indicate that triphenyltin hydroxide was not carcinogenic in Fischer 344 rats under conditions of this bioassay.

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 triphenyltin hydroxide-dosed groups and where such tumors were observed in at least 5 percent of the group.

None of the statistical tests for any site of either male or female rats indicated a significant positive association between chemical administration and tumor incidence. Based upon these statistical results there was no evidence that triphenyltin hydroxide was carcinogenic in Fischer 344 rats under the conditions of this test.

TABLE 3

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	0/20(0.00)	6/50(0.12)	0/50(0.00)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.005	---	---
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.667	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	94	---
Pituitary: Chromophobe Adenoma[b]	2/20(0.10)	5/48(0.10)	9/46(0.20)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.042	1.957
Lower Limit	---	0.192	0.463
Upper Limit	---	10.410	17.603
Weeks to First Observed Tumor	104	94	86
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant[b]	2/20(0.10)	2/50(0.04)	4/49(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.400	0.816
Lower Limit	---	0.032	0.131
Upper Limit	---	5.277	8.603
Weeks to First Observed Tumor	104	104	104

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	2/18(0.11)	2/41(0.05)	0/44(0.00)
P Values[c]	P = 0.041(N)	N.S.	N.S.
Relative Risk (Control)[d]	---	0.439	0.000
Lower Limit	---	0.035	0.000
Upper Limit	---	5.743	1.370
Weeks to First Observed Tumor	104	100	---
Pancreatic Islets: Islet-Cell Adenoma or Islet-Cell Carcinoma[b]	2/19(0.11)	3/48(0.06)	3/49(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.594	0.582
Lower Limit	---	0.076	0.074
Upper Limit	---	6.774	6.640
Weeks to First Observed Tumor	89	100	96
Testis: Interstitial-Cell Tumor[b]	17/19(0.89)	46/50(0.92)	49/50(0.98)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.028	1.095
Lower Limit	---	0.898	0.961
Upper Limit	---	1.275	1.185
Weeks to First Observed Tumor	89	63	76

TABLE 3 (CONCLUDED)

---

[a]Treated groups received doses of 37.5 or 75 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

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Basal-Cell Tumor[b]	2/20(0.10)	1/50(0.02)	0/50(0.00)
P Values[c]	P = 0.035(N)	N.S.	N.S.
Relative Risk (Control)[d]	---	0.200	0.000
Lower Limit	---	0.004	0.000
Upper Limit	---	3.681	1.845
Weeks to First Observed Tumor	104	67	---
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	4/20(0.20)	2/50(0.04)	3/50(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.200	0.300
Lower Limit	---	0.020	0.049
Upper Limit	---	1.297	1.642
Weeks to First Observed Tumor	93	73	84
Pituitary: Chromophobe Adenoma[b]	7/17(0.41)	32/47(0.68)	26/49(0.53)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.036	---	---
Relative Risk (Control)[d]	---	1.653	1.289
Lower Limit	---	0.936	0.705
Upper Limit	---	3.547	2.231
Weeks to First Observed Tumor	104	72	84

TABLE 4 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Mammary Gland: Fibroadenoma[b]	1/20(0.05)	8/50(0.16)	4/50(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	3.200	1.600
Lower Limit	---	0.432	0.175
Upper Limit	---	138.771	77.168
Weeks to First Observed Tumor	104	98	104

[a]Treated groups received doses of 37.5 or 75 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 $P < 0.05$.

In male rats the Cochran-Armitage test indicated a significant negative association between dose and the combined incidence of C-cell adenomas and C-cell carcinomas of the thyroid. The Fisher exact tests, however, were not significant.

In female rats the Cochran-Armitage test indicated a significant negative association between dose and the incidence of basal-cell tumors of the subcutaneous tissue. The Fisher exact tests, however, were not significant.

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 all 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 all of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in rats by triphenyltin hydroxide that could not be established under the conditions of this test.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

No consistent dose-related mean body weight depression was noted in either male or female mice (Figure 4). In female mice, however, mean body weight was lower in dosed animals than in controls beginning in week 45.

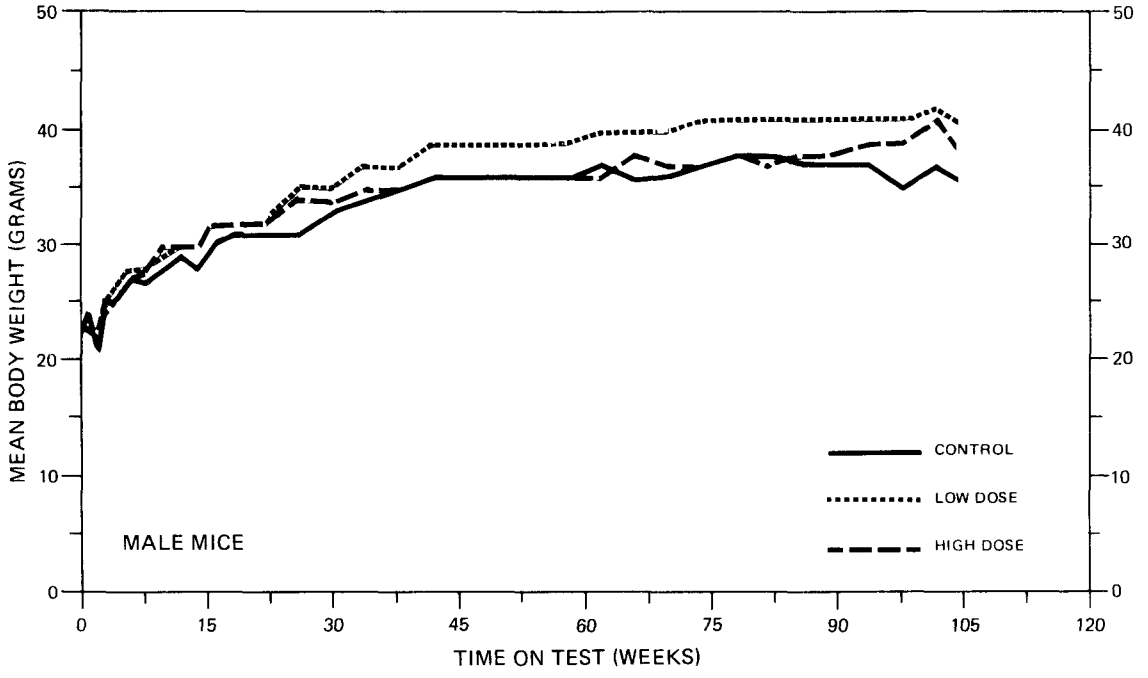
No abnormal clinical signs were recorded.

B. Survival

The estimated probabilities of survival for male and female mice in the control and triphenyltin hydroxide-dosed groups are shown in Figure 5. For male mice the Tarone test for association between increased dosage and elevated mortality was significant ($P = 0.017$); but for females it was not significant.

The percentages of male and female mice surviving on test are shown in Figure 6. For males, despite 4 missing high dose males and 6 missing low dose males, there were adequate numbers at risk from late-developing tumors. Sixty-six percent (33/50) of the high dose, 74 percent (37/50) of the low dose, and 95 percent (19/20) of the control mice survived on test until the termination of the study.

For females, despite 2 missing high dose, 8 missing low dose, and 2 missing control group mice, there were adequate numbers at risk from late-developing tumors. Seventy-six percent (38/50) of the high dose, 72 percent (36/50) of the low dose, and 65 percent (13/20) of the control mice survived on test until the end of the study.



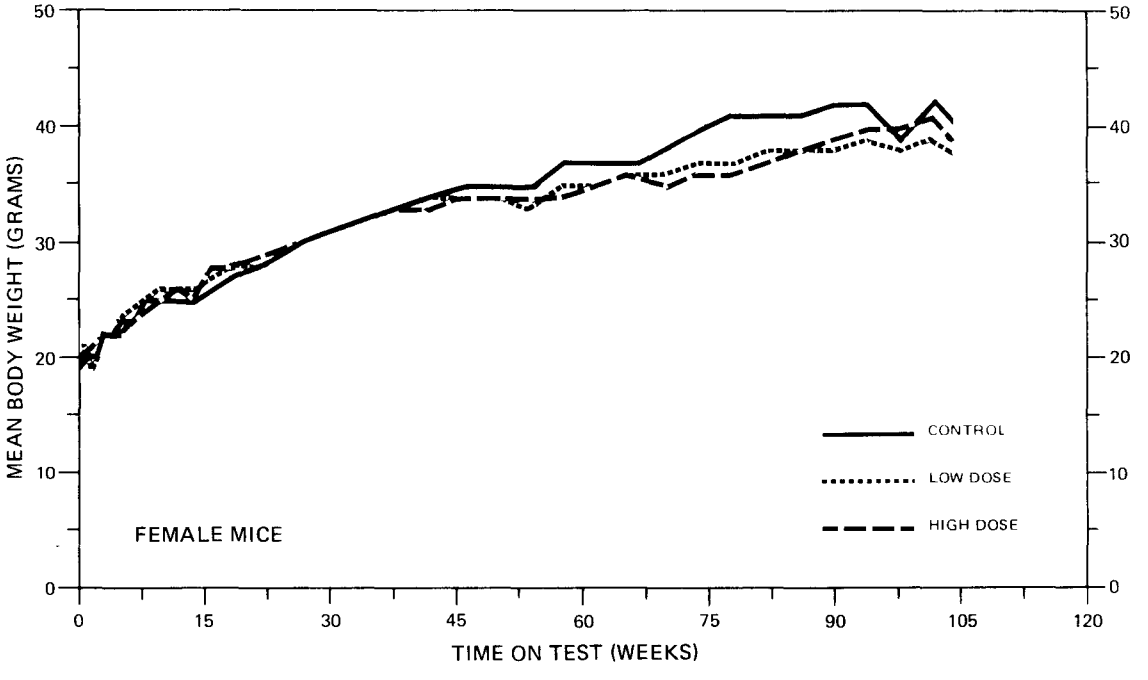


FIGURE 4
GROWTH CURVES FOR TRIPHENYLTIN HYDROXIDE CHRONIC STUDY MICE

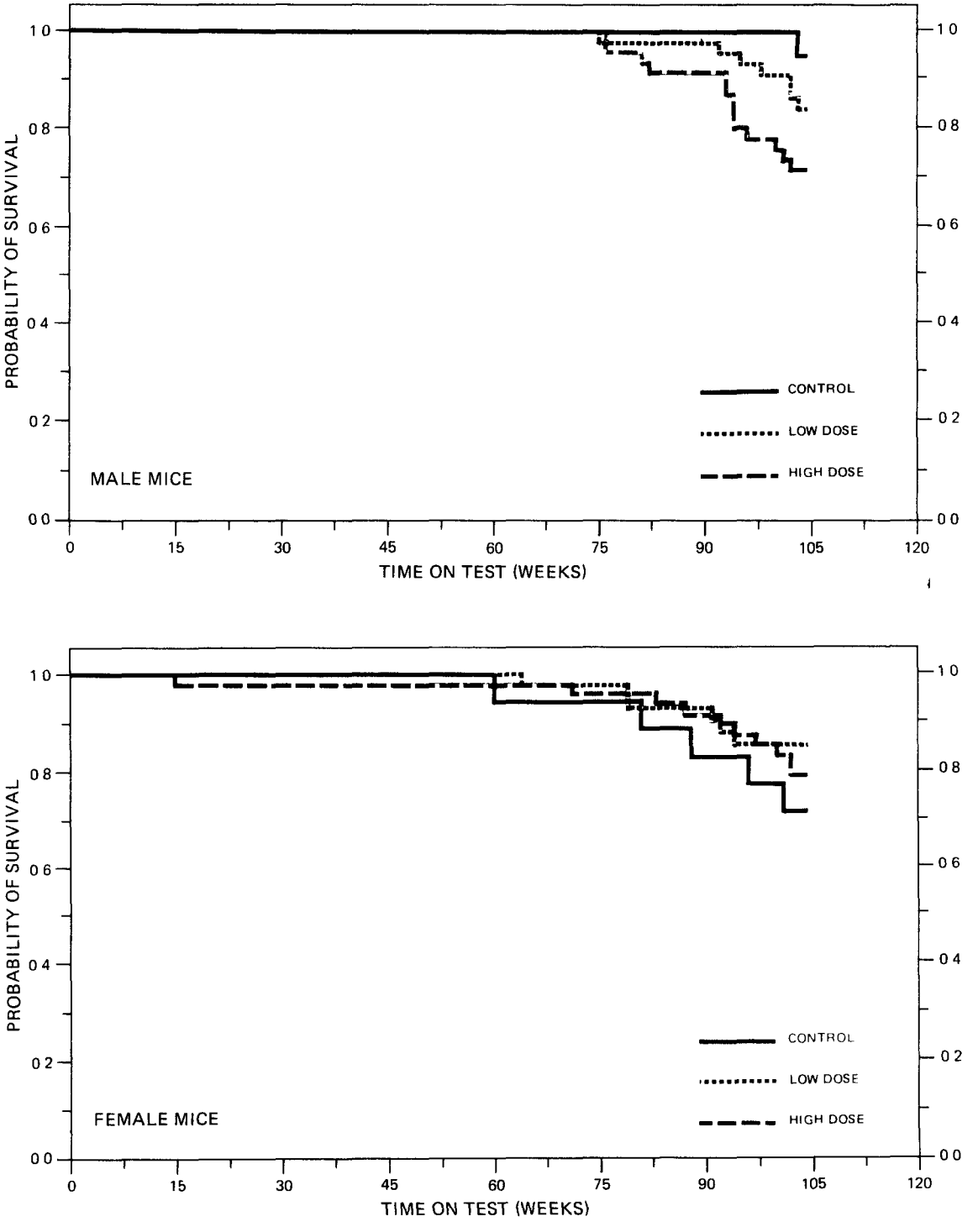
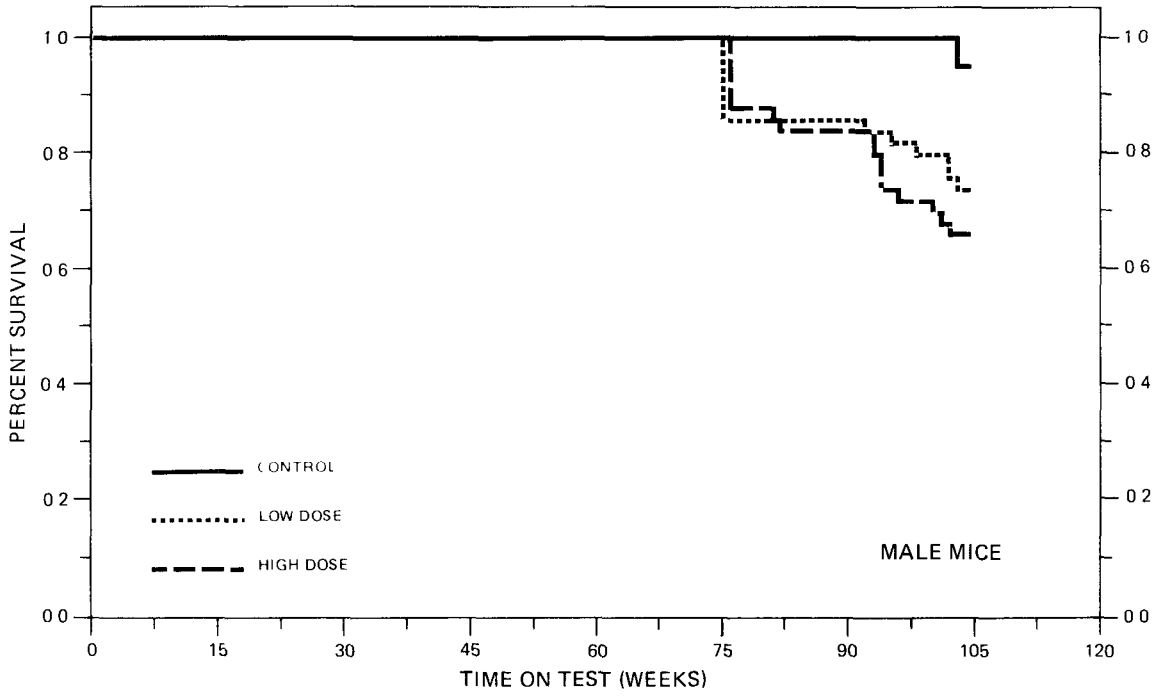


FIGURE 5
SURVIVAL PROBABILITY COMPARISONS OF TRIPHENYLTIN HYDROXIDE CHRONIC STUDY MICE



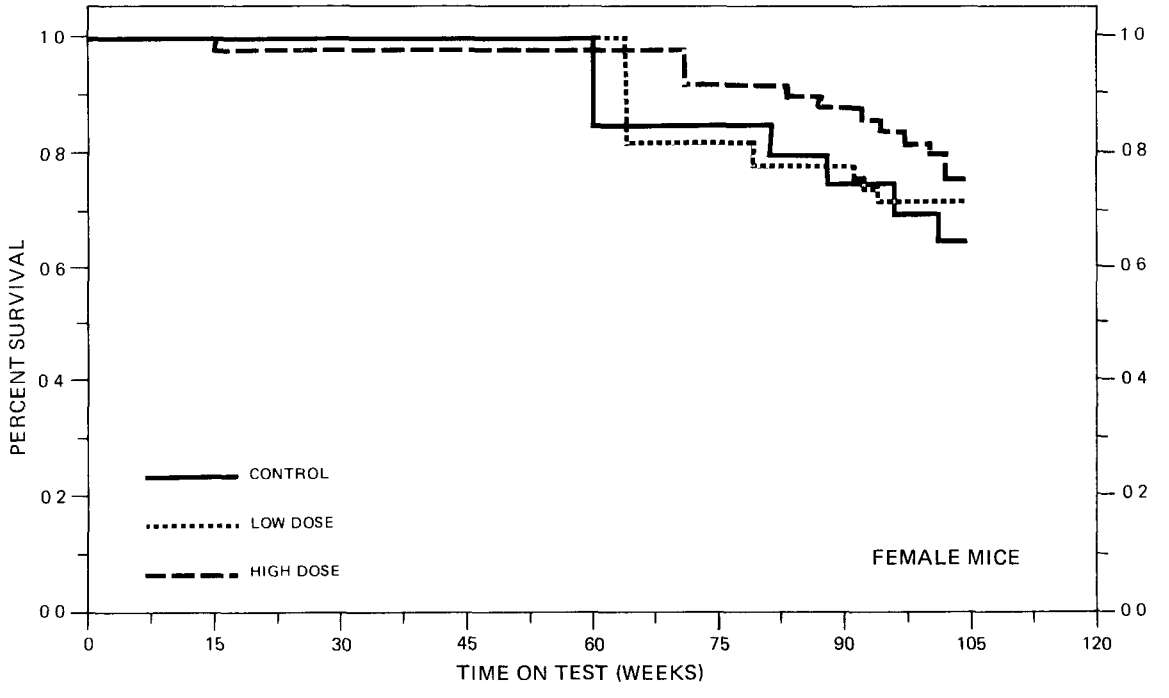


FIGURE 6
PERCENT SURVIVAL OF TRIPHENYLTIN HYDROXIDE CHRONIC STUDY MICE

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).

The observed neoplasms occurred with approximately equal frequency in dosed and control mice or occurred in insignificant numbers. These lesions are not uncommon in this strain of mice.

In addition, a number of degenerative, proliferative, and inflammatory changes were encountered in dosed and control mice. As with the neoplastic lesions, these changes are not uncommon in this strain of mice.

The results of this pathologic examination indicate that triphenyltin hydroxide was not carcinogenic in B6C3F1 mice 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 triphenyltin hydroxide-dosed groups and where such tumors were observed in at least 5 percent of the group.

None of the statistical tests for any site of either male or female mice indicated a significant positive association between chemical administration and tumor incidence. Based upon these

TABLE 5

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	3/20(0.15)	5/44(0.11)	6/45(0.13)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.758	0.889
Lower Limit	---	0.168	0.218
Upper Limit	---	4.536	5.104
Weeks to First Observed Tumor	104	102	104
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	2/20(0.10)	5/44(0.11)	10/46(0.22)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.136	2.174
Lower Limit	---	0.210	0.531
Upper Limit	---	11.319	19.281
Weeks to First Observed Tumor	103	98	76
Liver: Hepatocellular Carcinoma or Hepatocellular Adenoma[b]	5/19(0.26)	6/44(0.14)	10/44(0.23)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.518	0.864
Lower Limit	---	0.156	0.324
Upper Limit	---	1.932	2.871
Weeks to First Observed Tumor	104	75	76

TABLE 5 (CONCLUDED)

[a]Treated groups received doses of 37.5 or 75 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

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	6/18(0.33)	9/42(0.21)	14/48(0.29)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.643	0.875
Lower Limit	---	0.252	0.392
Upper Limit	---	1.924	2.429
Weeks to First Observed Tumor	88	79	83
Liver: Hepatocellular Adenoma or Hepatocellular Carcinoma[b]	1/18(0.06)	2/42(0.05)	4/48(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.857	1.500
Lower Limit	---	0.049	0.166
Upper Limit	---	49.369	72.294
Weeks to First Observed Tumor	104	104	97

[a]Treated groups received doses of 37.5 or 75 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.

statistical results there was no evidence that triphenyltin hydroxide was a carcinogen in B6C3F1 mice under the conditions of this test.

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 all 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 all of the confidence intervals have an upper limit greater than one, indicating the theoretical possibility of tumor induction in mice by triphenyltin hydroxide that could not be established under the conditions of this test.

V. DISCUSSION

In male mice there was a significant dose-related decrease in survival; however, in both species adequate numbers of animals in all groups survived sufficiently long to be at risk from late-developing tumors. Male rats and female mice had a slight depression of mean body weight gain relative to controls. In rats and female mice no significant accelerated mortality, retardation in growth, or other signs of toxicity were associated with the dietary administration of triphenyltin hydroxide. Therefore it is possible that the compound was not administered to these animals at the maximum tolerated concentration.

No tumors occurred in rats or mice at a significantly higher incidence in dosed groups than in corresponding control groups.

Under the conditions of this bioassay, there was no evidence for the carcinogenicity of triphenyltin hydroxide to Fischer 344 rats or to B6C3F1 mice.

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Review of the Bioassay of Triphenyltin Hydroxide* 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 Triphenyltin Hydroxide for carcinogenicity.

The reviewer agreed with the conclusion in the report that Triphenyltin Hydroxide was not carcinogenic in rats or mice, under the conditions of test. Although the control groups were smaller than the optimal size, he thought the study was adequate enough on which to base the conclusion. The reviewer moved that the report on the bioassay of Triphenyltin Hydroxide 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

* 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 TRIPHENYLTIN HYDROXIDE

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

	CONTROL(UNTR) 11-1335	LOW DOSE 11-1333	HIGH DOSE 11-1331
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(20)	(50)	(50)
BASAL-CELL TUMOR		2 (4%)	
SEBACEOUS ADENOMA		1 (2%)	
FIBROMA		2 (4%)	
CARCINOSARCOMA	1 (5%)		
NEUROFIBROMA	1 (5%)		
NEUROFIBROSARCOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(20)	(49)	(49)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (5%)	1 (2%)	2 (4%)
C-CELL CARCINOMA, METASTATIC		1 (2%)	
NEUROFIBROSARCOMA, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
MALIGNANT LYMPHOMA, NOS		3 (6%)	
LEUKEMIA,NOS		3 (6%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(19)	(50)	(50)
HEPATOCELLULAR ADENOMA		2 (4%)	

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

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 11-1335	LOW DOSE 11-1333	HIGH DOSE 11-1331
#PANCREAS	(19)	(48)	(49)
ADENOMA, NOS	1 (5%)		
#SMALL INTESTINE	(20)	(49)	(50)
SARCOMA, NOS			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(48)	(46)
CHROMOPHOBE ADENOMA	2 (10%)	5 (10%)	9 (20%)
#ADRENAL	(20)	(50)	(49)
PHEOCHROMOCYTOMA	2 (10%)	2 (4%)	3 (6%)
PHEOCHROMOCYTOMA, MALIGNANT			1 (2%)
#THYROID	(18)	(41)	(44)
FOLLICULAR-CELL ADENOMA	1 (6%)		
C-CELL ADENOMA	1 (6%)	1 (2%)	
C-CELL CARCINOMA	1 (6%)	1 (2%)	
#PANCREATIC ISLETS	(19)	(48)	(49)
ISLET-CELL ADENOMA	2 (11%)	2 (4%)	3 (6%)
ISLET-CELL CARCINOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
FIBROADENOMA			1 (2%)
#TESTIS	(19)	(50)	(50)
INTERSTITIAL-CELL TUMOR	17 (89%)	46 (92%)	49 (98%)
NERVOUS SYSTEM			
#BRAIN	(20)	(48)	(47)
GLIOMA, NOS		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			

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

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 11-1335	LOW DOSE 11-1333	HIGH DOSE 11-1331
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(50)	(50)
MESOTHELIOMA, NOS		1 (2%)	
*PERITONEUM	(20)	(50)	(50)
MESOTHELIOMA, NOS			1 (2%)
*TUNICA VAGINALIS	(20)	(50)	(50)
MESOTHELIOMA, NOS		2 (4%)	
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	2	6	
MORIBUND SACRIFICE	3	6	8
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	15	38	42
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A1 (CONCLUDED)

	CONTROL (UNTR) 11-1335	LOW DOSE 11-1333	HIGH DOSE 11-1331
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	18	49	50
TOTAL PRIMARY TUMORS	30	76	71
TOTAL ANIMALS WITH BENIGN TUMORS	17	47	50
TOTAL BENIGN TUMORS	28	64	67
TOTAL ANIMALS WITH MALIGNANT TUMORS	2	8	3
TOTAL MALIGNANT TUMORS	2	9	3
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	1
TOTAL SECONDARY TUMORS		1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT		3	1
TOTAL UNCERTAIN TUMORS		3	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 TRIPHENYLTIN HYDROXIDE

	CONTROL (UNTR) 11-1336	LOW DOSE 11-1334	HIGH DOSE 11-1332
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
BASAL-CELL CARCINOMA			1 (2%)
*SUBCUT TISSUE	(20)	(50)	(50)
BASAL-CELL TUMOR	2 (10%)	1 (2%)	
FIBROADENOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
BASAL-CELL CARCINOMA, METASTATIC			1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA		2 (4%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (5%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	2 (10%)	2 (4%)	1 (2%)
LEUKEMIA,NOS	2 (10%)		1 (2%)
#MESENTERIC L. NODE	(20)	(44)	(50)
MALIGNANT LYMPHOMA, NOS			1 (2%)
CIRCULATORY SYSTEM			
#HEART	(20)	(49)	(50)
SARCOMA, NOS		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(19)	(50)	(50)
NEOPLASTIC NODULE		1 (2%)	

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

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 11-1336	LOW DOSE 11-1334	HIGH DOSE 11-1332
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(17)	(47)	(49)
CHROMOPHOBE ADENOMA	7 (41%)	32 (68%)	26 (53%)
#ADRENAL	(20)	(48)	(50)
CORTICAL ADENOMA	1 (5%)		
PHEOCHROMOCYTOMA			1 (2%)
#THYROID	(17)	(47)	(42)
FOLLICULAR-CELL ADENOMA		1 (2%)	
C-CELL ADENOMA			1 (2%)
C-CELL CARCINOMA	1 (6%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
ADENOMA, NOS		1 (2%)	
FIBROADENOMA	1 (5%)	8 (16%)	4 (8%)
*MAMMARY DUCT	(20)	(50)	(50)
CYSTADENOMA, NOS		1 (2%)	
#UTERUS	(18)	(47)	(48)
ENDOMETRIAL STROMAL POLYP	1 (6%)	1 (2%)	1 (2%)
NERVOUS SYSTEM			
#BRAIN	(18)	(47)	(49)
GLIOMA, NOS		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE A2 (CONCLUDED)

	CONTROL (UNTR) 11-1336	LOW DOSE 11-1334	HIGH DOSE 11-1332
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
OMENTUM			
LIPOSARCOMA		1	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	2	3	
MORIBUND SACRIFICE		7	5
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	18	40	45
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	12	39	31
TOTAL PRIMARY TUMORS	18	53	39
TOTAL ANIMALS WITH BENIGN TUMORS	9	36	29
TOTAL BENIGN TUMORS	12	47	35
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	5	4
TOTAL MALIGNANT TUMORS	6	5	4
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

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH TRIPHENYLTIN HYDROXIDE

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

	CONTROL(UNTR) 22-2335	LOW DOSE 22-2333	HIGH DOSE 22-2331
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		6	4
ANIMALS NECROPSIED	20	44	46
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	44	45
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(20)	(44)	(45)
HEPATOCELLULAR CARCINOMA, METAST			4 (9%)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (10%)	4 (9%)	6 (13%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (5%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(44)	(46)
MALIGNANT LYMPHOMA, NOS		3 (7%)	6 (13%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			2 (4%)
MALIGNANT LYMPHOMA, MIXED TYPE			1 (2%)
LEUKEMIA,NOS		1 (2%)	
#LYMPH NODE	(20)	(38)	(37)
MALIGNANT LYMPHOMA, NOS	1 (5%)		
#MESENTERIC L. NODE	(20)	(38)	(37)
MALIGNANT LYMPHOMA, NOS	1 (5%)	1 (3%)	
#LIVER	(19)	(44)	(44)
GRANULOCYTIC SARCOMA		1 (2%)	
#SMALL INTESTINE	(19)	(44)	(44)
MALIG.LYMPHOMA, UNDIFFER-TYPE			1 (2%)
CIRCULATORY SYSTEM			
NONE			

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

TABLE B1 (CONTINUED)

	CONTROL (UNTR) 22-2335	LOW DOSE 22-2333	HIGH DOSE 22-2331
DIGESTIVE SYSTEM			
#LIVER	(19)	(44)	(44)
BILE DUCT CARCINOMA			1 (2%)
HEPATOCELLULAR ADENOMA	2 (11%)	5 (11%)	3 (7%)
HEPATOCELLULAR CARCINOMA	3 (16%)	1 (2%)	7 (16%)
#COLON	(18)	(41)	(43)
SARCOMA, NOS			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#ADRENAL	(16)	(36)	(37)
SARCOMA, NOS		1 (3%)	
#THYROID	(15)	(33)	(38)
FOLLICULAR-CELL ADENOMA			1 (3%)
REPRODUCTIVE SYSTEM			
#TESTIS	(20)	(43)	(45)
INTERSTITIAL-CELL TUMOR		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE B1 (CONCLUDED)

	CONTROL (UNTR) 22-2335	LOW DOSE 22-2333	HIGH DOSE 22-2331
BODY CAVITIES			
*MESENTERY	(20)	(44)	(46)
CARCINOMA, NOS	1 (5%)		
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	1	4	9
MORIBUND SACRIFICE		3	4
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	19	37	33
ANIMAL MISSING		6	4
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	10	19	22
TOTAL PRIMARY TUMORS	11	19	29
TOTAL ANIMALS WITH BENIGN TUMORS	4	10	8
TOTAL BENIGN TUMORS	4	10	10
TOTAL ANIMALS WITH MALIGNANT TUMORS	7	9	17
TOTAL MALIGNANT TUMORS	7	9	19
TOTAL ANIMALS WITH SECONDARY TUMORS#			4
TOTAL SECONDARY TUMORS			4
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 TRIPHENYLTIN HYDROXIDE

	CONTROL (UNTR) 22-2336	LOW DOSE 22-2334	HIGH DOSE 22-2332
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	2	8	2
ANIMALS NECROPSIED	18	42	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	18	42	48
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(18)	(40)	(46)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (3%)	2 (4%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(18)	(42)	(48)
MALIGNANT LYMPHOMA, NOS	2 (11%)	3 (7%)	7 (15%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (6%)	3 (7%)	2 (4%)
PLASMA-CELL TUMOR			1 (2%)
LEUKEMIA,NOS	2 (11%)		1 (2%)
*MEDIASTINUM	(18)	(42)	(48)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
#BONE MARROW	(10)	(35)	(29)
HEMANGIOSARCOMA		1 (3%)	
#SPLEEN	(18)	(39)	(45)
HEMANGIOSARCOMA		1 (3%)	
MALIGNANT LYMPHOMA, NOS			1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (3%)	1 (2%)
#MESENTERIC L. NODE	(15)	(40)	(38)
SARCOMA, NOS		1 (3%)	
MALIGNANT LYMPHOMA, NOS		1 (3%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (3%)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (7%)		

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

TABLE B2 (CONTINUED)

	CONTROL (UNTR) 22-2336	LOW DOSE 22-2334	HIGH DOSE 22-2332
#LIVER	(18)	(42)	(48)
MALIGNANT LYMPHOMA, NOS			1 (2%)
#THYMUS	(1)	(1)	(6)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (100%)		
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(18)	(42)	(48)
HEPATOCELLULAR ADENOMA	1 (6%)	2 (5%)	3 (6%)
HEPATOCELLULAR CARCINOMA			1 (2%)
SARCOMA, NOS		1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
NONE			
REPRODUCTIVE SYSTEM			
#UTERUS	(18)	(40)	(45)
ENDOMETRIAL STROMAL POLYP		1 (3%)	
#OVARY	(17)	(33)	(37)
ADENOCARCINOMA, NOS	1 (6%)		
NERVOUS SYSTEM			
#BRAIN	(18)	(40)	(45)
OLIGODENDROGLIOMA	1 (6%)		
SPECIAL SENSE ORGANS			
NONE			

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

TABLE B2 (CONTINUED)

	CONTROL (UNTR) 22-2336	LOW DOSE 22-2334	HIGH DOSE 22-2332
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(18)	(42)	(48)
HEMANGIOMA	1 (6%)		
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	5	3	8
MORIBUND SACRIFICE		3	2
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	13	36	38
ANIMAL MISSING	2	8	2

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2 (CONCLUDED)

	CONTROL (UNTR) 22-2336	LOW DOSE 22-2334	HIGH DOSE 22-2332
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	10	15	18
TOTAL PRIMARY TUMORS	11	17	21
TOTAL ANIMALS WITH BENIGN TUMORS	2	4	5
TOTAL BENIGN TUMORS	2	4	5
TOTAL ANIMALS WITH MALIGNANT TUMORS	8	11	14
TOTAL MALIGNANT TUMORS	9	13	15
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT			1
TOTAL UNCERTAIN TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH TRIPHENYLTIN HYDROXIDE

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

	CONTROL (UNTR) 11-1335	LOW DOSE 11-1333	HIGH DOSE 11-1331
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	
*SUBCUT TISSUE	(20)	(50)	(50)
HEMATOMA, NOS	1 (5%)		
INFLAMMATION ACUTE AND CHRONIC			1 (2%)
RESPIRATORY SYSTEM			
#TRACHEA	(20)	(48)	(48)
INFLAMMATION, NOS	2 (10%)		
#LUNG/BRONCHUS	(20)	(49)	(49)
HYPERPLASIA, EPITHELIAL			1 (2%)
#LUNG	(20)	(49)	(49)
HEMORRHAGE			1 (2%)
PNEUMONIA, ASPIRATION		1 (2%)	
PNEUMONIA, CHRONIC MURINE	9 (45%)	21 (43%)	16 (33%)
INFLAMMATION, FOCAL GRANULOMATOU	1 (5%)		
PERIVASCULITIS			1 (2%)
HYPERPLASIA, ADENOMATOUS	2 (10%)	1 (2%)	4 (8%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(18)	(45)	(47)
HYPERPLASIA, HEMATOPOIETIC		2 (4%)	1 (2%)
#SPLEEN	(19)	(50)	(50)
CONGESTION, NOS		1 (2%)	
HEMOSIDEROSIS	6 (32%)	9 (18%)	10 (20%)

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 11-1335	LOW DOSE 11-1333	HIGH DOSE 11-1331
LEUKEMOID REACTION			2 (4%)
HYPERPLASIA, LYMPHOID			1 (2%)
HEMATOPOIESIS	5 (26%)	5 (10%)	10 (20%)
#CERVICAL LYMPH NODE	(20)	(45)	(49)
CYST, NOS			1 (2%)
EDEMA, NOS			2 (4%)
#MESENTERIC L. NODE	(20)	(45)	(49)
EDEMA, NOS	2 (10%)	2 (4%)	1 (2%)
HYPERPLASIA, RETICULUM CELL			1 (2%)
#RENAL LYMPH NODE	(20)	(45)	(49)
EDEMA, NOS			1 (2%)
CIRCULATORY SYSTEM			
#HEART	(20)	(49)	(49)
ENDOCARDITIS, VERRUCOUS			1 (2%)
PERIVASCULITIS			1 (2%)
#MYOCARDIUM	(20)	(49)	(49)
INFLAMMATION, FOCAL	1 (5%)		
FIBROSIS	1 (5%)	2 (4%)	5 (10%)
FIBROSIS, FOCAL		1 (2%)	1 (2%)
DEGENERATION, NOS	7 (35%)	20 (41%)	15 (31%)
DEGENERATION, GRANULAR		1 (2%)	1 (2%)
DEGENERATION, HYALINE	4 (20%)	6 (12%)	9 (18%)
*AORTA	(20)	(50)	(50)
PERIARTERITIS			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(19)	(47)	(48)
INFLAMMATION, CHRONIC			1 (2%)
ATROPHY, FOCAL			1 (2%)
#LIVER	(19)	(50)	(50)
CYST, NOS		1 (2%)	
THROMBOSIS, NOS			1 (2%)
CONGESTION, NOS		1 (2%)	2 (4%)
DEGENERATION, NOS		3 (6%)	1 (2%)

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

TABLE C1 (CONTINUED)

	CONTROL(UNTR) 11-1335	LOW DOSE 11-1333	HIGH DOSE 11-1331
NECROSIS, FOCAL			1 (2%)
METAMORPHOSIS FATTY	1 (5%)		1 (2%)
BASOPHILIC CYTO CHANGE	4 (21%)	6 (12%)	8 (16%)
HYPERPLASIA, FOCAL	2 (11%)	8 (16%)	7 (14%)
LEUKEMOID REACTION			3 (6%)
#LIVER/CENTRILOBULAR	(19)	(50)	(50)
DEGENERATION, NOS			1 (2%)
NECROSIS, NOS		1 (2%)	
*BILE DUCT	(20)	(50)	(50)
HEMORRHAGE		1 (2%)	
HYPERPLASIA, NOS	5 (25%)	16 (32%)	11 (22%)
#PANCREAS	(19)	(48)	(49)
INFLAMMATION, NOS			1 (2%)
FIBROSIS			1 (2%)
PERIARTERITIS			2 (4%)
PERIVASCULITIS			1 (2%)
ATROPHY, FOCAL	1 (5%)	2 (4%)	2 (4%)
#PANCREATIC ACINUS	(19)	(48)	(49)
ATROPHY, NOS			2 (4%)
#STOMACH	(20)	(49)	(49)
ULCER, NOS			1 (2%)
GRANULATION, TISSUE			1 (2%)
HYPERPLASIA, EPITHELIAL			1 (2%)
#LARGE INTESTINE	(20)	(48)	(49)
NEMATODIASIS	6 (30%)	16 (33%)	17 (35%)
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(50)
CYST, NOS			1 (2%)
INFLAMMATION, CHRONIC	17 (85%)	42 (84%)	43 (86%)
HEMOSIDEROSIS			1 (2%)
#KIDNEY/TUBULE	(20)	(50)	(50)
BASOPHILIC CYTO CHANGE	1 (5%)	1 (2%)	1 (2%)
ENDOCRINE SYSTEM			
#ADRENAL	(20)	(50)	(49)
CONGESTION, NOS	1 (5%)		

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

TABLE C1 (CONTINUED)

	CONTROL(UNTR) 11-1335	LOW DOSE 11-1333	HIGH DOSE 11-1331
HEMOSIDEROSIS	1 (5%)		
#ADRENAL CORTEX	(20)	(50)	(49)
HYPERPLASIA, NOS		1 (2%)	
#ADRENAL MEDULLA	(20)	(50)	(49)
HYPERPLASIA, NOS		1 (2%)	
#THYROID	(18)	(41)	(44)
HYPERPLASIA, C-CELL	1 (6%)		2 (5%)
#PANCREATIC ISLETS	(19)	(48)	(49)
HYPERPLASIA, NOS			1 (2%)
REPRODUCTIVE SYSTEM			
*SEMINAL VESICLE	(20)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
#TESTIS	(19)	(50)	(50)
GRANULOMA, SPERMATIC			1 (2%)
DEGENERATION, NOS		1 (2%)	
ATROPHY, NOS	1 (5%)	3 (6%)	1 (2%)
NERVOUS SYSTEM			
#BRAIN	(20)	(48)	(47)
HEMORRHAGIC CYST		1 (2%)	
GLIOSIS			1 (2%)
ATROPHY, NOS		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(20)	(50)	(50)
INFLAMMATION, NOS			1 (2%)

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

TABLE C1 (CONCLUDED)

	CONTROL (UNTR) 11-1335	LOW DOSE 11-1333	HIGH DOSE 11-1331
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
NECROSIS, FAT		1	1
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	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 TRIPHENYLTIN HYDROXIDE

	CONTROL(UNTR) 11-1336	LOW DOSE 11-1334	HIGH DOSE 11-1332
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	50	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#TRACHEA	(16)	(49)	(48)
INFLAMMATION, NOS	1 (6%)		1 (2%)
#LUNG	(20)	(50)	(50)
PNEUMONIA, CHRONIC MURINE	9 (45%)	24 (48%)	18 (36%)
INFLAMMATION, FOCAL GRANULOMATOU		1 (2%)	
BASOPHILIC CYTO CHANGE		1 (2%)	
FOAM-CELL		2 (4%)	2 (4%)
HYPERPLASIA, ADENOMATOUS		1 (2%)	4 (8%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(17)	(46)	(50)
HEMOSIDEROSIS	3 (18%)	12 (26%)	12 (24%)
LEUKEMOID REACTION		1 (2%)	3 (6%)
HEMATOPOIESIS	3 (18%)	13 (28%)	8 (16%)
#CERVICAL LYMPH NODE	(20)	(44)	(50)
EDEMA, NOS		1 (2%)	
#MESENTERIC L. NODE	(20)	(44)	(50)
EDEMA, NOS		2 (5%)	1 (2%)
HYPERPLASIA, RETICULUM CELL		1 (2%)	1 (2%)
CIRCULATORY SYSTEM			
#MYOCARDIUM	(20)	(49)	(50)
INFLAMMATION, CHRONIC			1 (2%)

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 11-1336	LOW DOSE 11-1334	HIGH DOSE 11-1332
FIBROSIS	2 (10%)		1 (2%)
DEGENERATION, NOS	5 (25%)	19 (39%)	15 (30%)
DEGENERATION, HYALINE	3 (15%)	5 (10%)	6 (12%)
*AORTA	(20)	(50)	(50)
INFLAMMATION, NECROTIZING		1 (2%)	1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(20)	(46)	(49)
INFLAMMATION, CHRONIC		1 (2%)	
#LIVER	(19)	(50)	(50)
DEGENERATION, NOS	1 (5%)	2 (4%)	
NECROSIS, FOCAL	1 (5%)		
METAMORPHOSIS FATTY	1 (5%)		
BASOPHILIC CYTO CHANGE	4 (21%)	15 (30%)	13 (26%)
FOCAL CELLULAR CHANGE			1 (2%)
HYPERPLASIA, NOS		4 (8%)	1 (2%)
HYPERPLASIA, FOCAL	8 (42%)	13 (26%)	21 (42%)
LEUKEMOID REACTION		1 (2%)	3 (6%)
HEMATOPOIESIS			1 (2%)
#LIVER/CENTRILOBULAR	(19)	(50)	(50)
NECROSIS, NOS		2 (4%)	
#LIVER/PERIPORTAL	(19)	(50)	(50)
FIBROSIS		1 (2%)	
*BILE DUCT	(20)	(50)	(50)
HYPERPLASIA, NOS	6 (30%)	20 (40%)	17 (34%)
#PANCREAS	(18)	(49)	(50)
FIBROSIS	1 (6%)		
ATROPHY, NOS	1 (6%)		
ATROPHY, FOCAL	1 (6%)	4 (8%)	
#PANCREATIC ACINUS	(18)	(49)	(50)
ATROPHY, NOS	1 (6%)		1 (2%)
#STOMACH	(19)	(49)	(50)
CYST, NOS		1 (2%)	
#LARGE INTESTINE	(20)	(47)	(49)
NEMATODIASIS	7 (35%)	8 (17%)	6 (12%)

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 11-1336	LOW DOSE 11-1334	HIGH DOSE 11-1332
PARASITISM		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(50)
CYST, NOS		1 (2%)	
INFLAMMATION, CHRONIC	15 (75%)	43 (86%)	36 (72%)
#KIDNEY/CORTEX	(20)	(50)	(50)
CYST, NOS		1 (2%)	
#KIDNEY/PELVIS	(20)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(17)	(47)	(49)
CYST, NOS		3 (6%)	3 (6%)
HEMORRHAGE		1 (2%)	
HEMORRHAGIC CYST		1 (2%)	
#ADRENAL	(20)	(48)	(50)
CYST, NOS	1 (5%)		
LIPOIDOSIS			1 (2%)
ANGIECTASIS		1 (2%)	
#ADRENAL MEDULLA	(20)	(48)	(50)
HYPERPLASIA, NOS		1 (2%)	1 (2%)
#THYROID	(17)	(47)	(42)
INFLAMMATION, NECROTIZING	1 (6%)		
HYPERPLASIA, C-CELL	1 (6%)	3 (6%)	1 (2%)
#PANCREATIC ISLETS	(18)	(49)	(50)
HYPERPLASIA, NOS		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
DILATATION/DUCTS		2 (4%)	2 (4%)
RETENTION FLUID		1 (2%)	
CYSTIC DUCTS	1 (5%)	3 (6%)	1 (2%)

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

TABLE C2 (CONTINUED)

	CONTROL(UNTR) 11-1336	LOW DOSE 11-1334	HIGH DOSE 11-1332
#UTERUS	(18)	(47)	(48)
CYST, NOS		2 (4%)	1 (2%)
HEMORRHAGE		1 (2%)	
#CERVIX UTERI	(18)	(47)	(48)
CYST, NOS	1 (6%)		
#UTERUS/ENDOMETRIUM	(18)	(47)	(48)
HYPERPLASIA, NOS	3 (17%)	2 (4%)	2 (4%)
HYPERPLASIA, CYSTIC	1 (6%)	2 (4%)	
#OVARY	(17)	(47)	(45)
CYST, NOS			2 (4%)
FOLLICULAR CYST, NOS	1 (6%)	3 (6%)	
NERVOUS SYSTEM			
#BRAIN	(18)	(47)	(49)
HYDROCEPHALUS, NOS	1 (6%)		1 (2%)
ATROPHY, NOS	1 (6%)	6 (13%)	
#CEREBELLUM	(18)	(47)	(49)
HEMORRHAGE	1 (6%)		
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PELVIS	(20)	(50)	(50)
STEATITIS	1 (5%)		
*MESENTERY	(20)	(50)	(50)
HEMATOMA, ORGANIZED	1 (5%)		

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

TABLE C2 (CONCLUDED)

	CONTROL (UNTR) 11-1336	LOW DOSE 11-1334	HIGH DOSE 11-1332
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
STEATITIS		1	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED			3

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE TREATED WITH TRIPHENYLTIN HYDROXIDE

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

	CONTROL (UNTR) 22-2335	LOW DOSE 22-2333	HIGH DOSE 22-2331
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		6	4
ANIMALS NECROPSIED	20	44	46
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	44	45
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(20)	(44)	(45)
EDEMA, NOS			1 (2%)
PNEUMONIA, CHRONIC MURINE		2 (5%)	3 (7%)
PERIVASCULAR CUFFING	1 (5%)		
HEMATOPOIETIC SYSTEM			
#SPLEEN	(19)	(41)	(41)
HYPERPLASIA, RETICULUM CELL			1 (2%)
HYPERPLASIA, LYMPHOID		1 (2%)	
#LYMPH NODE	(20)	(38)	(37)
INFLAMMATION, NECROTIZING		1 (3%)	
HYPERPLASIA, NOS		1 (3%)	
HYPERPLASIA, RETICULUM CELL		1 (3%)	1 (3%)
#MESENTERIC L. NODE	(20)	(38)	(37)
INFLAMMATION, CHRONIC			1 (3%)
CIRCULATORY SYSTEM			
#HEART	(18)	(40)	(41)
MINERALIZATION			1 (2%)
#MYOCARDIUM	(18)	(40)	(41)
FIBROSIS, FOCAL			1 (2%)

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

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 22-2335	LOW DOSE 22-2333	HIGH DOSE 22-2331
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(18)	(36)	(34)
PERIVASCULAR CUFFING		1 (3%)	
#LIVER	(19)	(44)	(44)
INFLAMMATION, NECROTIZING		2 (5%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
PERIVASCULAR CUFFING	1 (5%)		
NECROSIS, NOS			1 (2%)
NECROSIS, FOCAL			1 (2%)
NECROSIS, HEMORRHAGIC			1 (2%)
INFARCT, NOS			1 (2%)
HYPERPLASIA, NOS	1 (5%)		2 (5%)
HEMATOPOIESIS		1 (2%)	
#LIVER/PERIPORTAL	(19)	(44)	(44)
INFLAMMATION, NOS		1 (2%)	
#BILE DUCT	(20)	(44)	(46)
DILATATION, NOS			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (5%)		
#PEYERS PATCH	(19)	(44)	(44)
HYPERPLASIA, NOS		1 (2%)	
#LARGE INTESTINE	(18)	(41)	(43)
PARASITISM	3 (17%)	5 (12%)	12 (28%)
#COLON	(18)	(41)	(43)
PARASITISM			3 (7%)
URINARY SYSTEM			
#KIDNEY	(19)	(44)	(41)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
PERIVASCULAR CUFFING	3 (16%)	2 (5%)	1 (2%)
#URINARY BLADDER	(19)	(38)	(33)
PERIVASCULAR CUFFING			1 (3%)
METAPLASIA, SQUAMOUS		1 (3%)	
ENDOCRINE SYSTEM			
#PANCREATIC ISLETS	(19)	(41)	(41)
HYPERPLASIA, NOS			1 (2%)

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

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 22-2335	LOW DOSE 22-2333	HIGH DOSE 22-2331
REPRODUCTIVE SYSTEM			
#PROSTATE	(20)	(38)	(40)
INFLAMMATION, NOS		1 (3%)	
#TESTIS	(20)	(43)	(45)
ATROPHY, NOS	1 (5%)		
NERVOUS SYSTEM			
#BRAIN	(19)	(44)	(43)
SPONGIOSIS		1 (2%)	
CORPORA AMYLACEA	3 (16%)	9 (20%)	14 (33%)
CALCIFICATION, FOCAL			1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(20)	(44)	(46)
STEATITIS	1 (5%)		
NECROSIS, FAT	1 (5%)		
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	4	13	9
ANIMAL MISSING/NO NECROPSY		6	4

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

TABLE D1 (CONCLUDED)

	CONTROL (UNTR) 22-2335	LOW DOSE 22-2333	HIGH DOSE 22-2331
AUTO/NECROPSY/NO HISTO			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 TRIPHENYLTIN HYDROXIDE

	CONTROL (UNTR) 22-2336	LOW DOSE 22-2334	HIGH DOSE 22-2332
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	2	8	2
ANIMALS NECROPSIED	18	42	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	18	42	48
INTEGUMENTARY SYSTEM			
*SKIN	(18)	(42)	(48)
ABSCESS, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(18)	(40)	(46)
ATELECTASIS		1 (3%)	
CONGESTION, NOS	1 (6%)	1 (3%)	
EDEMA, NOS	1 (6%)		
HEMORRHAGE		1 (3%)	1 (2%)
INFLAMMATION, INTERSTITIAL	1 (6%)	3 (8%)	1 (2%)
PNEUMONIA, CHRONIC MURINE	3 (17%)	2 (5%)	4 (9%)
PERIVASCULAR CUFFING	1 (6%)	3 (8%)	3 (7%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(18)	(39)	(45)
PERIVASCULAR CUFFING			1 (2%)
HYPERPLASIA, NOS		1 (3%)	1 (2%)
HYPERPLASIA, RETICULUM CELL		1 (3%)	
HYPERPLASIA, LYMPHOID		1 (3%)	2 (4%)
#LYMPH NODE	(15)	(40)	(38)
HYPERPLASIA, NOS			1 (3%)
#MESENTERIC L. NODE	(15)	(40)	(38)
HYPERPLASIA, NOS		2 (5%)	1 (3%)
HYPERPLASIA, LYMPHOID		1 (3%)	1 (3%)
CIRCULATORY SYSTEM			
*PULMONARY ARTERY	(18)	(42)	(48)
HYPERTROPHY, NOS			1 (2%)

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

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 22-2336	LOW DOSE 22-2334	HIGH DOSE 22-2332
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(16)	(40)	(39)
INFLAMMATION, SUPPURATIVE		1 (3%)	
PERIVASCULAR CUFFING		1 (3%)	1 (3%)
#LIVER	(18)	(42)	(48)
INFLAMMATION, FOCAL			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR		2 (5%)	2 (4%)
PERIVASCULAR CUFFING		2 (5%)	7 (15%)
NECROSIS, FOCAL	1 (6%)	3 (7%)	
HYPERPLASIA, NODULAR			1 (2%)
HYPERPLASIA, NOS			1 (2%)
ANGIECTASIS		1 (2%)	1 (2%)
#PEYERS PATCH	(17)	(41)	(45)
HYPERPLASIA, NOS			1 (2%)
#LARGE INTESTINE	(17)	(42)	(47)
NEMATODIASIS		2 (5%)	
PARASITISM		1 (2%)	12 (26%)
#COLON	(17)	(42)	(47)
PARASITISM			3 (6%)
URINARY SYSTEM			
#KIDNEY	(18)	(42)	(48)
INFLAMMATION, FOCAL		1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (6%)	1 (2%)	2 (4%)
PERIVASCULAR CUFFING	1 (6%)	4 (10%)	7 (15%)
ENDOCRINE SYSTEM			
#THYROID	(10)	(33)	(37)
HYPERPLASIA, CYSTIC	1 (10%)		
#THYROID FOLLICLE	(10)	(33)	(37)
DILATATION, NOS			1 (3%)
REPRODUCTIVE SYSTEM			
#UTERUS	(18)	(40)	(45)
CYST, NOS	1 (6%)	1 (3%)	

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

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 22-2336	LOW DOSE 22-2334	HIGH DOSE 22-2332
HEMORRHAGIC CYST	1 (6%)		
#CERVIX UTERI	(18)	(40)	(45)
INFLAMMATION, SUPPURATIVE	1 (6%)		
#UTERUS/ENDOMETRIUM	(18)	(40)	(45)
CYST, NOS	6 (33%)	9 (23%)	6 (13%)
INFLAMMATION, NOS	1 (6%)	2 (5%)	
INFLAMMATION, ACUTE		1 (3%)	
HYPERPLASIA, NOS		2 (5%)	
HYPERPLASIA, CYSTIC	3 (17%)	3 (8%)	9 (20%)
#OVARY	(17)	(33)	(37)
CYST, NOS	2 (12%)	3 (9%)	3 (8%)
FOLLICULAR CYST, NOS	3 (18%)	1 (3%)	
PAROVARIAN CYST	3 (18%)	1 (3%)	1 (3%)
HEMORRHAGIC CYST			1 (3%)
NERVOUS SYSTEM			
#BRAIN	(18)	(40)	(45)
SPONGIOSIS			1 (2%)
HEMORRHAGE	1 (6%)		
PERIVASCULAR CUFFING		1 (3%)	1 (2%)
CORPORA AMYLACEA	7 (39%)	2 (5%)	5 (11%)
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(18)	(42)	(48)
HYPERPLASIA, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(18)	(42)	(48)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
*MESENTERY	(18)	(42)	(48)
NECROSIS, FAT	1 (6%)	1 (2%)	

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

TABLE D2 (CONCLUDED)

	CONTROL (UNTR) 22-2336	LOW DOSE 22-2334	HIGH DOSE 22-2332
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(18)	(42)	(48)
PERIVASCULAR CUFFING		3 (7%)	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	6	2
ANIMAL MISSING/NO NECROPSY	2	8	2
AUTO/NECROPSY/HISTO PERF			1

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

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