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BIOASSAY OF TRIS (2,3-DIBROMOPROPYL) PHOSPHATE FOR POSSIBLE CARCINOGENICITY

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

TRIS (2,3-DIBROMOPROPYL) PHOSPHATE

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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 TRIS (2,3-DIBROMOPROPYL) PHOSPHATE 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 tris (2,3-dibromopropyl) phosphate 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 tris (2,3-dibromopropyl) phosphate was conducted by Mason Research Institute, Worcester, Massachusetts, initially under direct contract to the NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI Carcinogenesis Testing Program.

The experimental design was determined by the NCI Project Officers, Dr. J. H. Weisburger (1,2) and Dr. E. K. Weisburger (1). The principal investigators for the contract were Dr. E. Smith (3) and Dr. A. Handler (3). Animal treatment and observation were supervised by Mr. G. Wade (3) and Ms. E. Zepp (3). Chemical analysis was performed by Midwest Research Institute (4) and the analytical results were reviewed by Dr. N. Zimmerman (5).

Histopathologic examinations were performed by Dr. A. S. Krishna (3) and Dr. A. Russfield (3) at the Mason Research Institute, and the diagnoses included in this report represent the interpretation of these pathologists. 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. W. W. Belew (5) and Dr. J. R. Joiner (6), using methods selected for the Bioassay Program by Dr. J. J. Gart (8).

This report was prepared at METREK, a Division of The MITRE Corporation (5) under the direction of the NCI. Those responsible for this report at METREK are the project coordinator, Dr. L. W. Thomas (5), the task leader, Dr. M. R. Kornreich (5), the senior biologist, Ms. P. Walker (5) and the technical editor, Ms. P. A. Miller (5). The final report was reviewed by members of the participating organizations.

The statistical analysis was reviewed by members of the Mathematical Statistics and Applied Mathematics Section of the NCI: Dr. J. J. Gart (8), Mr. J. Nam (8), Dr. H. M. Pettigrew (8), and Dr. R. E. Tarone (8).

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), Dr. R. A. Griesemer (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), Dr. R. A. Squire (1,9), Dr. J. M. Ward (1), and Dr. C. E. Whitmire (1).

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SUMMARY

A bioassay of technical-grade tris (2,3-dibromopropyl) phosphate (TBP) for possible carcinogenicity was conducted using Fischer 344 rats and B6C3F1 mice. TBP was administered in the feed, at either of two concentrations, to groups of 55 male and 55 female rats, and 50 male and 50 female mice. The high and low dietary concentrations of TBP administered were, respectively, 100 and 50 ppm for the male and female rats, and 1000 and 500 ppm for the male and female mice. After a 103-week dosing period, observation of the rats and mice continued for 1 or 2 additional weeks. For each species, 55 animals of each sex were placed on test as controls. No TBP was added to their diet.

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

Kidney tubular-cell adenomas were observed at incidences which were significant for dosed rats of both sexes by all statistical tests applied. For male rats there was a significant positive association between the incidence of kidney tubular-cell adenocarcinomas and dietary concentration of TBP. Other neoplastic lesions appearing in the treated rats were not statistically significant when compared with the control groups.

Among mice, a number of malignant and benign tumors were associated with TBP administration. These tumors included renal tubular-cell carcinoma and adenoma; squamous-cell papilloma and carcinoma of the forestomach; hepatocellular carcinoma and adenoma; and bronchiolar/alveolar adenoma and carcinoma.

Renal tubular-cell carcinomas were observed at a statistically significant incidence in male mice but none were observed in females. Tubular-cell adenomas were observed in treated mice of both sexes, but not in their respective controls. The incidence of tubular-cell adenomas was significant in male mice but not in females.

Squamous-cell carcinomas were observed in forestomachs of mice of both sexes but not in their respective controls. The incidence was significant in females but not in males. The incidences of squamous-cell papillomas of the forestomach were significant in mice of both sexes.

Incidences of hepatocellular carcinoma and hepatocellular adenoma were each significant in female mice. Tumor incidence among male mice was not significant for hepatocellular carcinomas or hepatocellular adenomas.

The proportion of mice of each sex having bronchiolar/alveolar adenoma or carcinoma or both had a significant positive dose-related trend. The incidence of bronchiolar/alveolar carcinomas exhibited a significant positive dose-related trend for males, but not for females.

It is concluded that under the conditions of this study orally administered TBP was carcinogenic to B6C3F1 mice, causing increased incidences of tumors in livers, lungs, and stomachs of female mice and in kidneys, lungs, and stomachs of male mice. TBP was also carcinogenic in Fischer 344 rats, causing an increased incidence of kidney tumors in both sexes.

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I. INTRODUCTION

Tris (2,3-dibromopropyl) phosphate (TBP) (NCI No. CO3270) is a compound that has been widely used as a flame retardant for synthetic fabrics, particularly those made into sleepwear for infants and young children. Because of the potential for ingestion (via mouthing habits) and extensive dermal exposure of youngsters to this compound, and as a result of the minimal amount of data available from chronic studies, TBP was selected for inclusion in the National Cancer Institute (NCI) Carcinogenesis Testing Program.

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is 2,3-dibromo-1-propanol phosphate (3:1).* It is also known as tris (dibromopropyl) phosphate; Firemaster T23P; or simply as Tris or TBP.

Because of its low cost, effectiveness in relation to other chemicals, ease of application to synthetics, and general availability, TBP is one of the most widely utilized flame retardants (Daniher, 1976). It has been reported that approximately 3×10^6 pounds of the chemical have been used annually by the U.S. textiles industry in recent years (Osterberg, 1976). The compound is primarily used to treat such fabrics as polyester, acetate, and triacetate (Simpson, 1976). In addition to its use by the textile industry, TBP is also a fire retardant additive for polystyrene and polyurethane foams,

*The CAS registry number is 126-72-7.

polyvinyl chloride and phenolic resins, intumescent and nonintumescent paints, paper coatings, and rubber.

Exposure to TBP occurs in the general population primarily among those who wear TBP-treated garments. In April 1976, the U.S. Consumer Product Safety Commission estimated that approximately 60 percent of childrens' sleepwear was treated with TBP (Simpson, 1976). Occupational exposure of workers in the textile industry as well as in other TBP-utilizing industries is also likely.

Studies conducted by St. John et al. (1976) and Brieger et al. (1968) failed to indicate any evidence of TBP absorption following dermal contact with treated fabric. However, TBP applied directly to the skin of rats and humans was subsequently absorbed (St. John et al., 1976). The surface concentration of TBP varies among fabrics but most surface TBP can be washed out. After three laundering cycles, the surface concentration of a polyester fabric sample was reduced from an initial level of 4300 ppm to 65 ppm and an acetate fabric sample from 600 ppm to 90 ppm (Morrow et al., 1976). TBP may be extracted from treated fabric by saliva (Brieger et al., 1968). Thus, infants and young children who mouth blankets and clothing may experience chronic exposure through ingestion as well as dermal absorption. TBP was shown to cause dose-related allergic sensitization in human subjects exposed to the chemical under conditions of maximization testing (Morrow et al., 1976), and the chemical was judged by the authors to be a weak to mild sensitizer.

Positive results were noted in an in vitro test system utilizing increases in DNA repair activity of human cells exposed to the test chemical as an indicator of chemically induced damage to the genetic material (Stich, 1976). TBP was also found to induce basepair substitution mutations in a histidine-requiring strain of Salmonella typhimurium (the Ames Test using Strain TA 1535) (Prival et al., 1977). Mutagenic activity was extractable from TBP-treated fabrics even after three cycles of laundering with detergent (Prival et al., 1977).

II. MATERIALS AND METHODS

A. Chemicals

The tris (2,3-dibromopropyl) phosphate (TBP) utilized for the chronic bioassay was manufactured by Michigan Chemical Corporation under the trade name Firemaster LV-T23P. The compound was analyzed by Midwest Research Institute. Thin-layer chromatography was performed utilizing two solvent systems (benzene:isopropanol and chloroform:ethyl acetate). Each plate showed only one spot. High-pressure liquid chromatography (Waters ALC/CPL 301) showed the presence of one homogeneous peak. Nuclear Magnetic Resonance (Varian AA 100) spectra conformed to reference spectra provided by Sadtler Research for Firemaster-grade tris (2,3-dibromopropyl) phosphate. Infrared analysis was consistent with the structure of the compound and no extraneous peaks were noted.

Throughout this report the term TBP is used in referring to this material.

To determine the concentration of 1,2-dibromo-3-chloropropane (DBCP) present as a contaminant in the batch of TBP used in this bioassay, analyses were performed at Midwest Research Institute using vapor-phase chromatography. No DBCP was detected using methodology providing a sensitivity of 100 ppm.

B. Dietary Preparation

The basal laboratory diet for both treated and control animals was Wayne Lab-Blox® (Allied Mills, Inc., Chicago, Illinois). TBP was

administered to the treated animals as a component of the diet. The chemical was mixed with ground Wayne Lab-Blox® meal using a 6 kg capacity Patterson-Kelley twin-shell stainless-steel V-blender. The treated diets were prepared once weekly and stored at 4°C.

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. Animals of both species were supplied by the Frederick Cancer Research Center, Frederick, Maryland. Treated and control animals for both species were received in separate shipments.

Upon arrival, a random sample of animals was examined for nematode infestation and other signs of disease. The remaining animals were quarantined for 2 weeks prior to initiation of test. Animals were assigned to groups and distributed among cages so that average body weight per cage was approximately equal for a given sex and species.

D. Animal Maintenance

All animals were housed by species in rooms having a temperature range of 23° to 34°C. Incoming air was filtered through Tri-Dek® 15/40 denier Dacron® filters (Tri-Dim Filter Corp., Hawthorne, New Jersey) providing six changes of room air per hour. Fluorescent lighting was provided on a 12-hour-daily cycle.

Rats were housed five per cage by sex in suspended polycarbonate cages equipped with nonwoven fiber filter sheets. For the first 8 months of test, corncob bedding (SAN-I-CEL®, Paxton Processing Company, Paxton, Illinois) was supplied. Hardwood chips (Aspen bedding, American Excelsior Company, Baltimore, Maryland) were substituted for the remainder of the study. Bedding and clean cages were provided two or three times weekly. Stainless steel cage racks (Fenco Cage Products, Boston, Massachusetts) were cleaned once every two weeks and disposable filters were replaced with the same frequency.

Mice were housed five per cage by sex in shoe box type polycarbonate cages fitted with stainless steel lids (Lab Products, Inc., Garfield, New Jersey) and nonwoven fiber filter bonnets. Ground corncob bedding (Bed-o-Cobs®, The Andersons Cob Division, Maumee, Ohio) was supplied for the first 4 months of test. Thereafter, it was replaced by Aspen bedding. Clean cages, lids, and bedding were provided twice weekly. Reusable filters and pipe racks were sanitized once every 2 weeks throughout the study.

Food and water were available ad libitum. Water was available from 250 ml polycarbonate water bottles equipped with rubber stoppers and stainless steel sipper tubes. Bottles were replaced twice weekly and, for rats only, water was supplied as needed between changes.

All rats used in this study were housed in a room with other rats receiving diets containing* 2-chloro-p-phenylenediamine sulfate

*CAS registry numbers are given in parentheses.

(61702-44-1); o-anisidine hydrochloride (134-29-0); and p-anisidine hydrochloride (20265-97-8).

All mice used in this study were housed with other mice receiving diets containing o-anisidine hydrochloride (134-29-0); N-(1-naphthyl) ethylenediamine dihydrochloride (1465-25-4);2-chloro-p-phenylenediamine sulfate (61702-44-1); p-anisidine hydrochloride (20265-97-8); 2,3,5,6-tetrachloro-4-nitroanisole (2438-88-2); aniline hydrochloride (142-04-1); and acetone (67-64-1).

E. Selection of Initial Concentrations

In order to establish the maximum tolerated concentrations of TBP for use in the chronic study, 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. TBP in corn oil was administered by gavage to five of the six rat groups at dosages of 1, 3, 10, 30, and 100 mg/kg/day and five of the six mouse groups at dosages of 10, 30, 100, 300, and 1000 mg/kg/day. The sixth group of each species served as a control group, receiving only corn oil. Intubation was performed 5 days a week for 8 weeks.

In male rats a slight depression in mean body weight was observed at 30 and 100 mg/kg/day and one animal died at 100 mg/kg/day. No depression in mean body weight or mortality were seen in the female rats. The high dose selected for the chronic study was 10 mg/kg/day for rats of both sexes. Slight depression in mean body weight was

observed in male mice at 300 mg/kg/day. Two males and three females died at 1000 mg/kg/day. The high dose selected for the chronic study was 100 mg/kg/day for mice of both sexes.

In the chronic study, TBP was administered in the diet (instead of by gavage) at a concentration of 0.01 percent (100 ppm) for rats and 0.1 percent (1000 ppm) for mice. Expressed in mg/kg/day,* the initial dosage for rats was approximately 5 mg/kg/day, 50 percent of the intended dosage (of 10 mg/kg/day), and in mice it was approximately 160 mg/kg/day, 160 percent of the intended dosage. Because mean body weight in both species increased during the chronic study at a faster rate than food consumption, dosages on a body weight basis would progressively decrease to a slight extent. Taking this effect into account, it is estimated that during the chronic study the time-weighted average dose for rats would have been about 40 percent and for mice about 140 percent of the intended dosage. These estimates are consistent with the lack of body weight effect in the rats and the definite compound-related depression of mean body weight observed in mice.

F. Experimental Design

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

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*The conversion was based on an estimated average body weight, during the subchronic study, of 200 g/rat and 25 g/mouse, and food consumption of 10 g/day/rat and 4 g/day/mouse.

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

The low dose, high dose, and control rats were all approximately 6 weeks old at the time they were placed on test. Control rats were placed on test one week earlier than treated rats. The high and low dietary concentrations of TBP were 100 and 50 ppm, respectively. Treated rats were supplied with dosed feed for a total of 103 weeks followed by a 1- or 2-week observation period.

The low dose, high dose, and control mice were all approximately 6 weeks old at the time they were placed on test but control mice were placed on test 2 months earlier than treated mice. The high and low dietary concentrations of TBP administered to males and females were 1000 and 500 ppm, respectively. Treated mice were supplied with dosed feed for a total of 103 weeks followed by a 1-week observation period.

G. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment. Body weights were recorded twice weekly for the first 12 weeks of the study and at monthly intervals thereafter. From the first day, all animals were inspected twice daily for mortality. Food consumption, for two cages from each group, was monitored for seven consecutive days once a month for the first nine months of the bioassay and for three consecutive days each month thereafter. The presence of tissue masses and lesions was determined by monthly observation and palpation of each animal.

TABLE 1

DESIGN SUMMARY FOR FISCHER 344 RATS
TBP FEEDING EXPERIMENT

	INITIAL GROUP SIZE	TBP CONCENTRATION[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)
MALE				
CONTROL	55	0	-	107
LOW DOSE	55	50	103	
		0		1
HIGH DOSE	55	100	103	
		0		1
FEMALE				
CONTROL	55	0	-	107
LOW DOSE	55	50	103	
		0		1
HIGH DOSE	55	100	103	
		0		2

[a]Concentrations in parts per million.

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
TBP FEEDING EXPERIMENT

	INITIAL GROUP SIZE	TBP CONCENTRATION[a]	OBSERVATION PERIOD	
			TREATED (WEEKS)	UNTREATED (WEEKS)
MALE				
CONTROL	55	0		105
LOW DOSE	50	500	103	
		0		1
HIGH DOSE	50	1000	103	
		0		1
FEMALE				
CONTROL	55	0		105
LOW DOSE	50	500	103	
		0		1
HIGH DOSE	50	1000	103	
		0		1

[a]Concentrations in parts per million.

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

Slides were prepared from the following tissues: skin, subcutaneous tissue, lungs and bronchi, trachea, bone marrow, spleen, lymph nodes, thymus, heart, salivary gland, liver, gallbladder (mice), pancreas, esophagus, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, testis, prostate, brain, eye, uterus, mammary gland, and ovary.

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

A few tissues were not examined for some animals, particularly for those that died early. Also, some animals were missing, cannibalized, or judged to be in such an advanced state of autolysis as to preclude histopathologic interpretation. Thus, the number of animals for which particular organs, tissues, or lesions were examined

microscopically varies and does not necessarily represent the number of animals that were placed on experiment in each group.

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

No appreciable differences in mean body weight between dosed and control rats were noted (Figure 1).

Subcutaneous palpable masses were observed in all male groups, but with a higher frequency in the treated animals. Protrusion, discoloration, and encrustation of the eyes and jaundice were noted in both treated and control male groups. Yellowing of the eyes was reported only in the treated male groups. Emaciation was observed only in the treated males. A urogenital bloody exudate was noted in few low dose males. High numbers of females in the control, low dose, and high dose groups were observed to have palpable subcutaneous masses. Discoloration, protrusion, and encrustation of the eyes were noted in all female groups but occurred more frequently among high dose females. Alopecia, not associated with visible lesions, was also observed in all groups but with a higher frequency in the controls (10/55 controls, 2/50 low dose, 1/50 high dose).

B. Survival

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

For both male and female rats the Tarone test indicated no significant association between increased dosage and accelerated mortality. In male rats, 73 percent (40/55) of the high dose, 64 percent (35/55) of the low dose, and 71 percent (39/55) of the control group

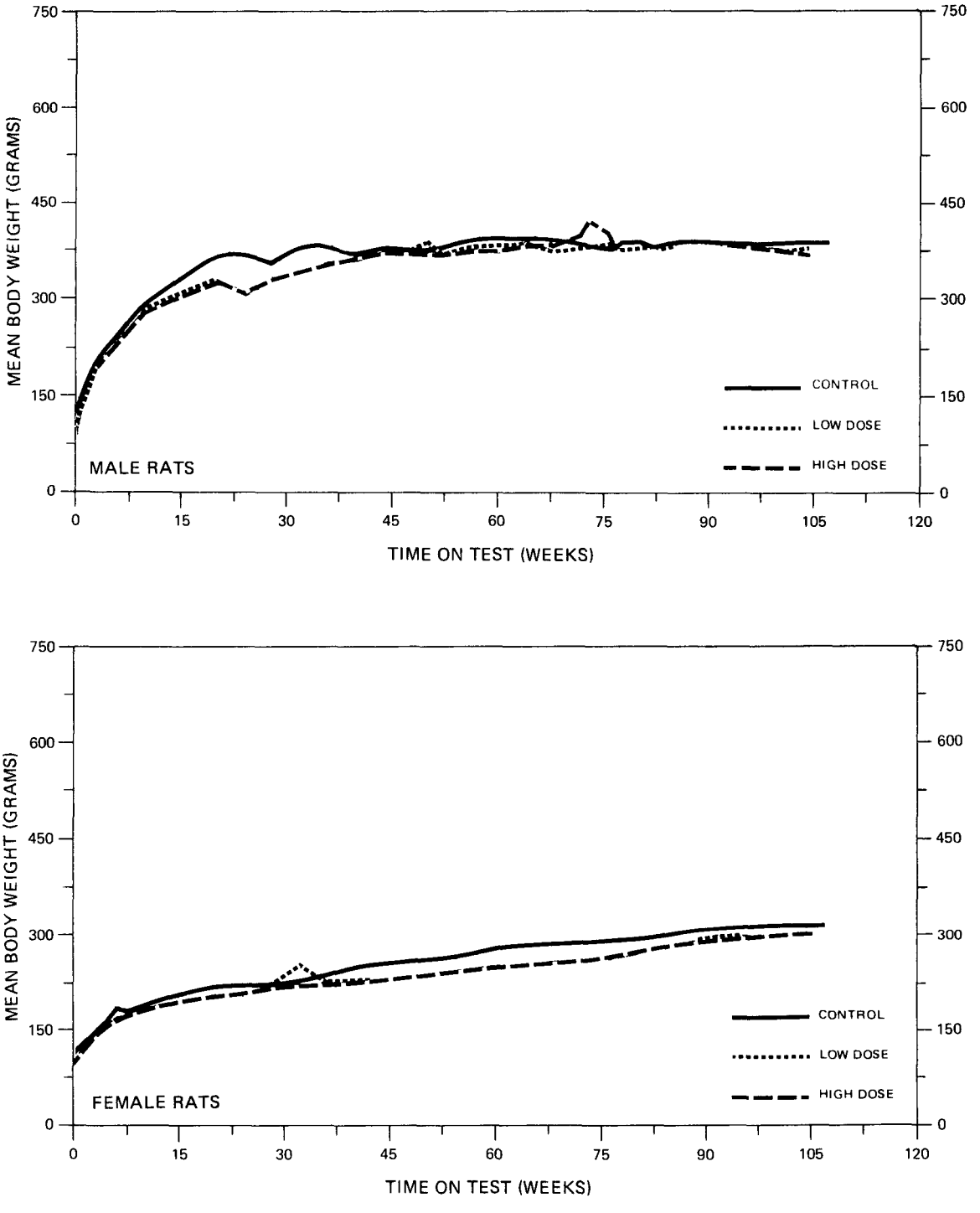
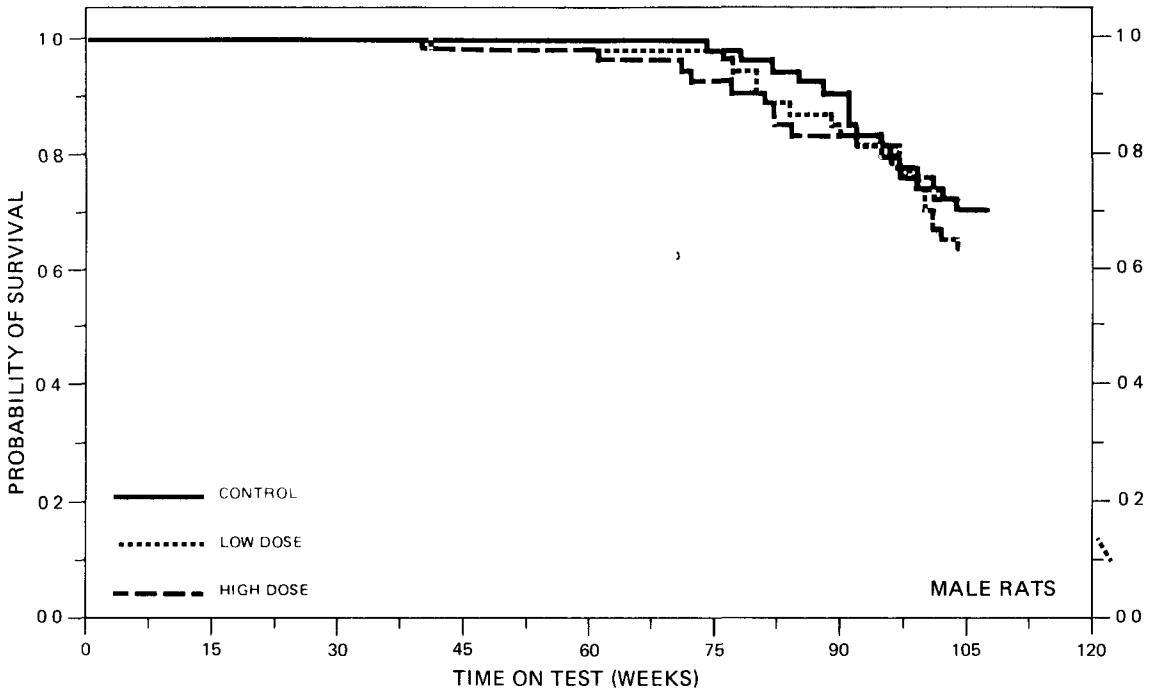


FIGURE 1
GROWTH CURVES FOR TBP CHRONIC STUDY RATS



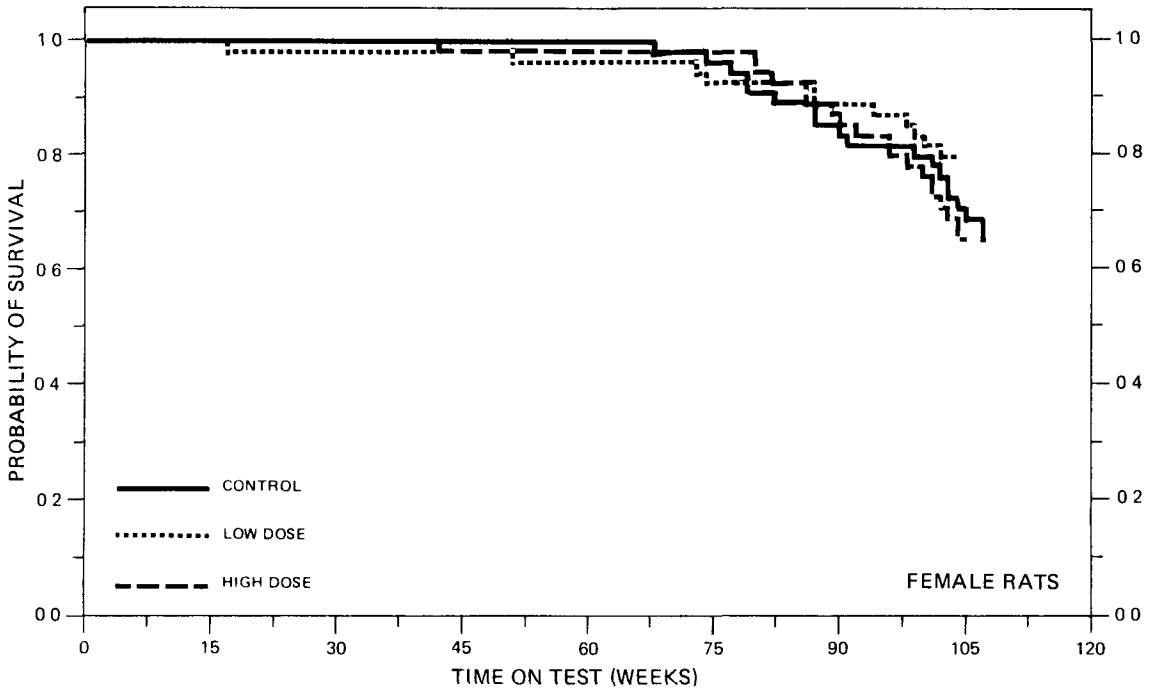


FIGURE 2
SURVIVAL COMPARISONS OF TBP CHRONIC STUDY RATS

lived to the end of the test. In female rats, 65 percent (36/55) of the high dose, 80 percent (44/55) of the low dose, and 65 percent (36/55) of the control group survived to termination of the study. Thus, an adequate number of rats in all groups survived sufficiently long to be at risk from late-developing tumors.

C. Pathology

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

Renal tubular-cell adenomas were seen in 26/54 (48 percent) low dose and 26/54 (48 percent) high dose males, and in 4/54 (7 percent) low dose and 10/54 (19 percent) high dose females but no tumors of the renal tubular epithelium were found in either male or female controls. The renal tubular-cell adenomas found in treated rats varied in size from microscopic lesions having a diameter of three or four normal tubules to much larger tumors. All such lesions consisted of nodules of poorly organized tubules compressing the surrounding parenchyma. Cytoplasm was markedly basophilic and nuclei were vesicular with a prominent small nucleolus. Multiple tubular adenomas were frequently observed.

Three of 54 (6 percent) high dose males had tumors classified as renal-cell carcinomas (tubular-cell adenocarcinomas). These were much larger than the adenomas, sometimes bulging through the kidney capsule. The cellular pattern suggested elongated, poorly organized

tubules interspersed with large areas of hemorrhage and necrosis. Cytoplasm was abundant, weakly acidophilic, and often foamy and vacuolated. Nuclei showed marked pleomorphism and occasional mitotic figures.

The only nonneoplastic lesions that appeared to be related to TBP administration occurred in the renal tubules. In 6/54 (11 percent) high dose males and 35/54 (65 percent) high dose females, a few tubular cells were slightly enlarged and showed nuclear dysplasia consisting of nuclear enlargement, chromatin clumping, and parachromatin clearing. These lesions were not observed in the control or low dose groups. Kidney tumors were not observed in those rats for which dysplasia was reported.

Selected kidney slides from male and female high dose and control rats were stained with an acid fast stain and examined microscopically. No evidence of acid fast intranuclear inclusions in the renal epithelial cells suggestive of toxicity from lead or certain other heavy metal compounds was found.

A variety of neoplasms were observed with similar frequencies in treated and control rats. The most common of these among male rats were interstitial-cell tumors of the testes, leukemia and malignant lymphomas, adrenal pheochromocytoma, and pituitary chromophobe adenoma. Tumors occurring with similar frequencies in treated and control female rats include leukemia, pituitary tumors (carcinomas, chromophobe adenomas, and basophil adenomas), mammary gland fibroadenoma, and endometrial stromal polyp.

TBP feeding had no apparent effect on the incidence of chronic nephritis commonly seen in aged rats, especially males. Nonneoplastic degenerative or inflammatory lesions were seen in all groups of both sexes. Their incidence was not related to feeding with this compound.

Under the conditions of this bioassay, there was histopathologic evidence for the carcinogenicity of TBP in Fischer 344 rats, as feeding TBP was associated with neoplasms of the renal tubules.

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

In both male and female dosed rats the incidence of tubular-cell neoplasms of the kidney was significant. For females the Cochran-Armitage test indicated a significant ($P = 0.001$) positive association between dosage and the incidence of tubular-cell adenomas. The Fisher exact test confirmed this result with a significantly ($P = 0.001$) higher incidence in the high dose than in the control group. For males, when incidences were combined so that the numerator represented rats with either a tubular-cell adenoma or a tubular-cell adenocarcinoma of the kidney, the Cochran-Armitage test and both

TABLE 3

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	0/54(0.00)	3/55(0.05)	0/55(0.00)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.014	---	---
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.589	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	95	---
Hematopoietic System: Leukemia[b]	17/54(0.31)	13/55(0.24)	7/55(0.13)
P Values[c]	P = 0.013(N)	N.S.	P = 0.016(N)
Relative Risk (Control)[d]	---	0.751	0.404
Lower Limit	---	0.375	0.154
Upper Limit	---	1.472	0.935
Weeks to First Observed Tumor	85	80	84
Liver: Neoplastic Nodule or Hepatocellular Carcinoma[b]	0/54(0.00)	1/55(0.02)	4/54(0.07)
P Values[c]	P = 0.026	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.053	0.925
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	99	84

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Kidney: Tubular-Cell Adenoma[b]	0/53(0.00)	26/54(0.48)	26/54(0.48)
P Values[c]	P < 0.001	P < 0.001	P < 0.001
Departure from Linear Trend[e]	P = 0.002	---	---
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	8.387	8.387
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	76	82
Kidney: Tubular-Cell Adenocarcinoma[b]	0/53(0.00)	0/54(0.00)	3/54(0.06)
P Values[c]	P = 0.038	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite
Lower Limit	---	---	0.589
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	40
Kidney: Tubular-Cell Adenoma or Tubular-Cell Adenocarcinoma[b]	0/53(0.00)	26/54(0.48)	29/54(0.54)
P Values[c]	P < 0.001	P < 0.001	P < 0.001
Departure from Linear Trend[e]	P = 0.009	---	---
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	8.387	9.429
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	76	40

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Pituitary: Chromophobe Adenoma[b]	4/48(0.08)	7/50(0.14)	3/50(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.680	0.720
Lower Limit	---	0.459	0.111
Upper Limit	---	7.369	4.035
Weeks to First Observed Tumor	91	92	84
Pituitary: Basophil Adenoma[b]	0/48(0.00)	3/50(0.06)	2/50(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.578	0.284
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	76	104
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant[b]	14/54(0.26)	11/55(0.20)	16/55(0.29)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.771	1.122
Lower Limit	---	0.349	0.572
Upper Limit	---	1.660	2.228
Weeks to First Observed Tumor	74	80	81

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	3/53(0.06)	3/51(0.06)	4/52(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.039	1.359
Lower Limit	---	0.145	0.242
Upper Limit	---	7.423	8.869
Weeks to First Observed Tumor	107	104	104
Pancreatic Islets: Islet-Cell Adenoma[b]	1/53(0.02)	3/53(0.06)	1/51(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	3.000	1.039
Lower Limit	---	0.250	0.013
Upper Limit	---	154.426	78.491
Weeks to First Observed Tumor	107	95	84
Preputial Gland: Carcinoma NOS or Adenocarcinoma[b]	1/54(0.02)	2/55(0.04)	4/55(0.07)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.964	3.927
Lower Limit	---	0.105	0.406
Upper Limit	---	113.749	189.701
Weeks to First Observed Tumor	107	90	77

TABLE 3 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Preputial Gland: Adenoma NOS or Carcinoma NOS or Adenocarcinoma NOS[b]	1/54(0.02)	3/55(0.05)	7/55(0.13)
P Values[c]	P = 0.019	N.S.	P = 0.032
Relative Risk (Control)[d]	---	2.946	6.873
Lower Limit	---	0.246	0.931
Upper Limit	---	151.741	303.440
Weeks to First Observed Tumor	107	90	77
Testis: Interstitial-Cell Tumor[b]	53/54(0.98)	46/55(0.84)	50/55(0.91)
P Values[c]	N.S.	P = 0.009(N)	N.S.
Departure from Linear Trend[e]	P = 0.022	---	---
Relative Risk (Control)[d]	---	0.852	0.926
Lower Limit	---	0.819	0.892
Upper Limit	---	0.975	1.032
Weeks to First Observed Tumor	74	41	40

[a]Treated groups received time-weighted average doses of 50 or 100 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 TBP[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Leukemia[b]	9/54(0.17)	10/55(0.18)	9/55(0.16)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.091	0.982
Lower Limit	---	0.433	0.375
Upper Limit	---	2.795	2.577
Weeks to First Observed Tumor	91	98	82
Kidney: Tubular-Cell Adenoma[b]	0/52(0.00)	4/54(0.07)	10/54(0.19)
P Values[c]	P = 0.001	N.S.	P = 0.001
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.891	2.858
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	104	89
Pituitary: Carcinoma NOS[b]	3/48(0.06)	1/54(0.02)	1/52(0.02)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.296	0.308
Lower Limit	---	0.006	0.006
Upper Limit	---	3.547	3.679
Weeks to First Observed Tumor	90	104	105

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Pituitary: Chromophobe Adenoma[b]	15/48(0.31)	22/54(0.41)	24/52(0.46)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.304	1.477
Lower Limit	---	0.738	0.854
Upper Limit	---	2.369	2.627
Weeks to First Observed Tumor	74	94	86
Adrenal: Pheochromocytoma[b]	3/53(0.06)	4/53(0.08)	2/54(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.359	0.654
Lower Limit	---	0.242	0.057
Upper Limit	---	8.869	5.484
Weeks to First Observed Tumor	107	104	104
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	4/49(0.08)	3/53(0.06)	4/53(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.693	0.925
Lower Limit	---	0.106	0.182
Upper Limit	---	3.896	4.709
Weeks to First Observed Tumor	107	104	98

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Mammary Gland: Fibroadenoma[b]	16/54(0.30)	10/55(0.18)	19/55(0.35)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.614	1.166
Lower Limit	---	0.275	0.640
Upper Limit	---	1.303	2.152
Weeks to First Observed Tumor	99	99	42
Clitoral Gland: Adenoma NOS[b]	0/54(0.00)	3/55(0.05)	0/55(0.00)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.014	---	---
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.589	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	100	---
Uterus: Endometrial Stromal Polyp[b]	16/52(0.31)	14/54(0.26)	11/55(0.20)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.843	0.650
Lower Limit	---	0.434	0.308
Upper Limit	---	1.682	1.373
Weeks to First Observed Tumor	68	104	98

TABLE 4 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Ovary: Sertoli-Cell Tumor[b]	0/53(0.00)	0/53(0.00)	3/55(0.05)
P Values[c]	P = 0.041	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite
Lower Limit	---	---	0.578
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	105

[a]Treated groups received time-weighted average doses of 50 or 100 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 $P < 0.05$.

Fisher exact tests were significant ($P < 0.001$). On the basis of these results, there was a significant association between the administration of TBP and the increased incidence of tubular-cell adenomas of the kidney in both male and female rats.

In male rats the Cochran-Armitage test indicated a significant ($P = 0.026$) positive association between dosage and the combined incidence of hepatocellular carcinomas and neoplastic nodules of the liver. The Fisher exact tests, however, were not significant.

In male rats the Cochran-Armitage test indicated a significant ($P = 0.019$) positive association between dosage and the combined incidence of adenomas, carcinomas, or adenocarcinomas of the preputial gland. The Fisher exact test comparing the high dose to the control group, however, had a probability level of $P = 0.032$, a marginal result which was not significant under the Bonferroni inequality.

In female rats the Cochran-Armitage test indicated a significant ($P = 0.041$) positive association between dosage and the incidence of Sertoli-cell tumors of the ovary. The Fisher exact tests, however, were not significant.

The possibility of a negative association between dosage and incidence was noted for leukemia in male rats. This apparent negative trend may result from the unusually high incidence of leukemia in the control group (17/45 [31 percent]). The incidence in historical untreated male Fischer 344 control rats compiled by this laboratory for the NCI Carcinogenesis Testing Program was 57/534 (11 percent).

The Fisher exact test indicated a significantly ($P = 0.009$) lower incidence of interstitial-cell tumors of the testis in the low dose males than in the control group. The Cochran-Armitage test and the Fisher exact comparison of high dose to control, however, were not significant.

For a number of tumors in both male and female rats the control group had significantly ($P < 0.05$) higher incidences than was commonly found in the historical control Fischer 344 rats at Mason Research Institute for the NCI Carcinogenesis Testing Program. Among males, 26 percent (14/54) of the TBP control rats had pheochromocytoma compared with 12 percent (65/534) of the historical controls. Among TBP control females, 30 percent (16/54) had mammary fibroadenomas and 31 percent (16/52) had endometrial stromal polyps of the uterus compared to 19 percent (112/589) and 16 percent (95/589), respectively, in the historical controls.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

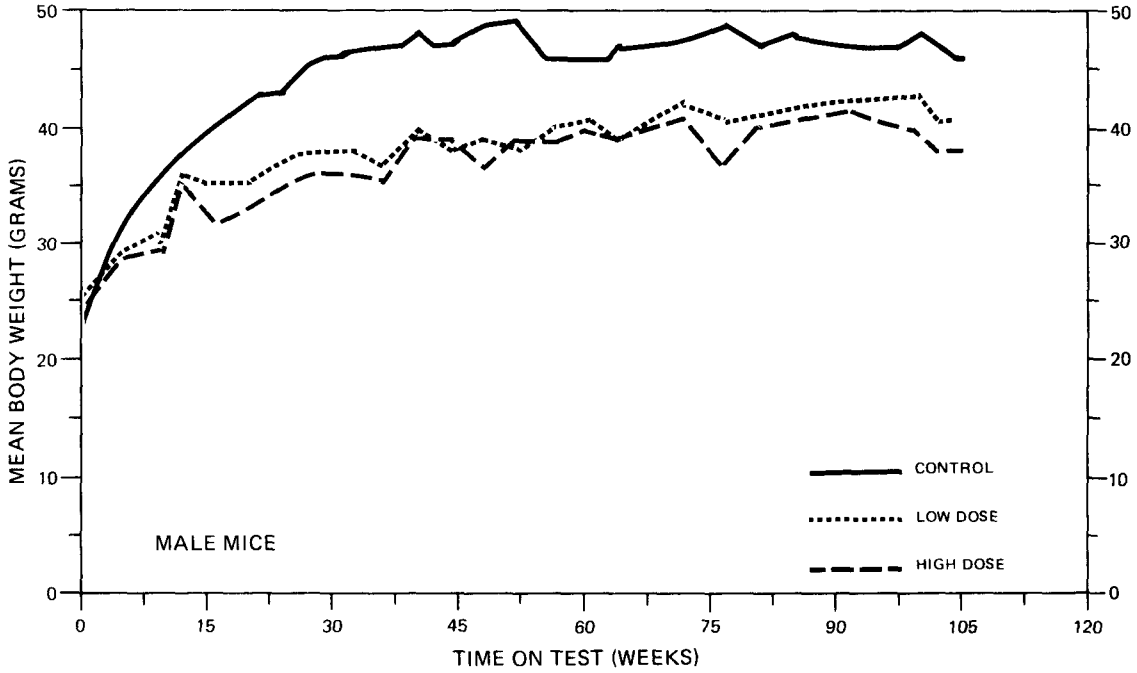
Mean group body weights of TBP-treated mice of both sexes were appreciably depressed relative to control mice during the chronic bioassay (Figure 3). Mean body weights of high dose mice were only slightly depressed, however, relative to low dose mice.

The clinical sign observed with the greatest frequency in both males and females was alopecia (i.e., 42/55, 37/50, 43/50 in control, low dose and high dose males, respectively, and 48/55, 39/50, 45/50 in control, low dose and high dose females, respectively). Other clinical signs observed with much lower frequency in both sexes included palpable masses, abdominal distention, and exophthalmia. Distension in the urogenital area was reported in all male groups but in no females, and emaciation was recorded for one low dose and one high dose female but for no other animals.

B. Survival

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

The Tarone tests for association between increased dosage and accelerated mortality were not significant for either male or female mice. In males 86 percent (43/50) of the high dose, 76 percent (38/50) of the low dose, and 80 percent (44/55) of the control mice survived until the end of the study. In females 76 percent (38/50) of the high dose, 74 percent (37/50) of the low dose and 80 percent



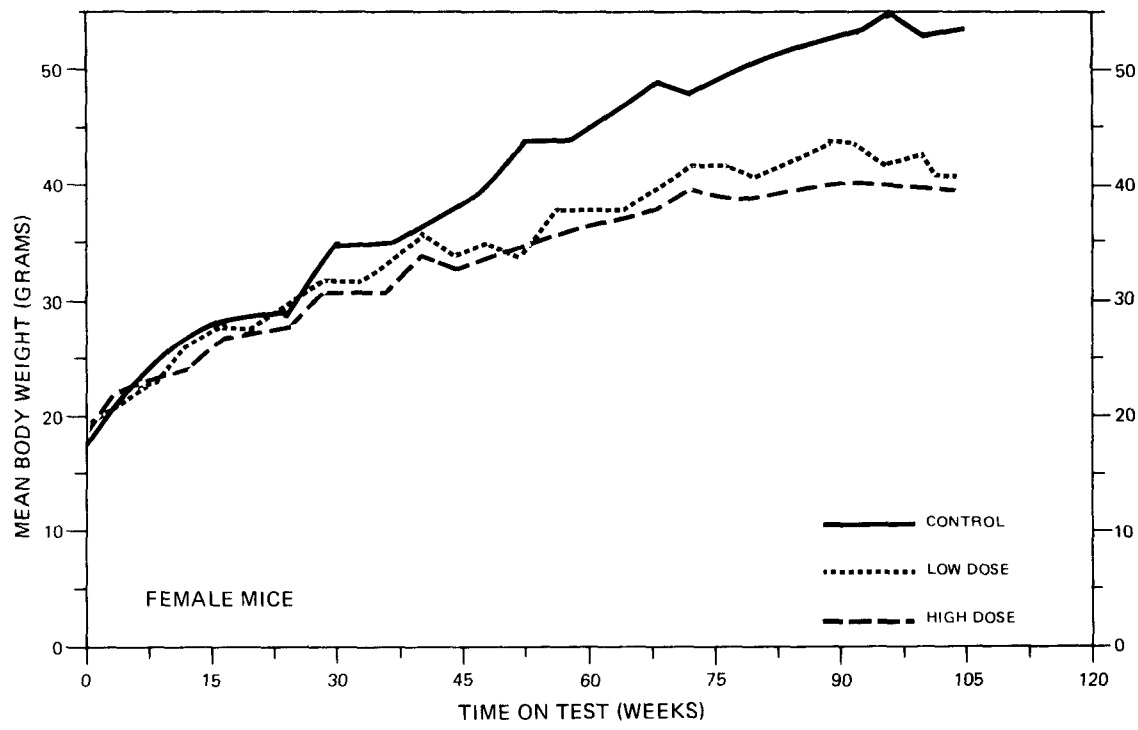
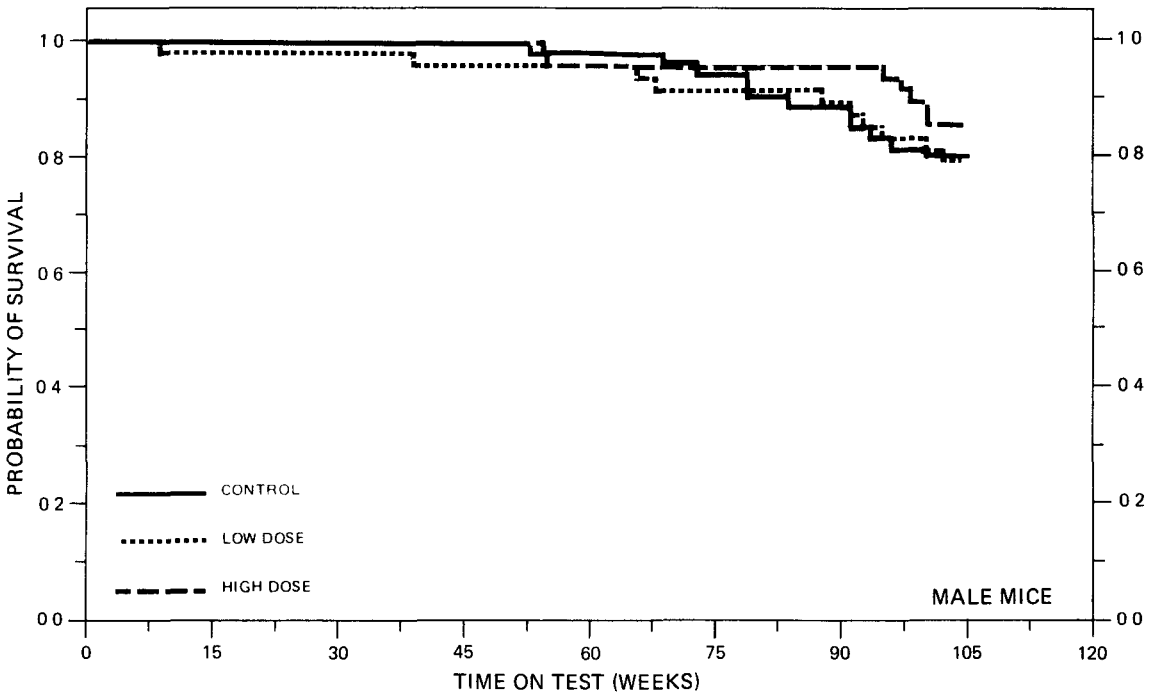


FIGURE 3
GROWTH CURVES FOR TBP CHRONIC STUDY MICE



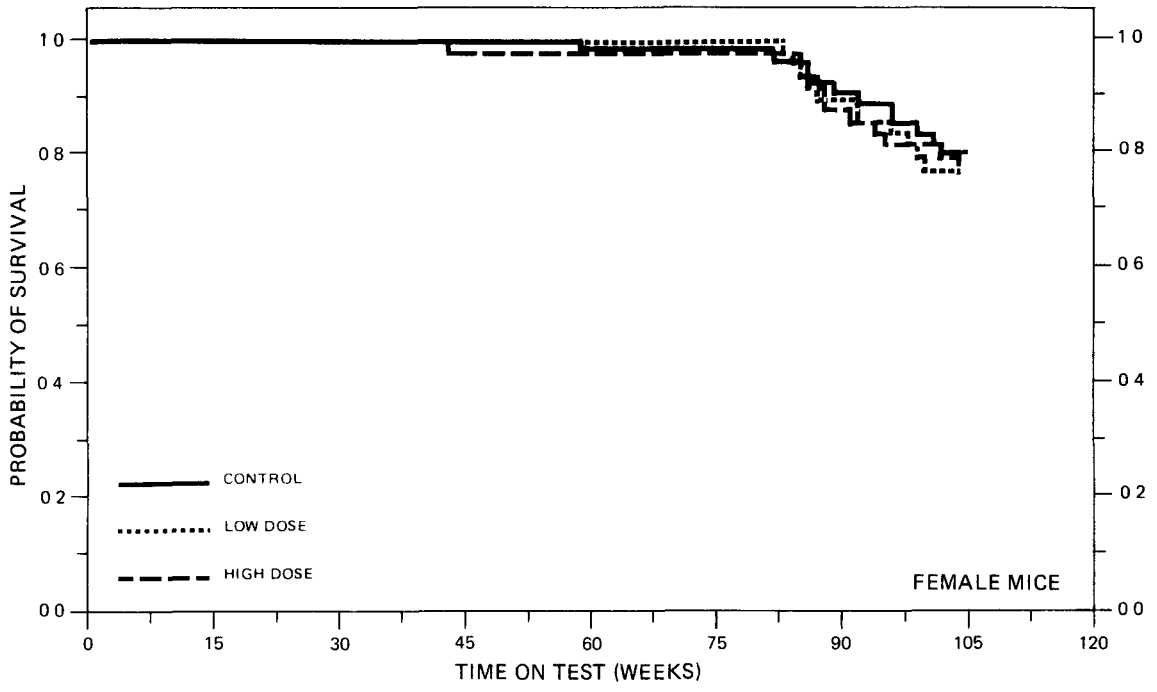


FIGURE 4
SURVIVAL COMPARISONS OF TBP CHRONIC STUDY MICE

(44/55) of the control mice survived until the end of the study. These high survival rates, plus the consideration that the mouse study was run for 104 to 105 weeks, means that a sufficient number of mice were at risk from late-developing tumors.

C. Pathology

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

In treated males, renal tubular-cell adenoma occurred in 3/50 (6 percent) low dose and 9/49 (18 percent) high dose mice. In treated females, there were renal tubular-cell adenomas in 2/50 (4 percent) low dose and 2/46 (4 percent) high dose mice. No renal tubular-cell adenomas were observed in control groups. Renal tubular-cell adenocarcinomas were observed in 1/50 (2 percent) low dose and 5/49 (10 percent) high dose males. Renal tubular-cell adenocarcinomas were not observed in any treated females or in control mice of either sex.

Renal tubular-cell adenomas were composed of nodules of small, well-organized neoplastic tubules compressing the surrounding parenchyma. The size of these lesions varied from the diameter of six or seven normal tubules to a few millimeters. Cytoplasm of the tumor cells tended to be acidophilic and the nuclei were rounded and uniform. Although mitotic figures were often seen, there were no nuclear characteristics of malignancy. Renal tubular-cell carcinomas were much larger than adenomas, often invading the renal capsule.

Tubular organization was indistinct or absent. Cytoplasm was acidophilic and often contained large vacuoles. Nuclei varied in size, shape, and chromatin pattern and occasional nucleoli were prominent. Variable amounts of hemorrhage, necrosis, and calcification were associated with renal tubular-cell carcinomas.

Renal tubular dysplasia was observed in 30/49 (61 percent) high dose males, 37/50 (74 percent) low dose males, 12/46 (26 percent) high dose females and 1/50 (2 percent) low dose females. In these mice, normal tubular architecture was retained but occasional tubular cells were hypertrophied and contained very large bizarre nuclei with abnormal chromatin patterns and occasionally enlarged nucleoli. Tubular dysplasia was not seen in any controls.

Selected kidney slides from male and female high dose and control mice were stained with an acid fast stain and examined microscopically. No evidence of acid fast intranuclear inclusions in the renal epithelial cells suggestive of toxicity from lead or certain other heavy metal compounds was found.

Squamous-cell papillomas of the forestomach were found in 10/47 (21 percent) low dose and 11/48 (23 percent) high dose males and in 10/48 (21 percent) low dose and 18/44 (41 percent) high dose females. There were squamous-cell carcinomas of the forestomach in 2/48 (4 percent) high dose males, and in 4/48 (8 percent) low dose and 4/44 (9 percent) high dose females. No gastric neoplasms were found in 51 control males. There were squamous-cell papillomas of the forestomach in 2/53 (4 percent) control females.

Squamous-cell papillomas were defined as papillary lesions showing marked superficial hyperkeratosis. Beneath this was a thick layer of acanthotic squamous epithelium. Chronic inflammation was frequently found in the submucosa below the lesion, but the basal layer of the epithelium appeared intact.

The squamous-cell carcinomas of the forestomach also often showed superficial hyperkeratinization. However, the underlying epithelial cells had lost their normal architecture. Nuclei were pleomorphic with abundant normal and abnormal mitotic figures, variation in size and shape, and bizarre chromatin patterns. The basal layer of epithelial cells appeared to have lost its cohesion so that tumor cells grew down into the submucosa in a disorganized fashion and appeared as small islands deep in the stomach wall.

Other malignant gastric tumors found in the treated mice but not in the controls were a basal-cell carcinoma of the forestomach in a high dose male and a leiomyosarcoma of the stomach wall in a high dose female. There was one squamous-cell carcinoma of the esophagus in a high dose female.

Bronchiolar/alveolar adenomas or carcinomas occurred in 12/54 (22 percent) control males, 18/44 (41 percent) low dose males, 25/50 (50 percent) high dose males, 4/55 (7 percent) control females, 9/50 (18 percent) low dose females, and 17/50 (34 percent) high dose females.

Bronchiolar/alveolar adenomas were well-circumscribed lesions compressing the surrounding pulmonary parenchyma and often having subpleural locations. Tumor cells were arranged in ribbons or in more or less well-organized tubules. Cytoplasm was moderate in amount and faintly basophilic. Individual cells tended to be columnar. Nuclei were rounded and uniform with a normal chromatin pattern.

Bronchiolar/alveolar carcinomas tended to be larger than the adenomas, but were actually differentiated from them by two characteristics: (1) nuclear pleomorphism with parachromatin clearing and an abnormal chromatin pattern; and (2) a tendency to invade the surrounding parenchyma or neighboring bronchioles.

A dose-related increase in hepatocellular adenomas or carcinomas was noted in female mice. The observed combined incidences of mice with hepatocellular adenoma or hepatocellular carcinoma were 11/54 (20 percent) control females, 23/50 (46 percent) low dose females, and 35/49 (71 percent) high dose females. In male mice, however, no such dose-related increase in hepatocellular neoplasms was apparent.

Hepatocellular carcinomas were large lesions usually occupying the bulk of a lobe and compressing adjacent normal parenchyma. They showed no evidence of normal architectural pattern but consisted of trabeculae arranged in random fashion, often around large sinusoids. Cytoplasm was often abundant and faintly basophilic. Nuclei showed varying degrees of pleomorphism, some resembling normal hepatocytes and others having clearly abnormal chromatin patterns. Occasional

mitotic figures were seen. Some of these tumors invaded hepatic blood vessels and a few metastasized, usually to the lung.

The distinction between hepatocellular carcinomas and hepatocellular adenomas was not always clear. Tumors classified as adenomas were always smaller than carcinomas, occupying only a small portion of a lobe. Basophilia and nuclear pleomorphism were less frequently observed and no metastasis or vascular invasion were seen.

Cystadenomas of the Harderian gland were detected macroscopically and confirmed histologically in 0/55 control females, 4/50 (8 percent) low dose females, 2/50 (4 percent) high dose females, 1/55 (2 percent) control males, 1/50 (2 percent) low dose males and 2/50 (4 percent) high dose males. Since these lesions are rare, they may represent an effect of TBP feeding even though they were observed at low incidences and a dose-related effect was not apparent.

The Harderian gland tumors seen were small, well-circumscribed lesions. Cells were arranged in large, well-organized glands, often with a papillary component. Cell shapes varied from low cuboidal to high columnar. Nuclei were round, dark, uniform, and placed at the basal end in columnar cells. Cytoplasm was abundant and contained innumerable small vacuoles.

Other tumors found in treated mice but not in the controls included one interstitial-cell tumor of the testis in a low dose male, five assorted ovarian tumors (one malignant) in high dose females, one ovarian granulosa-cell tumor in a low dose female, ten assorted

uterine tumors in low dose females, two endometrial stromal polyps and one uterine adenocarcinoma in high dose females, and an osteoma of the skull in a high dose female. Tumors found in the controls but not in the treated mice included one mammary adenocarcinoma type B, a follicular adenoma of the thyroid gland, and a thymoma (all in females).

Nonneoplastic inflammatory or degenerative changes were occasionally seen in all groups of mice. Their nature and incidence could not be related to TBP administration.

Under the conditions of this bioassay histopathologic evidence was provided for the carcinogenicity of TBP in B6C3F1 mice because feeding of TBP was associated with neoplasms of the renal tubules in both sexes, marked increases in the incidence of squamous tumors of the forestomach in both sexes, increases in the incidence of lung tumors in both sexes, and increases in the incidence of hepatocellular neoplasms in females.

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

TABLE 5

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

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Stomach: Squamous-Cell Carcinoma[b]	0/51(0.00)	0/47(0.00)	2/48(0.04)
P Values[c]	N.S.	---	N.S.
Relative Risk (Control)[d]	---	---	Infinite
Lower Limit	---	---	0.314
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	95
Stomach: Squamous-Cell Papilloma or Squamous-Cell Carcinoma[b]	0/51(0.00)	10/47(0.21)	13/48(0.27)
P Values[c]	P < 0.001	P < 0.001	P < 0.001
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	3.229	4.265
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	94	95
Lung: Alveolar/Bronchiolar Carcinoma[b]	6/54(0.11)	8/44(0.18)	13/50(0.26)
P Values[c]	P = 0.033	N.S.	P = 0.043
Relative Risk (Control)[d]	---	1.636	2.340
Lower Limit	---	0.538	0.904
Upper Limit	---	5.281	6.922
Weeks to First Observed Tumor	105	88	100

TABLE 5 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	12/54(0.22)	18/44(0.41)	25/50(0.50)
P Values[c]	P = 0.003	P = 0.038	P = 0.003
Relative Risk (Control)[d]	---	1.841	2.250
Lower Limit	---	0.946	1.236
Upper Limit	---	3.666	4.274
Weeks to First Observed Tumor	79	88	54
Kidney: Tubular-Cell Adenocarcinoma[b]	0/54(0.00)	1/50(0.02)	5/49(0.10)
P Values[c]	P = 0.009	N.S.	P = 0.022
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.058	1.388
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	104	98
Kidney: Tubular-Cell Adenoma or Tubular-Cell Adenocarcinoma[b]	0/54(0.00)	4/50(0.08)	14/49(0.29)
P Values[c]	P < 0.001	N.S.	P < 0.001
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.999	4.798
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	100	98

TABLE 5 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Malignant Lymphoma[b]	4/55(0.07)	5/50(0.10)	4/50(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.375	1.110
Lower Limit	---	0.314	0.214
Upper Limit	---	6.559	5.600
Weeks to First Observed Tumor	105	91	104
Liver: Hepatocellular Carcinoma[b]	24/54(0.44)	20/49(0.41)	19/49(0.39)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.918	0.872
Lower Limit	---	0.557	0.522
Upper Limit	---	1.495	1.436
Weeks to First Observed Tumor	53	92	95
Liver: Hepatocellular Adenoma or Hepatocellular Carcinoma[b]	28/54(0.52)	31/49(0.63)	23/49(0.47)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.220	0.905
Lower Limit	---	0.846	0.587
Upper Limit	---	1.737	1.384
Weeks to First Observed Tumor	53	92	95

TABLE 5 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Circulatory System: Hemangioma[b]	1/55(0.02)	3/49(0.06)	0/50(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	3.367	0.000
Lower Limit	---	0.281	0.000
Upper Limit	---	173.066	20.522
Weeks to First Observed Tumor	105	104	---

[a]Treated groups received time-weighted average doses of 500 or 1000 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 TBP[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Stomach: Squamous-Cell Carcinoma[b]	0/53(0.00)	4/48(0.08)	4/44(0.09)
P Values[c]	P = 0.038	P = 0.048	P = 0.039
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	1.023	1.116
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	96	104
Stomach: Squamous-Cell Papilloma or Squamous-Cell Carcinoma[b]	2/53(0.04)	14/48(0.29)	22/44(0.50)
P Values[c]	P < 0.001	P < 0.001	P < 0.001
Relative Risk (Control)[d]	---	7.729	13.250
Lower Limit	---	1.908	3.552
Upper Limit	---	66.800	108.262
Weeks to First Observed Tumor	105	92	102
Lung: Alveolar/Bronchiolar Carcinoma[b]	1/55(0.02)	1/50(0.02)	3/50(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.100	3.300
Lower Limit	---	0.014	0.273
Upper Limit	---	84.647	169.657
Weeks to First Observed Tumor	105	104	104

TABLE 6 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	4/55(0.07)	9/50(0.18)	17/50(0.34)
P Values[c]	P = 0.001	N.S.	P < 0.001
Relative Risk (Control)[d]	---	2.475	4.675
Lower Limit	---	0.741	1.659
Upper Limit	---	10.349	17.743
Weeks to First Observed Tumor	105	83	104
Hematopoietic System: Malignant Lymphoma[b]	14/55(0.25)	14/50(0.28)	10/50(0.20)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.100	0.786
Lower Limit	---	0.540	0.345
Upper Limit	---	2.228	1.718
Weeks to First Observed Tumor	86	92	91
Hematopoietic System: Malignant Lymphoma or Leukemia[b]	18/55(0.33)	15/50(0.30)	10/50(0.20)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.917	0.611
Lower Limit	---	0.484	0.279
Upper Limit	---	1.706	1.254
Weeks to First Observed Tumor	86	85	91

TABLE 6 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	7/54(0.13)	12/50(0.24)	20/49(0.41)
P Values[c]	P = 0.001	N.S.	P = 0.001
Relative Risk (Control)[d]	---	1.851	3.149
Lower Limit	---	0.732	1.421
Upper Limit	---	5.101	7.932
Weeks to First Observed Tumor	101	98	85
Liver: Hepatocellular Adenoma or Hepatocellular Carcinoma[b]	11/54(0.20)	23/50(0.46)	35/49(0.71)
P Values[c]	P < 0.001	P = 0.005	P < 0.001
Relative Risk (Control)[d]	---	2.258	3.506
Lower Limit	---	1.193	2.030
Upper Limit	---	4.508	6.236
Weeks to First Observed Tumor	59	98	85
Circulatory System: Hemangioma[b]	3/55(0.02)	6/50(0.12)	6/50(0.12)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	2.200	2.200
Lower Limit	---	0.497	0.497
Upper Limit	---	12.953	12.952
Weeks to First Observed Tumor	82	104	43

TABLE 6 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Subcutaneous Tissue: Fibrosarcoma[b]	0/55(0.00)	3/50(0.06)	0/50(0.00)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.012	---	---
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.660	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	83	---
Uterus: Endometrial Stromal Polyp[b]	0/54(0.00)	6/49(0.12)	2/46(0.04)
P Values[c]	N.S.	P = 0.010	N.S.
Departure from Linear Trend[e]	P = 0.009	---	---
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	1.760	0.347
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	99	104
Harderian Gland: Cystadenoma NOS[b]	0/55(0.00)	3/50(0.06)	0/50(0.00)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.012	---	---
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.660	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	98	---

TABLE 6 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Kidney: Tubular-Cell Adenoma[b]	0/55(0.00)	2/50(0.04)	2/46(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.325	0.353
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	85	104

[a]Treated groups received time-weighted average doses of 500 or 1000 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.

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

A high incidence of stomach tumors was noted in both male and female dosed mice. Statistical tests were performed combining the incidences of squamous-cell papillomas and squamous-cell carcinomas, so that the measurement of interest was the proportion of mice having either the papilloma or the carcinoma or both. The Cochran-Armitage test indicated a significant ($P < 0.001$) positive association between the incidence of either squamous-cell papillomas or squamous-cell carcinomas and TBP dosage in both sexes. Fisher exact tests confirmed these results in both sexes by indicating significance ($P < 0.001$) in comparisons of either the low dose or the high dose groups to the control groups. The spontaneous tumor rates observed in the controls were not significantly different from the 2/625 in males and 6/575 in females observed in the historical control B6C3F1 mice as compiled to date for the NCI Carcinogenesis Testing Program at Mason Research Institute. Based upon these results there was a significant positive association between the administration of TBP under the conditions of this experiment and an elevated incidence of stomach tumors (squamous-cell carcinomas and papillomas) in both male and female B6C3F1 mice.

For both sexes the dosed mice exhibited a high incidence of lung tumors. Statistical tests were performed combining the incidences of alveolar/bronchiolar adenomas and alveolar/bronchiolar carcinomas, so that the measurement of interest was the proportion of mice having either the adenoma or the carcinoma or both. The Cochran-Armitage test indicated a positive association between TBP dosage and the

incidence of alveolar/bronchiolar neoplasms in both male ($P = 0.003$) and female ($P = 0.001$) mice. Fisher exact tests showed a significant difference between the control groups and the high dose groups for both male ($P = 0.003$) and female ($P < 0.001$) mice. For the male mice the comparison between the control group and the low dose group had a probability level of $P = 0.038$, a marginal result which was not significant under the Bonferroni inequality. The spontaneous tumor rates for the combination of alveolar/bronchiolar carcinomas and alveolar/bronchiolar adenomas observed in the controls were not significantly different from the 21/575 (4 percent) observed in female historical control B6C3F1 mice at Mason Research Institute for the NCI Carcinogenesis Testing Program, but they were significantly ($P < 0.05$) higher than the 70/625 (11 percent) observed in the historical control males. Based upon these results there was a positive association between the administration of TBP and an elevated incidence of lung tumors in both male and female mice under the conditions of this experiment.

A high incidence of liver tumors was noted in dosed female mice. When incidences were combined so that the numerator represented mice having either a hepatocellular carcinoma or a hepatocellular adenoma the Cochran-Armitage test indicated a highly significant ($P < 0.001$) positive association between dosage and the incidence of hepatocellular carcinomas or adenomas. Fisher exact tests confirmed these results in comparing the control group to either the low dose ($P = 0.005$) or the high dose ($P < 0.001$) group. The spontaneous tumor

rate observed in the control (11/54 or 20 percent) was significantly ($P < 0.05$) higher than the incidence (29/575 or 5 percent) observed in the female historical controls. Based upon these results there was a significant positive association between the administration of TBP and an elevated incidence of liver tumors in female mice under the conditions of this experiment.

In male mice there was a high incidence of kidney tumors. When incidences were combined so that the numerator represented mice with either a tubular-cell adenoma or a tubular-cell adenocarcinoma, the Cochran-Armitage test indicated a significant ($P < 0.001$) positive association between dosage and incidence. The Fisher exact tests confirmed this relationship with the significant ($P < 0.001$) comparison of high dose to control group. The spontaneous tumor rate observed in the control group was not significantly different from the 0/625 observed in the historical control B6C3F1 male mice. When only tubular-cell adenocarcinomas were considered, again both the Cochran-Armitage test ($P = 0.009$) and the Fisher exact test comparing high dose to control ($P = 0.022$) were significant. Based upon these results there was a significant positive association between the administration of TBP and an elevated incidence of kidney tumors in male mice under the conditions of this experiment.

In female mice the Fisher exact test showed a significantly ($P = 0.010$) higher incidence of endometrial stromal polyps in the low dose group than in the control group. No other statistical tests were significant, however.

V. DISCUSSION

In both species adequate numbers of animals in all groups survived long enough to be at risk from late-developing tumors. The similarity of mean group body weights for control rats and dosed rats throughout this bioassay indicates that feeding of TBP did not interfere with the growth of rats. Dose-related depression of mean group body weights was, however, observed among mice.

Renal tubular-cell adenomas were observed in 48 percent (26/54) of the low dose male rats, 48 percent (26/54) of the high dose male rats, 7 percent (4/54) of the low dose female rats, and 19 percent (10/54) of the high dose female rats. Renal tubular-cell adenocarcinomas were observed only in 6 percent (3/54) of high dose male rats. No neoplasms were observed in kidneys of control rats. There was a significant positive association between the incidence of renal tubular-cell adenomas in female rats and dietary concentration of TBP. In addition, the incidence of tubular-cell adenomas in high dose female rats was significantly higher than that in controls. For male rats, the combined incidence of renal tubular-cell adenomas and renal tubular-cell adenocarcinomas was significant by all statistical tests applied.

The incidence of renal tubular-cell adenocarcinomas in low and high dose male mice was 2 percent (1/50) and 10 percent (5/49), respectively, as compared to none in the control group. This indicated a significant positive trend and a significant increase at the high

dose level. No renal tubular-cell adenocarcinomas were observed in female mice. The incidences of renal tubular-cell adenoma in low and high dose males were 6 percent (3/50) and 18 percent (9/49), respectively, as compared to none in the control group. This also indicated a significant positive trend and a significant increase at the high dose level. In the females, renal tubular-cell adenoma occurred in 4 percent of each treated group (2/50 low dose and 2/46 high dose), as compared to none in the control group, but this incidence was not statistically significant.

Either squamous-cell papillomas or squamous-cell carcinomas of the forestomach occurred in low and high dose mice, respectively, in 21 percent (10/48) and 27 percent (13/48) of the male and 29 percent (14/48) and 50 percent (22/44) of the female mice, as compared to none in the male control and 4 percent in the female control group. This indicated a highly significant positive trend and a highly significant increase of this tumor in both sexes at both dose levels. These tumors were combined for purposes of statistical analysis since they may have a common pathogenesis. Most of the observed squamous-cell tumors of the forestomach, however, were interpreted as benign. The incidence of squamous-cell carcinoma of the forestomach in low and high dose females was 8 percent (4/48) and 9 percent (4/44), respectively, as compared to none in the control group. This indicated a significant positive trend, and suggests a relationship to TBP administration. In the males, squamous-cell carcinoma occurred only in 4

percent (2/48) of the high dose group; this incidence was not statistically significant. The incidences of squamous-cell papillomas and squamous-cell carcinomas are suggestive of carcinogenicity because squamous-cell carcinomas of the forestomach rarely occur spontaneously.

A high incidence of liver tumors was observed in female mice treated with TBP. The proportion of female mice having hepatocellular carcinomas or adenomas or both was significantly higher in treated groups than control groups for all statistical tests applied. When only hepatocellular adenomas were considered, once again all tests were significant. When only the incidence of hepatocellular carcinomas was considered, the positive dose-related trend was significant and tumor incidence in the high dose group was significantly higher than in the control group. Tumor incidence among male mice was not significant for hepatocellular carcinoma or adenoma.

A high incidence of lung tumors was apparent in both male and female mice. The proportion of mice of each sex having alveolar/bronchiolar adenoma or carcinoma or both exhibited a statistically significant positive association with increased dietary concentration of TBP. The incidence of alveolar/bronchiolar carcinomas alone exhibited a significant positive dose-related trend for males, but not for females.

1,2-Dibromo-3-chloropropane (DBCP) is a common contaminant of TBP (Kerst, 1974). In a bioassay conducted for the NCI Carcinogenesis Testing Program at Hazleton Laboratories America, Inc., Vienna,

Virginia, DBCP administered by gavage was found to cause a high incidence of squamous-cell carcinomas of the forestomach in rats and mice and also caused a significant increase in the incidence of adenocarcinomas of the mammary gland in female rats. DBCP also caused toxic nephropathy in both rats and mice. Levels of DBCP in the batch of TBP used for this bioassay did not exceed 100 ppm. Although the combined incidences of squamous-cell carcinomas and squamous-cell papillomas of the forestomach were significant in male and female mice, other DBCP-related lesions were not observed at increased incidences in TBP-dosed animals. The incidences of squamous-cell carcinomas of the forestomach in male and female rats and the incidence of mammary adenocarcinomas in female rats did not exceed those in controls. Toxic nephropathy was not reported in rats or mice in this bioassay, although dysplastic lesions were observed in kidneys of TBP-treated rats. The types of dysplastic lesions found in the TBP bioassay were not observed in DBCP-treated rats or mice. It is concluded that the results of this bioassay are due principally to TBP administration.

The ability of TBP to induce base-pair substitution mutations in histidine-requiring strains of Salmonella typhimurium supports the positive findings of this bioassay. TBP gave positive Ames test results both with and without activation by hepatic microsomes derived from Spraque-Dawley rats, indicating that TBP can behave as a direct-acting mutagen (Prival et al., 1977). The mutagenicity of TBP was, however, enhanced by metabolic activation. Prival et al. (1977)

found no significant quantitative differences in mutagenicity among nine different commercial samples of TBP obtained from five different suppliers. These samples included both HV (high in volatiles) and LV (low in volatiles) grades. A highly purified sample of TBP had approximately the same mutagenic activity as the commercial samples (Prival et al., 1977). The authors concluded that it was highly unlikely that the mutagenicity of TBP was due to the presence of an impurity (Prival et al., 1977).

It is concluded that under the conditions of this study orally administered TBP was carcinogenic to B6C3F1 mice, causing increased incidences of neoplasms in livers, lungs, and stomachs of female mice and in kidneys, lungs and stomachs of male mice. TBP was also carcinogenic in Fischer 344 rats, causing an increased incidence of kidney tumors in male and female animals.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH TBP

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

	CONTROL (UNTR) 01-0360	LOW DOSE 01-0405	HIGH DOSE 01-0410
ANIMALS INITIALLY IN STUDY	55	55	55
ANIMALS NECROPSIED	54	55	55
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	54	55	55
INTEGUMENTARY SYSTEM			
*SKIN	(54)	(55)	(55)
SQUAMOUS CELL PAPILLOMA	2 (4%)		2 (4%)
FIBROMA	2 (4%)		
*SUBCUT TISSUE	(54)	(55)	(55)
FIBROMA	2 (4%)	1 (2%)	1 (2%)
FIBROSARCOMA		2 (4%)	
RESPIRATORY SYSTEM			
#LUNG	(54)	(55)	(55)
ALVEOLAR/BRONCHIOLAR ADENOMA		2 (4%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	
PHEOCHROMOCYTOMA, METASTATIC			1 (2%)
OSTEOSARCOMA, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(54)	(55)	(55)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
UNDIFFERENTIATED LEUKEMIA	13 (24%)	12 (22%)	6 (11%)
LYMPHOCYTIC LEUKEMIA	4 (7%)	1 (2%)	1 (2%)
#MEDIASTINAL L.NODE	(53)	(51)	(51)
ALVEOLAR/BRONCHIOLAR CA, METASTA		1 (2%)	
PHEOCHROMOCYTOMA, METASTATIC			1 (2%)
CIRCULATORY SYSTEM			
#HEART	(54)	(55)	(55)
PHEOCHROMOCYTOMA, METASTATIC			1 (2%)

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

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 01-0360	LOW DOSE 01-0405	HIGH DOSE 01-0410
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(54)	(53)	(54)
ACINAR-CELL ADENOMA		1 (2%)	1 (2%)
#LIVER	(54)	(55)	(54)
NEOPLASTIC NODULE			2 (4%)
HEPATOCELLULAR CARCINOMA		1 (2%)	2 (4%)
*BILE DUCT	(54)	(55)	(55)
BILE DUCT CARCINOMA			1 (2%)
#STOMACH	(53)	(54)	(52)
SQUAMOUS CELL PAPILLOMA		2 (4%)	
SQUAMOUS CELL CARCINOMA	2 (4%)	1 (2%)	
BASAL-CELL CARCINOMA		1 (2%)	1 (2%)
#JEJUNUM	(52)	(53)	(51)
MUCINOUS ADENOCARCINOMA		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(53)	(54)	(54)
TUBULAR-CELL ADENOMA		26 (48%)	26 (48%)
TUBULAR-CELL ADENOCARCINOMA			3 (6%)
#URINARY BLADDER	(51)	(51)	(49)
TRANSITIONAL-CELL PAPILLOMA		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(48)	(50)	(50)
CARCINOMA, NOS		1 (2%)	
ADENOMA, NOS		1 (2%)	
CHROMOPHOBE ADENOMA	4 (8%)	7 (14%)	3 (6%)
CHROMOPHOBE CARCINOMA		1 (2%)	
ACIDOPHIL ADENOMA	1 (2%)		
BASOPHIL ADENOMA		3 (6%)	2 (4%)
#ADRENAL	(54)	(55)	(55)
CORTICAL ADENOMA	1 (2%)		
PHEOCHROMOCYTOMA	12 (22%)	8 (15%)	13 (24%)
PHEOCHROMOCYTOMA, MALIGNANT	2 (4%)	3 (5%)	3 (5%)

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

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 01-0360	LOW DOSE 01-0405	HIGH DOSE 01-0410
#THYROID	(53)	(51)	(52)
FOLLICULAR-CELL CARCINOMA			2 (4%)
C-CELL ADENOMA	3 (6%)	2 (4%)	3 (6%)
C-CELL CARCINOMA		1 (2%)	1 (2%)
#PANCREATIC ISLETS	(53)	(53)	(51)
ISLET-CELL ADENOMA	1 (2%)	3 (6%)	1 (2%)
ISLET-CELL CARCINOMA	1 (2%)		1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(54)	(55)	(55)
ADENOMA, NOS			1 (2%)
INTRADUCTAL PAPILLOMA	1 (2%)		
FIBROADENOMA	1 (2%)		1 (2%)
*PREPUTIAL GLAND	(54)	(55)	(55)
CARCINOMA,NOS	1 (2%)	2 (4%)	3 (5%)
ADENOMA, NOS		1 (2%)	3 (5%)
ADENOCARCINOMA, NOS			1 (2%)
#TESTIS	(54)	(55)	(55)
INTERSTITIAL-CELL TUMOR	53 (98%)	46 (84%)	50 (91%)
NERVOUS SYSTEM			
#BRAIN	(54)	(55)	(55)
CERUMINOUS CARCINOMA, METASTATIC	1 (2%)		
ASTROCYTOMA			1 (2%)
SPECIAL SENSE ORGANS			
*EYE	(54)	(55)	(55)
SQUAMOUS CELL CARCINOMA	1 (2%)		
*EAR	(54)	(55)	(55)
CERUMINOUS CARCINOMA	1 (2%)		
*EAR CANAL	(54)	(55)	(55)
SEBACEOUS ADENOCARCINOMA		1 (2%)	
CERUMINOUS CARCINOMA	1 (2%)		

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

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 01-0360	LOW DOSE 01-0405	HIGH DOSE 01-0410
MUSCULOSKELETAL SYSTEM			
*SKULL	(54)	(55)	(55)
OSTEOSARCOMA			1 (2%)
*MANDIBLE	(54)	(55)	(55)
OSTEOSARCOMA		1 (2%)	
*STERNUM	(54)	(55)	(55)
PHEOCHROMOCYTOMA, METASTATIC			1 (2%)
*RIB	(54)	(55)	(55)
ALVEOLAR/BRONCHIOLAR CA, METASTA		1 (2%)	
BODY CAVITIES			
*ABDOMINAL CAVITY	(54)	(55)	(55)
MESOTHELIOMA, NOS		1 (2%)	
*PERITONEUM	(54)	(55)	(55)
MESOTHELIOMA, NOS		1 (2%)	
*PELVIS	(54)	(55)	(55)
CHORDOMA			1 (2%)
*MESENTERY	(54)	(55)	(55)
FIBROSARCOMA		1 (2%)	1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(54)	(55)	(55)
MESOTHELIOMA, NOS	2 (4%)		
DIAPHRAGM			
FIBROSARCOMA, METASTATIC			1
OMENTUM			
FIBROSARCOMA		1	

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

TABLE A1 (CONCLUDED)

	CONTROL (UNTR) 01-0360	LOW DOSE 01-0405	HIGH DOSE 01-0410
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	55	55	55
NATURAL DEATH@	6	3	7
MORIBUND SACRIFICE	10	17	8
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	39	35	40
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	54	54	55
TOTAL PRIMARY TUMORS	112	138	138
TOTAL ANIMALS WITH BENIGN TUMORS	53	51	51
TOTAL BENIGN TUMORS	83	104	107
TOTAL ANIMALS WITH MALIGNANT TUMORS	26	26	24
TOTAL MALIGNANT TUMORS	27	32	29
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	1	3
TOTAL SECONDARY TUMORS	1	2	6
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	2	2	2
TOTAL UNCERTAIN TUMORS	2	2	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

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

	CONTROL (UNTR) 02-0360	LOW DOSE 02-0405	HIGH DOSE 02-0410
ANIMALS INITIALLY IN STUDY	55	55	55
ANIMALS NECROPSIED	54	55	55
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	54	55	55
INTEGUMENTARY SYSTEM			
*SKIN	(54)	(55)	(55)
SQUAMOUS CELL PAPILLOMA	2 (4%)	1 (2%)	
SQUAMOUS CELL CARCINOMA	2 (4%)	1 (2%)	2 (4%)
*SUBCUT TISSUE	(54)	(55)	(55)
FIBROMA	1 (2%)	1 (2%)	
FIBROSARCOMA			1 (2%)
LIPOMA		2 (4%)	
LIPOSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(53)	(54)	(55)
BILE DUCT CARCINOMA, METASTATIC			1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	2 (4%)	
ADENOSQUAMOUS CARCINOMA		1 (2%)	
FIBROSARCOMA, METASTATIC			2 (4%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(54)	(55)	(55)
UNDIFFERENTIATED LEUKEMIA	8 (15%)	9 (16%)	9 (16%)
LYMPHOCYTIC LEUKEMIA	1 (2%)	1 (2%)	
#BONE MARROW	(53)	(54)	(52)
FIBROSARCOMA, METASTATIC			1 (2%)
#SPLEEN	(52)	(54)	(55)
NEUROFIBROSARCOMA, UNC PRIM OR M	1 (2%)		
#LYMPH NODE	(51)	(54)	(54)
BILE DUCT CARCINOMA, METASTATIC			1 (2%)

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

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 02-0360	LOW DOSE 02-0405	HIGH DOSE 02-0410
#MEDIASTINAL L.NODE	(51)	(54)	(54)
UNDIFFERENTIATED CARCINOMA METAS	1 (2%)		
#MESENTERIC L. NODE	(51)	(54)	(54)
UNDIFFERENTIATED CARCINOMA METAS	1 (2%)		
BILE DUCT CARCINOMA, METASTATIC			1 (2%)
#THYMUS	(42)	(50)	(45)
THYMOMA			1 (2%)
CIRCULATORY SYSTEM			
#HEART	(53)	(54)	(55)
NEUROFIBROSARCOMA, UNC PRIM OR M	1 (2%)		
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(52)	(54)	(55)
ADENOMA, NOS	3 (6%)		
ACINAR-CELL ADENOMA			2 (4%)
#LIVER	(53)	(54)	(55)
NECROTIC NODULE	1 (2%)	1 (2%)	
HEPATOCELLULAR CARCINOMA			1 (2%)
NEUROFIBROSARCOMA, UNC PRIM OR M	1 (2%)		
*BILE DUCT	(54)	(55)	(55)
BILE DUCT CARCINOMA			2 (4%)
#PANCREAS	(52)	(53)	(54)
BILE DUCT CARCINOMA, METASTATIC			1 (2%)
#STOMACH	(51)	(54)	(52)
SQUAMOUS CELL PAPILLOMA	1 (2%)		
SQUAMOUS CELL CARCINOMA	1 (2%)	1 (2%)	
BASAL-CELL CARCINOMA		1 (2%)	1 (2%)
ADENOCARCINOMA, NOS	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(52)	(54)	(54)
TUBULAR-CELL ADENOMA		4 (7%)	10 (19%)

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

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 02-0360	LOW DOSE 02-0405	HIGH DOSE 02-0410
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(54)	(52)
CARCINOMA, NOS	3 (6%)	1 (2%)	1 (2%)
ADENOMA, NOS	1 (2%)		
CHROMOPHOBE ADENOMA	15 (31%)	22 (41%)	24 (46%)
CHROMOPHOBE CARCINOMA	1 (2%)		
ACIDOPHIL ADENOMA	1 (2%)	2 (4%)	
BASOPHIL ADENOMA			1 (2%)
#ADRENAL	(53)	(53)	(54)
CORTICAL ADENOMA	1 (2%)	1 (2%)	2 (4%)
PHEOCHROMOCYTOMA	3 (6%)	4 (8%)	2 (4%)
ANGIOLIPOMA	1 (2%)		
#THYROID	(49)	(53)	(53)
UNDIFFERENTIATED CARCINOMA	1 (2%)		
FOLLICULAR-CELL ADENOMA			1 (2%)
C-CELL ADENOMA	1 (2%)	1 (2%)	4 (8%)
C-CELL CARCINOMA	3 (6%)	2 (4%)	
#PANCREATIC ISLETS	(52)	(53)	(54)
ISLET-CELL ADENOMA	1 (2%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(54)	(55)	(55)
PAPILLOMATOSIS		1 (2%)	
ADENOMA, NOS	1 (2%)		2 (4%)
ADENOCARCINOMA, NOS	2 (4%)		2 (4%)
FIBROSARCOMA			1 (2%)
FIBROADENOMA	16 (30%)	10 (18%)	19 (35%)
*CLITORAL GLAND	(54)	(55)	(55)
CARCINOMA, NOS	2 (4%)		1 (2%)
ADENOMA, NOS		3 (5%)	
ADENOCARCINOMA, NOS		1 (2%)	
#UTERUS	(52)	(54)	(55)
ENDOMETRIAL STROMAL POLYP	16 (31%)	14 (26%)	11 (20%)
ENDOMETRIAL STROMAL SARCOMA		1 (2%)	1 (2%)
HEMANGIOMA		2 (4%)	
#UTERUS/ENDOMETRIUM	(52)	(54)	(55)
ADENOCARCINOMA, NOS		1 (2%)	1 (2%)

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

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 02-0360	LOW DOSE 02-0405	HIGH DOSE 02-0410
#OVARY	(53)	(53)	(55)
GRANULOSA-CELL TUMOR	1 (2%)		1 (2%)
GRANULOSA-CELL CARCINOMA			1 (2%)
SERTOLI-CELL TUMOR			3 (5%)
TUBULAR ADENOMA	2 (4%)		
NERVOUS SYSTEM			
#BRAIN	(52)	(54)	(54)
CARCINOMA, NOS, METASTATIC	2 (4%)		
CHROMOPHOBE CARCINOMA, METASTATI	1 (2%)		
ASTROCYTOMA			2 (4%)
SPECIAL SENSE ORGANS			
*EYE	(54)	(55)	(55)
SQUAMOUS CELL CARCINOMA	2 (4%)		
*EAR CANAL	(54)	(55)	(55)
CERUMINOUS CARCINOMA	1 (2%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(54)	(55)	(55)
MESOTHELIOMA, NOS			2 (4%)
*PLEURA	(54)	(55)	(55)
MESOTHELIOMA, NOS			1 (2%)
*MESENTERY	(54)	(55)	(55)
FIBROSARCOMA			2 (4%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(54)	(55)	(55)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)		

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

TABLE A2 (CONCLUDED)

	CONTROL (UNTR) 02-0360	LOW DOSE 02-0405	HIGH DOSE 02-0410
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	55	55	55
NATURAL DEATH@	6	2	4
MORIBUND SACRIFICE	13	9	15
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	36	44	36
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	52	47	54
TOTAL PRIMARY TUMORS	100	92	115
TOTAL ANIMALS WITH BENIGN TUMORS	45	43	47
TOTAL BENIGN TUMORS	67	70	82
TOTAL ANIMALS WITH MALIGNANT TUMORS	24	19	24
TOTAL MALIGNANT TUMORS	28	21	29
TOTAL ANIMALS WITH SECONDARY TUMORS#	5		3
TOTAL SECONDARY TUMORS	6		7
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT	2	1	3
TOTAL UNCERTAIN TUMORS	2	1	4
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC	1		
TOTAL UNCERTAIN TUMORS	3		

* 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 TBP

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

	CONTROL (UNTR) 05-0360	LOW DOSE 05-0415	HIGH DOSE 05-0420
ANIMALS INITIALLY IN STUDY	55	50	50
ANIMALS NECROPSIED	55	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	55	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(55)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)		
SEBACEOUS ADENOMA			1 (2%)
*SUBCUTIISSUE	(55)	(50)	(50)
FIBROMA	2 (4%)		
FIBROSARCOMA	1 (2%)	2 (4%)	1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(54)	(44)	(50)
HEPATOCELLULAR CARCINOMA, METAST	4 (7%)	1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	6 (11%)	11 (25%)	12 (24%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	6 (11%)	8 (18%)	13 (26%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(55)	(50)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
MALIGNANT LYMPHOMA, MIXED TYPE	2 (4%)	2 (4%)	2 (4%)
#SPLEEN	(51)	(47)	(49)
HEMANGIOMA	1 (2%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	
#MEDIASTINAL L.NODE	(48)	(43)	(44)
FIBROSARCOMA, METASTATIC			1 (2%)
#MESENTERIC L. NODE	(48)	(43)	(44)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)	1 (2%)	
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	1 (2%)

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

TABLE B1 (CONTINUED)

	CONTROL (UNTR) 05-0360	LOW DOSE 05-0415	HIGH DOSE 05-0420
#LIVER	(54)	(49)	(49)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
#JEJUNUM	(50)	(47)	(48)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)		
CIRCULATORY SYSTEM			
#HEART	(55)	(49)	(50)
HEMANGIOMA		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(54)	(49)	(49)
HEPATOCELLULAR ADENOMA	4 (7%)	11 (22%)	4 (8%)
HEPATOCELLULAR CARCINOMA	24 (44%)	20 (41%)	19 (39%)
#PANCREAS	(49)	(46)	(49)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	
#STOMACH	(51)	(47)	(48)
SQUAMOUS CELL PAPILLOMA		10 (21%)	11 (23%)
SQUAMOUS CELL CARCINOMA			2 (4%)
BASAL-CELL CARCINOMA			1 (2%)
URINARY SYSTEM			
#KIDNEY	(54)	(50)	(49)
TUBULAR-CELL ADENOMA		3 (6%)	9 (18%)
TUBULAR-CELL ADENOCARCINOMA		1 (2%)	5 (10%)
#KIDNEY/PELVIS	(54)	(50)	(49)
TRANSITIONAL-CELL PAPILLOMA	1 (2%)		
#URINARY BLADDER	(48)	(38)	(47)
HEMANGIOMA		2 (5%)	
HEMANGIOSARCOMA			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(39)	(38)	(43)
CHROMOPHOBE ADENOMA		1 (3%)	

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

TABLE B1 (CONTINUED)

	CONTROL (UNTR) 05-0360	LOW DOSE 05-0415	HIGH DOSE 05-0420
#ADRENAL	(50)	(42)	(48)
CORTICAL ADENOMA	1 (2%)		1 (2%)
PHEOCHROMOCYTOMA		1 (2%)	
#ADRENAL/CAPSULE	(50)	(42)	(48)
ADENOMA, NOS	5 (10%)	1 (2%)	
#PANCREATIC ISLETS	(49)	(46)	(49)
ISLET-CELL ADENOMA	2 (4%)		
REPRODUCTIVE SYSTEM			
#TESTIS	(54)	(49)	(50)
INTERSTITIAL-CELL TUMOR		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(55)	(50)	(50)
CYSTADENOMA, NOS	1 (2%)	1 (2%)	2 (4%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM	(55)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CA, METASTA			1 (2%)
*PERITONEUM	(55)	(50)	(50)
MESOTHELIOMA, NOS		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(55)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)

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

TABLE B1 (CONCLUDED)

	CONTROL (UNTR) 05-0360	LOW DOSE 05-0415	HIGH DOSE 05-0420
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	55	50	50
NATURAL DEATH@	9	7	3
MORIBUND SACRIFICE	2	4	4
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED		1	
TERMINAL SACRIFICE	44	38	43
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	43	41	43
TOTAL PRIMARY TUMORS	59	80	86
TOTAL ANIMALS WITH BENIGN TUMORS	22	29	28
TOTAL BENIGN TUMORS	24	43	40
TOTAL ANIMALS WITH MALIGNANT TUMORS	29	30	34
TOTAL MALIGNANT TUMORS	35	36	46
TOTAL ANIMALS WITH SECONDARY TUMORS#	4	2	4
TOTAL SECONDARY TUMORS	5	3	4
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT		1	
TOTAL UNCERTAIN TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

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

	CONTROL (UNTR) 06-0360	LOW DOSE 06-0415	HIGH DOSE 06-0420
ANIMALS INITIALLY IN STUDY	55	50	50
ANIMALS NECROPSIED	55	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	55	50	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(55)	(50)	(50)
FIBROSARCOMA		3 (6%)	
HEMANGIOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(55)	(50)	(50)
HEPATOCELLULAR CARCINOMA, METAST	2 (4%)	1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (5%)	8 (16%)	14 (28%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	1 (2%)	3 (6%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(55)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	1 (2%)		1 (2%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	2 (4%)	1 (2%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)	2 (4%)	1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE	6 (11%)	4 (8%)	4 (8%)
LYMPHOCYTIC LEUKEMIA	4 (7%)	1 (2%)	
#SPLEEN	(53)	(47)	(46)
HEMANGIOMA		1 (2%)	1 (2%)
HEMANGIOSARCOMA	2 (4%)		
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)	3 (6%)	1 (2%)
#LYMPH NODE	(47)	(43)	(45)
MALIGNANT LYMPHOMA, MIXED TYPE			1 (2%)
#MEDIASTINAL L.NODE	(47)	(43)	(45)
ALVEOLAR/BRONCHIOLAR CA, METASTA			1 (2%)
#MESENTERIC L. NODE	(47)	(43)	(45)
MALIGNANT LYMPHOMA, MIXED TYPE	2 (4%)	3 (7%)	2 (4%)

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

TABLE B2 (CONTINUED)

	CONTROL (UNTR) 06-0360	LOW DOSE 06-0415	HIGH DOSE 06-0420
#LIVER	(54)	(50)	(49)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
#KIDNEY	(55)	(50)	(46)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	
#THYMUS	(35)	(41)	(36)
THYMOMA	1 (3%)		
CIRCULATORY SYSTEM			
#HEART	(55)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CA, METASTA			1 (2%)
HEMANGIOMA	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(54)	(50)	(49)
HEPATOCELLULAR ADENOMA	4 (7%)	11 (22%)	15 (31%)
HEPATOCELLULAR CARCINOMA	7 (13%)	12 (24%)	20 (41%)
HEMANGIOMA	1 (2%)	2 (4%)	1 (2%)
#ESOPHAGUS	(51)	(47)	(45)
SQUAMOUS CELL CARCINOMA			1 (2%)
#STOMACH	(53)	(48)	(44)
SQUAMOUS CELL PAPILLOMA	2 (4%)	10 (21%)	18 (41%)
SQUAMOUS CELL CARCINOMA		4 (8%)	4 (9%)
LEIOMYOSARCOMA			1 (2%)
URINARY SYSTEM			
#KIDNEY	(55)	(50)	(46)
TUBULAR-CELL ADENOMA		2 (4%)	2 (4%)
#URINARY BLADDER	(50)	(43)	(43)
HEMANGIOMA			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(42)	(38)	(39)
CHROMOPHOBE ADENOMA	2 (5%)	1 (3%)	

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

TABLE B2 (CONTINUED)

	CONTROL (UNTR) 06-0360	LOW DOSE 06-0415	HIGH DOSE 06-0420
BASOPHIL ADENOMA	1 (2%)		2 (5%)
#ADRENAL	(50)	(48)	(47)
PHEOCHROMOCYTOMA	1 (2%)	1 (2%)	
#ADRENAL/CAPSULE	(50)	(48)	(47)
ADENOMA, NOS			2 (4%)
#THYROID	(48)	(44)	(40)
FOLLICULAR-CELL ADENOMA	1 (2%)		
#PANCREATIC ISLETS	(49)	(47)	(44)
ISLET-CELL ADENOMA			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(55)	(50)	(50)
ACINAR-CELL CARCINOMA	1 (2%)		
FIBROADENOMA	1 (2%)		
#UTERUS	(54)	(49)	(46)
NEOPLASM, NOS, MALIGNANT	1 (2%)		
ADENOCARCINOMA, NOS			1 (2%)
LEIOMYOSARCOMA		1 (2%)	
ENDOMETRIAL STROMAL POLYP		6 (12%)	2 (4%)
HEMANGIOMA		3 (6%)	
#OVARY	(50)	(47)	(44)
CYSTADENOMA, NOS			1 (2%)
PAPILLARY CYSTADENOMA, NOS			1 (2%)
GRANULOSA-CELL TUMOR		1 (2%)	
GRANULOSA-CELL CARCINOMA			1 (2%)
HEMANGIOMA			2 (5%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(55)	(50)	(50)
CYSTADENOMA, NOS		3 (6%)	
PAPILLARY CYSTADENOMA, NOS		1 (2%)	2 (4%)

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

TABLE B2 (CONTINUED)

	CONTROL (UNTR) 06-0360	LOW DOSE 06-0415	HIGH DOSE 06-0420
MUSCULOSKELETAL SYSTEM			
*SKULL	(55)	(50)	(50)
OSTEOMA			1 (2%)
BODY CAVITIES			
*PERITONEUM	(55)	(50)	(50)
MESOTHELIOMA, NOS	1 (2%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(55)	(50)	(50)
MESOTHELIOMA, NOS			1 (2%)
HEMANGIOMA			1 (2%)
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	55	50	50
NATURAL DEATH@	7	5	6
MORIBUND SACRIFICE	4	7	5
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED		1	1
TERMINAL SACRIFICE	44	37	38
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B2 (CONCLUDED)

	CONTROL (UNTR) 06-0360	LOW DOSE 06-0415	HIGH DOSE 06-0420
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	34	42	44
TOTAL PRIMARY TUMORS	50	86	109
TOTAL ANIMALS WITH BENIGN TUMORS	15	33	34
TOTAL BENIGN TUMORS	19	49	67
TOTAL ANIMALS WITH MALIGNANT TUMORS	27	26	30
TOTAL MALIGNANT TUMORS	30	36	41
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	1	1
TOTAL SECONDARY TUMORS	2	1	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	1	1
TOTAL UNCERTAIN TUMORS	1	1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

APPENDIX C

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

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

	CONTROL (UNTR) 01-0360	LOW DOSE 01-0405	HIGH DOSE 01-0410
ANIMALS INITIALLY IN STUDY	55	55	55
ANIMALS NECROPSIED	54	55	55
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	54	55	55
INTEGUMENTARY SYSTEM			
*SKIN	(54)	(55)	(55)
EPIDERMAL INCLUSION CYST			3 (5%)
ULCER, NOS		1 (2%)	
ABSCESS, NOS		1 (2%)	
ULCER, HEALED			1 (2%)
*SUBCUT TISSUE	(54)	(55)	(55)
EPIDERMAL INCLUSION CYST		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(54)	(55)	(55)
BRONCHIECTASIS	1 (2%)	1 (2%)	
#LUNG	(54)	(55)	(55)
BRONCHOPNEUMONIA, NOS	2 (4%)	2 (4%)	1 (2%)
PNEUMONIA, CHRONIC MURINE	2 (4%)		3 (5%)
METAPLASIA, NOS		1 (2%)	2 (4%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(52)	(54)	(52)
FIBROSIS, FOCAL	1 (2%)	1 (2%)	
HYPOPLASIA, NOS			1 (2%)
HYPERPLASIA, NOS	7 (13%)	6 (11%)	5 (10%)
#SPLEEN	(54)	(54)	(52)
FIBROSIS, FOCAL	1 (2%)		
NECROSIS, FOCAL			1 (2%)
HEMOSIDEROSIS	1 (2%)		
HEMATOPOIESIS	1 (2%)		
#CERVICAL LYMPH NODE	(53)	(51)	(51)
HYPERPLASIA, NOS		1 (2%)	

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-0360	LOW DOSE 01-0405	HIGH DOSE 01-0410
#LUMBAR LYMPH NODE	(53)	(51)	(51)
HEMORRHAGE		1 (2%)	
#RENAL LYMPH NODE	(53)	(51)	(51)
HEMOSIDEROSIS		1 (2%)	
CIRCULATORY SYSTEM			
#HEART	(54)	(55)	(55)
THROMBUS, MURAL	1 (2%)	1 (2%)	
PERIARTERITIS	1 (2%)		
#MYOCARDIUM	(54)	(55)	(55)
INFLAMMATION, FOCAL	1 (2%)		
DEGENERATION, NOS	16 (30%)	22 (40%)	12 (22%)
*AORTA	(54)	(55)	(55)
THROMBOSIS, NOS		1 (2%)	
MEDIAL CALCIFICATION		1 (2%)	
*CELIAC ARTERY	(54)	(55)	(55)
THROMBOSIS, NOS	1 (2%)		
*MESENTERIC ARTERY	(54)	(55)	(55)
THROMBUS, MURAL		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(54)	(55)	(54)
CONGESTION, CHRONIC PASSIVE		1 (2%)	
HEMORRHAGE		1 (2%)	
CHOLANGIOFIBROSIS	9 (17%)		5 (9%)
NECROSIS, FOCAL	1 (2%)		2 (4%)
NECROSIS, FAT	1 (2%)		
METAMORPHOSIS FATTY		2 (4%)	1 (2%)
BASOPHILIC CYTO CHANGE		1 (2%)	
FOCAL CELLULAR CHANGE			1 (2%)
CLEAR-CELL CHANGE	1 (2%)		
#LIVER/CENTRILOBULAR	(54)	(55)	(54)
NECROSIS, NOS			1 (2%)
*BILE DUCT	(54)	(55)	(55)
INFLAMMATION, NOS	1 (2%)		

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-0360	LOW DOSE 01-0405	HIGH DOSE 01-0410
HYPERPLASIA, NOS			1 (2%)
#PANCREAS	(53)	(53)	(51)
DILATATION/DUCTS	1 (2%)		
PERIARTERITIS		1 (2%)	
ATROPHY, NOS		1 (2%)	
ATROPHY, FOCAL			2 (4%)
#STOMACH	(53)	(54)	(52)
ULCER, NOS	2 (4%)	1 (2%)	2 (4%)
EROSION	1 (2%)		
CALCIFICATION, NOS		2 (4%)	
HYPERPLASIA, BASAL CELL	14 (26%)	12 (22%)	14 (27%)
#COLON	(52)	(50)	(47)
HYPERTROPHY, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(53)	(54)	(54)
HYDRONEPHROSIS		1 (2%)	
PYELONEPHRITIS, NOS		1 (2%)	
GLOMERULONEPHRITIS, CHRONIC		1 (2%)	
PYELONEPHRITIS, CHRONIC		2 (4%)	
NEPHROSIS, NOS	26 (49%)	8 (15%)	24 (44%)
NEPHROSIS, CHOLEMIC	2 (4%)	1 (2%)	1 (2%)
#KIDNEY/TUBULE	(53)	(54)	(54)
NECROSIS, NOS	1 (2%)		
DYSPLASIA, NOS			6 (11%)
#URINARY BLADDER	(51)	(51)	(49)
INFLAMMATION, ACUTE HEMORRHAGIC		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(48)	(50)	(50)
HEMORRHAGE	1 (2%)		
HYPERPLASIA, FOCAL	1 (2%)		
HYPERPLASIA, BASOPHILIC	2 (4%)		
#ADRENAL	(54)	(55)	(55)
CYST, NOS	1 (2%)		
HEMORRHAGE		1 (2%)	

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

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-0360	LOW DOSE 01-0405	HIGH DOSE 01-0410
HEMORRHAGIC CYST			1 (2%)
#ADRENAL CORTEX	(54)	(55)	(55)
HYPERPLASIA, NOS	1 (2%)		
#ADRENAL MEDULLA	(54)	(55)	(55)
HYPERPLASIA, NOS			3 (5%)
#THYROID	(53)	(51)	(52)
HYPERPLASIA, C-CELL			1 (2%)
#PARATHYROID	(26)	(23)	(19)
HYPERPLASIA, NOS		6 (26%)	
#PANCREATIC ISLETS	(53)	(53)	(51)
HYPERPLASIA, NOS	1 (2%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(54)	(55)	(55)
GALACTOCELE		1 (2%)	
INFLAMMATION, GRANULOMATOUS		1 (2%)	
LACTATION		1 (2%)	
*PREPUTIAL GLAND	(54)	(55)	(55)
ABSCESS, NOS	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)		
#PROSTATE	(52)	(55)	(53)
INFLAMMATION ACUTE AND CHRONIC	1 (2%)		
#TESTIS	(54)	(55)	(55)
ATROPHY, NOS		1 (2%)	
HYPERPLASIA, INTERSTITIAL CELL		2 (4%)	2 (4%)
NERVOUS SYSTEM			
#CEREBRAL VENTRICLE	(54)	(55)	(55)
HEMORRHAGE	1 (2%)		
#BRAIN	(54)	(55)	(55)
HYDROCEPHALUS, NOS		1 (2%)	
HEMORRHAGE	1 (2%)	1 (2%)	
#CEREBELLUM	(54)	(55)	(55)
HEMORRHAGE		1 (2%)	

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

TABLE C1 (CONCLUDED)

	CONTROL (UNTR) 01-0360	LOW DOSE 01-0405	HIGH DOSE 01-0410
SPECIAL SENSE ORGANS			
*EYE	(54)	(55)	(55)
HEMORRHAGE	1 (2%)	1 (2%)	
CATARACT		1 (2%)	
*EYE/LACRIMAL GLAND	(54)	(55)	(55)
INFLAMMATION, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(54)	(55)	(55)
PETECHIA		1 (2%)	
NECROSIS, FAT	9 (17%)	4 (7%)	5 (9%)
ALL OTHER SYSTEMS			
THORAX			
PERIARTERITIS			1
OMENTUM			
INFLAMMATION, GRANULOMATOUS		1	
SPECIAL MORPHOLOGY SUMMARY			
AUTOLYSIS/NO NECROPSY	1		

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

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

	CONTROL (UNTR) 02-0360	LOW DOSE 02-0405	HIGH DOSE 02-0410
ANIMALS INITIALLY IN STUDY	55	55	55
ANIMALS NECROPSIED	54	55	55
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	54	55	55
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(53)	(54)	(55)
BRONCHIECTASIS		1 (2%)	
#LUNG	(53)	(54)	(55)
PNEUMONIA, CHRONIC MURINE	3 (6%)	1 (2%)	1 (2%)
METAPLASIA, NOS	1 (2%)	2 (4%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(53)	(54)	(52)
HISTIOCYTOSIS	1 (2%)		
HYPERPLASIA, HEMATOPOIETIC		3 (6%)	1 (2%)
HYPOPLASIA, HEMATOPOIETIC		1 (2%)	
#SPLEEN	(52)	(54)	(55)
INFARCT, NOS			1 (2%)
HEMATOPOIESIS	1 (2%)	1 (2%)	
#LUMBAR LYMPH NODE	(51)	(54)	(54)
INFLAMMATION, CHRONIC	1 (2%)		
HYPERPLASIA, NOS		1 (2%)	
#RENAL LYMPH NODE	(51)	(54)	(54)
INFLAMMATION, CHRONIC	1 (2%)		
CIRCULATORY SYSTEM			
#HEART	(53)	(54)	(55)
PERIARTERITIS			1 (2%)

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 02-0360	LOW DOSE 02-0405	HIGH DOSE 02-0410
#MYOCARDIUM	(53)	(54)	(55)
INFLAMMATION, CHRONIC		1 (2%)	
DEGENERATION, NOS	6 (11%)	7 (13%)	3 (5%)
DIGESTIVE SYSTEM			
#LIVER	(53)	(54)	(55)
CHOLANGIOFIBROSIS	2 (4%)		
METAMORPHOSIS FATTY	6 (11%)	4 (7%)	2 (4%)
BASOPHILIC CYTO CHANGE	10 (19%)	14 (26%)	12 (22%)
CLEAR-CELL CHANGE		1 (2%)	
#PANCREAS	(52)	(53)	(54)
INFLAMMATION, FOCAL			7 (13%)
INFLAMMATION, CHRONIC		1 (2%)	
ATROPHY, FOCAL	1 (2%)		
#STOMACH	(51)	(54)	(52)
ULCER, NOS	1 (2%)	1 (2%)	1 (2%)
HYPERPLASIA, BASAL CELL	11 (22%)	9 (17%)	22 (42%)
URINARY SYSTEM			
#KIDNEY	(52)	(54)	(54)
PYELONEPHRITIS, CHRONIC			1 (2%)
NEPHROSIS, NOS	2 (4%)	2 (4%)	
NEPHROSIS, CHOLEMIC	1 (2%)	1 (2%)	
GLOMERULOSCLEROSIS, NOS	1 (2%)		
CALCIFICATION, FOCAL	5 (10%)		
#KIDNEY/TUBULE	(52)	(54)	(54)
FOCAL CELLULAR CHANGE		3 (6%)	
DYSPLASIA, NOS			35 (65%)
ENDOCRINE SYSTEM			
#PITUITARY	(48)	(54)	(52)
HEMORRHAGIC CYST			1 (2%)
HYPERPLASIA, NOS	1 (2%)	1 (2%)	
#ADRENAL	(53)	(53)	(54)
NECROSIS, NOS		1 (2%)	

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

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 02-0360	LOW DOSE 02-0405	HIGH DOSE 02-0410
#ADRENAL CORTEX	(53)	(53)	(54)
HYPERPLASIA, NOS	1 (2%)		1 (2%)
#ADRENAL MEDULLA	(53)	(53)	(54)
NECROSIS, NOS	1 (2%)		
HYPERPLASIA, NOS		1 (2%)	
#PARATHYROID	(15)	(26)	(26)
HYPERPLASIA, NOS	1 (7%)		
#PANCREATIC ISLETS	(52)	(53)	(54)
HYPERPLASIA, NOS	1 (2%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(54)	(55)	(55)
GALACTOCELE	6 (11%)	8 (15%)	2 (4%)
ABSCESS, NOS		1 (2%)	
LACTATION			1 (2%)
#UTERUS	(52)	(54)	(55)
HYDROMETRA	2 (4%)	2 (4%)	
EPIDERMAL INCLUSION CYST		1 (2%)	
THROMBOSIS, NOS	1 (2%)	1 (2%)	
PYOMETRA		1 (2%)	
ABSCESS, NOS			1 (2%)
#CERVIX UTERI	(52)	(54)	(55)
POLYP, INFLAMMATORY	1 (2%)		
#UTERUS/ENDOMETRIUM	(52)	(54)	(55)
CYST, NOS			1 (2%)
INFLAMMATION ACUTE AND CHRONIC		1 (2%)	
HYPERPLASIA, CYSTIC			1 (2%)
#OVARY/OVIDUCT	(52)	(54)	(55)
ABSCESS, NOS	1 (2%)	3 (6%)	2 (4%)
#PARAMETRIUM	(52)	(54)	(55)
CYST, NOS			1 (2%)
#OVARY	(53)	(53)	(55)
CYST, NOS			1 (2%)
ABSCESS, NOS			1 (2%)

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

TABLE C2 (CONCLUDED)

	CONTROL (UNTR) 02-0360	LOW DOSE 02-0405	HIGH DOSE 02-0410
INFLAMMATION, CHRONIC	1 (2%)		
NERVOUS SYSTEM			
#BRAIN/MENINGES	(52)	(54)	(54)
INFLAMMATION, ACUTE			1 (2%)
#BRAIN	(52)	(54)	(54)
HYDROCEPHALUS, NOS		3 (6%)	1 (2%)
HEMORRHAGE			1 (2%)
SPECIAL SENSE ORGANS			
*EYE	(54)	(55)	(55)
PHTHISIS BULBI		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*SKULL	(54)	(55)	(55)
OSTEOSCLEROSIS		1 (2%)	
BODY CAVITIES			
*ABDOMINAL CAVITY	(54)	(55)	(55)
NECROSIS, FAT	6 (11%)	2 (4%)	4 (7%)
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
INFLAMMATION, GRANULOMATOUS			1
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		2	
AUTO/NECROPSY/HISTO PERF		1	
AUTOLYSIS/NO NECROPSY	1		

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

APPENDIX D

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

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

	CONTROL (UNTR) 05-0360	LOW DOSE 05-0415	HIGH DOSE 05-0420
ANIMALS INITIALLY IN STUDY	55	50	50
ANIMALS NECROPSIED	55	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	55	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(55)	(50)	(50)
EPIDERMAL INCLUSION CYST	1 (2%)		1 (2%)
PERIVASCULITIS		1 (2%)	
CALCIFICATION, NOS		1 (2%)	
POLYP, INFLAMMATORY	1 (2%)		
*SUBCUT TISSUE	(55)	(50)	(50)
HEMATOMA, NOS			1 (2%)
GRANULOMA, NOS			1 (2%)
RESPIRATORY SYSTEM			
*LARYNX	(55)	(50)	(50)
HYPERPLASIA, PSEUDOEPITHELIOMATO			1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(51)	(44)	(48)
HYPERPLASIA, HEMATOPOIETIC			1 (2%)
#SPLEEN	(51)	(47)	(49)
CONGESTION, NOS		1 (2%)	
HEMATOPOIESIS	2 (4%)	1 (2%)	3 (6%)
#MESENTERIC L. NODE	(48)	(43)	(44)
CONGESTION, NOS	6 (13%)		
HYPERPLASIA, NOS	1 (2%)		
HISTIOCYTOSIS	1 (2%)		
HEMATOPOIESIS		1 (2%)	
CIRCULATORY SYSTEM			
NONE			

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

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 05-0360	LOW DOSE 05-0415	HIGH DOSE 05-0420
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(53)	(50)	(49)
CALCULUS, NOS			1 (2%)
#LIVER	(54)	(49)	(49)
BASOPHILIC CYTO CHANGE		1 (2%)	
HYPERPLASIA, NOS	1 (2%)		
*GALLBLADDER	(55)	(50)	(50)
DILATATION, NOS			1 (2%)
*BILE DUCT	(55)	(50)	(50)
DILATATION, NOS		1 (2%)	
#PANCREAS	(49)	(46)	(49)
CYST, NOS		1 (2%)	
ATROPHY, NOS	1 (2%)		
#STOMACH	(51)	(47)	(48)
EPIDERMAL INCLUSION CYST		1 (2%)	
INFLAMMATION, ACUTE	1 (2%)		
ATYPIA, NOS	1 (2%)		
HYPERPLASIA, BASAL CELL			1 (2%)
URINARY SYSTEM			
#KIDNEY	(54)	(50)	(49)
HYDRONEPHROSIS	1 (2%)		
CYST, NOS			1 (2%)
PYELONEPHRITIS, ACUTE	1 (2%)		
INFLAMMATION, CHRONIC		1 (2%)	
PYELONEPHRITIS, CHRONIC	1 (2%)		
DYSPLASIA, NOS		37 (74%)	30 (61%)
#URINARY BLADDER	(48)	(38)	(47)
CALCULUS, NOS	1 (2%)	1 (3%)	2 (4%)
HYPERPLASIA, EPITHELIAL	1 (2%)	3 (8%)	
DYSPLASIA, NOS		1 (3%)	
ENDOCRINE SYSTEM			
#PANCREATIC ISLETS	(49)	(46)	(49)
HYPERPLASIA, NOS	12 (24%)	3 (7%)	1 (2%)

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

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 05-0360	LOW DOSE 05-0415	HIGH DOSE 05-0420
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(55)	(50)	(50)
CALCULUS, NOS	1 (2%)		
DILATATION, NOS		1 (2%)	
EPIDERMAL INCLUSION CYST			1 (2%)
ABSCESS, NOS			1 (2%)
#PROSTATE	(52)	(42)	(39)
INFLAMMATION, ACUTE	1 (2%)		
#TESTIS	(54)	(49)	(50)
ATROPHY, FOCAL			2 (4%)
HYPOSPERMATOGENESIS			1 (2%)
*SCROTUM	(55)	(50)	(50)
HEMATOMA, NOS			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(52)	(46)	(50)
PERIVASCULITIS		1 (2%)	
SPECIAL SENSE ORGANS			
*EYE	(55)	(50)	(50)
INFLAMMATION, ACUTE	1 (2%)		
CATARACT	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(55)	(50)	(50)
NECROSIS, FAT	5 (9%)		
*PERITONEUM	(55)	(50)	(50)
NECROSIS, FAT		1 (2%)	

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

TABLE D1 (CONCLUDED)

	CONTROL (UNTR) 05-0360	LOW DOSE 05-0415	HIGH DOSE 05-0420
ALL OTHER SYSTEMS			
OMENTUM			
HEMATOMA, NOS	1		
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	8	5	
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 TBP

	CONTROL (UNTR) 06-0360	LOW DOSE 06-0415	HIGH DOSE 06-0420
ANIMALS INITIALLY IN STUDY	55	50	50
ANIMALS NECROPSIED	55	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	55	50	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(55)	(50)	(50)
ATELECTASIS	1 (2%)		
HEMORRHAGE			2 (4%)
BRONCHOPNEUMONIA, NOS			1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(52)	(49)	(46)
MYELOFIBROSIS	31 (60%)	31 (63%)	30 (65%)
HYPERPLASIA, HEMATOPOIETIC	1 (2%)		
#SPLEEN	(53)	(47)	(46)
HEMATOPOIESIS	1 (2%)		4 (9%)
#MESENTERIC L. NODE	(47)	(43)	(45)
CONGESTION, NOS	1 (2%)		
HYPERPLASIA, NOS	2 (4%)		1 (2%)
CIRCULATORY SYSTEM			
#HEART	(55)	(50)	(50)
PERIARTERITIS	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(54)	(50)	(49)
NECROSIS, FOCAL		1 (2%)	

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

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 06-0360	LOW DOSE 06-0415	HIGH DOSE 06-0420
METAMORPHOSIS FATTY		1 (2%)	3 (6%)
#PANCREAS	(49)	(47)	(44)
DILATATION/DUCTS	1 (2%)	1 (2%)	
CYST, NOS			1 (2%)
INFLAMMATION, CHRONIC	2 (4%)		
ATROPHY, NOS	1 (2%)	4 (9%)	2 (5%)
#ESOPHAGUS	(51)	(47)	(45)
HYPERPLASIA, BASAL CELL			2 (4%)
#STOMACH	(53)	(48)	(44)
ULCER, NOS	1 (2%)		
EROSION	1 (2%)		
HYPERPLASIA, EPITHELIAL	2 (4%)		
HYPERPLASIA, BASAL CELL			3 (7%)
#JEJUNUM	(52)	(48)	(46)
DIVERTICULUM		1 (2%)	
AMYLOIDOSIS		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(55)	(50)	(46)
EYELONEPHRITIS, CHRONIC	1 (2%)		
NEPHROPATHY			1 (2%)
INFARCT, FOCAL			1 (2%)
DYSPLASIA, NOS		1 (2%)	12 (26%)
#URINARY BLADDER	(50)	(43)	(43)
INFLAMMATION, CHRONIC	1 (2%)		9 (21%)
DYSPLASIA, NOS		1 (2%)	
ENDOCRINE SYSTEM			
#PANCREATIC ISLETS	(49)	(47)	(44)
HYPERPLASIA, NOS	3 (6%)	1 (2%)	
REPRODUCTIVE SYSTEM			
#UTERUS	(54)	(49)	(46)
HYDROMETRA	3 (6%)		
PYOMETRA			1 (2%)

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

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 06-0360	LOW DOSE 06-0415	HIGH DOSE 06-0420
#UTERUS/ENDOMETRIUM	(54)	(49)	(46)
HYPERPLASIA, CYSTIC	15 (28%)	16 (33%)	23 (50%)
#OVARY	(50)	(47)	(44)
CYST, NOS	7 (14%)	1 (2%)	1 (2%)
THROMBOSIS, NOS			2 (5%)
HEMORRHAGIC CYST	1 (2%)		
ABSCESS, NOS	1 (2%)		
AMYLOIDOSIS		1 (2%)	
NERVOUS SYSTEM			
#BRAIN/MENINGES	(55)	(48)	(48)
INFLAMMATION, NOS	1 (2%)		
#BRAIN	(55)	(48)	(48)
HYDROCEPHALUS, NOS	2 (4%)		
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(55)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(55)	(50)	(50)
NECROSIS, FAT	7 (13%)	3 (6%)	2 (4%)
*PERITONEUM	(55)	(50)	(50)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, ACUTE		1 (2%)	
*MESENTERY	(55)	(50)	(50)
CYST, NOS	1 (2%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(55)	(50)	(50)
PERIARTERITIS	1 (2%)		1 (2%)

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

TABLE D2 (CONCLUDED)

	CONTROL (UNTR) 06-0360	LOW DOSE 06-0415	HIGH DOSE 06-0420
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	4	1
AUTO/NECROPSY/HISTO PERF			1

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

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Review of the Bioassay of Tris(2,3-dibromopropyl)phosphate* (TRIS) for Carcinogenicity by the Data Evaluation/Risk Assessment Subgroup of the Clearinghouse on Environmental Carcinogens

March 6, 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 laboratory animal sciences, 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 Tris(2,3-dibromopropyl)phosphate (TRIS) for carcinogenicity.

The primary reviewer noted that TRIS has been shown to be mutagenic. He agreed with the conclusion in the report that TRIS was carcinogenic in both rats and mice. After a brief description of the experimental design, he noted that the tumors were detected after a relatively long latent period. Based on the multiple target organ effect, the primary reviewer suggested TRIS may be a direct acting carcinogen.

The secondary reviewer agreed with the earlier critique of the study. He pointed out, however, the lower incidence of leukemia among the treated male rats as compared to their associated controls. He said that such a negative trend also should be noted as an effect.

It was moved that the report on TRIS be accepted as written. The motion was seconded and approved unanimously.

Members present were

Gerald N. Wogan (Chairman), Massachusetts Institute of Technology
Arnold Brown, Mayo Clinic
Lawrence Garfinkel, American Cancer Society
E. Cuyler Hammond, American Cancer Society
Joseph Highland, Environmental Defense Fund
Henry Pitot, University of Wisconsin Medical Center
George Roush, Jr., Monsanto Company
Sheldon Samuels, Industrial Union Department, AFL-CIO
Michael Shimkin, University of California at San Diego
John Weisburger, American Health Foundation
Sidney Wolfe, Health Research Group

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

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