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No. 274

TOXICOLOGY AND CARCINOGENESIS STUDIES OF TRIS(2-ETHYLHEXYL)PHOSPHATE (CAS NO. 78-42-2) IN F344/N RATS AND B6C3F$_1$ MICE (GAVAGE STUDIES)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

NATIONAL TOXICOLOGY PROGRAM

The National Toxicology Program (NTP), established in 1978, develops and evaluates scientific information about potentially toxic and hazardous chemicals. This knowledge can be used for protecting the health of the American people and for the primary prevention of disease. By bringing together the relevant programs, staff, and resources from the U.S. Public Health Service, DHHS, the National Toxicology Program has centralized and strengthened activities relating to toxicology research, testing and test development/validation efforts, and the dissemination of toxicological information to the public and scientific communities and to the research and regulatory agencies.

The NTP is made up of four charter DHHS agencies: the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research, Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS.

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF TRIS(2-ETHYLHEXYL)PHOSPHATE (CAS NO. 78-42-2) IN F344/N RATS AND B6C3F$_1$ MICE (GAVAGE STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

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NOTE TO THE READER

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for testing in the NTP Carcinogenesis Program are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential. Negative results, in which the test animals do not have a greater incidence of cancer than control animals, do not necessarily mean that a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical has the potential for hazard to humans. The determination of the risk to humans from chemicals found to be carcinogenic in animals requires a wider analysis which extends beyond the purview of this study.

Five categories of interpretative conclusions were adopted in June 1983 for use in the Technical Reports series to specifically emphasize consistency and the concept of actual evidence of carcinogenicity. For each definitive study result (male rats, female rats, male mice, female mice), one of the following quintet will be selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either potency or mechanism.

- **Clear Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of malignant neoplasms, studies that exhibit a substantially increased incidence of benign neoplasms, or studies that exhibit an increased incidence of a combination of malignant and benign neoplasms where each increases with dose.
- **Some Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of benign neoplasms, studies that exhibit marginal increases in neoplasms of several organs/tissues, or studies that exhibit a slight increase in uncommon malignant or benign neoplasms.
- **Equivocal Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related marginal increase of neoplasms.
- **No Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.
- **Inadequate Study of Carcinogenicity** demonstrates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as valid for showing either the presence or absence of a carcinogenic effect.

Additionally, the following concepts (as patterned from the International Agency for Research on Cancer Monographs) have been adopted by the NTP to give further clarification of these issues:

> The term *chemical carcinogenesis* generally means the induction by chemicals of neoplasms not usually observed, the earlier induction by chemicals of neoplasms that are commonly observed, or the induction by chemicals of more neoplasms than are generally found. Different mechanisms may be involved in these situations. Etymologically, the term *carcinogenesis* means induction of cancer, that is, of malignant neoplasms; however, the commonly accepted meaning is the induction of various types of neoplasms or of a combination of malignant and benign neoplasms. In the Technical Reports, the words *tumor* and *neoplasm* are used interchangeably.

This study was initiated by the National Cancer Institute's Carcinogenesis Testing Program, now part of the National Institute of Environmental Health Sciences, National Toxicology Program. The study described in this Technical Report has been conducted under NTP health and safety requirements and/or guidelines for toxicity studies. Individual toxicology testing contractors are required to demonstrate corporate health and safety programs in compliance with NTP chemical health and safety requirements and to meet or exceed all applicable Federal, state, and local health and safety regulations.

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to identify any mistakes so that corrective action may be taken. Further, anyone who is aware of related ongoing or published studies not mentioned in this report is encouraged to make this information known to the NTP. Comments and questions about the National Toxicology Program Technical Reports on Toxicology and Carcinogenesis Studies should be directed to Dr. J.E. Huff, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709 (919-541-3780).

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge (and while supplies last) from the NTP Public Information Office, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709.

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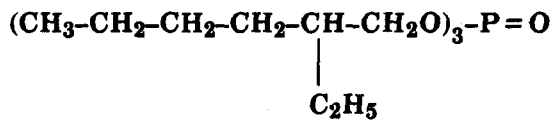

TRIS(2-ETHYLHEXYL)PHOSPHATE

CAS NO. 78-42-2

Specific gravity 0.93
Boiling point 295° C
Vapor pressure 1.9 mm Hg at 200° C

Molecular formula $C_{24}H_{51}O_4P$
Molecular weight 434.64

Synonyms and Trade Names: TOF, trioctyl phosphate, phosphoric acid tri (2-ethylhexyl) ester, Flexol® TOF, Kronitex®

ABSTRACT

Two-year toxicology and carcinogenesis studies of tris(2-ethylhexyl)phosphate were conducted by administering the test chemical in corn oil by gavage, 5 days per week for 103 weeks, to groups of 50 male and 50 female F344/N rats and B6C3F$_1$ mice. Male rats received doses of 2,000 or 4,000 mg/kg body weight, female rats received 1,000 or 2,000 mg/kg, and male and female mice received 500 or 1,000 mg/kg. Fifty vehicle control animals of each sex and species received 10 ml/kg body weight (rats) or 3.3 ml/kg (mice) corn oil by gavage on the same schedule.

Inflammation of the gastric mucosa in mice and mild weight depression in rats and mice were the only dose-related effects observed in the preliminary studies. In the 2-year studies, survival rates and mean body weight gains of dosed female rats and dosed mice were comparable to those of their respective vehicle controls. Survival rates of dosed male rats were comparable to that of the vehicle controls, but body weight gains were depressed. One nonneoplastic lesion, follicular cell hyperplasia of the thyroid, was observed at increased incidences in dosed male and female mice.

Two compound-related increased incidences of neoplasms could not be discounted. In male rats, the incidence of pheochromocytoma of adrenal glands increased with dose (2/50, 4%; 9/50, 18%; 12/50, 24%). There were also two additional malignant pheochromocytomas in the high dose group. However, the incidence of adrenal pheochromocytoma in vehicle controls of this study (2/50, 4%) was low compared with the 25% incidence observed in two previous studies in this laboratory or the overall historical incidence of 18% observed throughout the Program, and thus the evidence of carcinogenicity was considered to be equivocal. In female mice, the incidence of hepatocellular carcinoma (0/48; 4/50; 7/50) in high dose animals (1,000 mg/kg) was significantly increased relative to that of the vehicle controls.

Decreased incidences were observed for acinar cell adenomas of the pancreas in dosed male rats (14/50, 28%; 5/48, 10%; 2/49, 4%) and for fibroadenomas of the mammary glands in low dose female rats (11/50, 22%; 2/50, 4%; 7/50, 14%). Hemangiosarcomas of the circulatory system in male mice (7/50, 14%; 0/50; 1/49, 2%) and lymphomas of the hematopoietic system in female mice (14/49, 29%; 10/50, 20%; 6/50, 12%) were decreased compared with vehicle controls. A decrease in the incidence of lymphomas and an increased incidence of carcinomas of the liver in female mice (both seen in this study) were observed in studies of di(2-ethylhexyl)adipate. Increased incidences of liver carcinomas

and decreased incidences of mammary fibroadenomas were observed also in female rats in the di(2-ethylhexyl)phthalate studies. A possible common link among these three chemicals may be metabolic conversion to 2-ethylhexanol.

Tris(2-ethylhexyl)phosphate was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 in the presence or absence of 9000 × g (S9) fractions from Aroclor 1254-induced Sprague-Dawley rat or Syrian hamster liver.

An audit of the experimental data from these carcinogenesis studies was conducted by the National Toxicology Program. No data discrepancies were found that significantly influenced the final interpretation of these experiments.

Under the conditions of these studies, a comparison of concurrent and historical controls indicated that there was *equivocal evidence of carcinogenicity** in male F344/N rats receiving 2,000 and 4,000 mg/kg tris(2-ethylhexyl)phosphate, as evidenced by increased incidences of pheochromocytomas of the adrenal glands. There was *no evidence of carcinogenicity* in female F344/N rats or in male $B6C3F_1$ mice receiving tris(2-ethylhexyl)phosphate. There was *some evidence of carcinogenicity* in female $B6C3F_1$ mice that received 1,000 mg/kg tris(2-ethylhexyl)phosphate, as shown by an increased incidence of hepatocellular carcinoma. Tris(2-ethylhexyl)phosphate was associated with increased incidences of follicular cell hyperplasias of the thyroid gland in male and female $B6C3F_1$ mice.

*Categories of evidence of carcinogenicity are defined in the Note to Reader on page 2.

CONTRIBUTORS

This NTP Technical Report on tris(2-ethylhexyl)phosphate is based on the 13-week studies that began in September 1978 and ended in January 1979 and on the 2-year studies that began in January 1980 and ended in January 1982 at Litton Bionetics, Inc.

National Toxicology Program
P.O. Box 12233
Research Triangle Park,
North Carolina 27709
(Evaluated Experiment, Interpreted Results, and Reported Findings)

H.B. Matthews, Ph.D., Chemical Manager

Gary A. Boorman, D.V.M., Ph.D.
Rajendra S. Chhabra, Ph.D.
Joseph K. Haseman, Ph.D.
C.W. Jameson, Ph.D.
E.E. McConnell, D.V.M.
John A. Moore, D.V.M.
G. Rao, D.V.M., Ph.D.
B.A. Schwetz, D.V.M., Ph.D.
Raymond W. Tennant, Ph.D.

NTP Pathology Working Group
(Evaluated Pathology Report and Selected Slides on 10/12/82)

Scot Eustis, D.V.M., Ph.D, NTP, Chairperson

Gary A. Boorman, D.V.M., Ph.D.
NTP
F.M. Garner, D.V.M.
Pathology Associates
A.W. Macklin, D.V.M., Ph.D.
Burroughs Wellcome
Henk Solleveld, D.V.M., Ph.D.
NTP

Principal Contributors at Litton Bionetics, Inc.
Kensington, Maryland
(Conducted Prechronic and Chronic Studies and Evaluated Tissues)

Carter D. Johnston, Ph.D.
Principal Investigator
Jerry M. Fitzgerald, Ph.D.
Chemist
Richard Montali, D.V.M.
Pathologist (Rats)
Allan G. Manus, D.V.M.
Principal Investigator
John Langloss, D.V.M.
Pathologist (Mice)

Principal Contributors at Experimental Pathology Laboratory
Herndon, VA
(Provided Pathology Quality Assurance)

Jerry Hardisty, D.V.M.

Principal Contributors at Carltech Associates, Inc.
Rockville, Maryland
(Contractor for Technical Report Preparation)

William D. Theriault, Ph.D.
Project Manager
Abigail C. Jacobs, Ph.D.
Senior Scientist
John Warner, M.S.
Chemist/Statistician

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated this Technical Report are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (1) To ascertain that all relevant literature data have been adequately cited and interpreted; (2) to determine if the design and conditions of the NTP studies were appropriate; (3) to ensure that the Technical Report presented the experimental results and conclusions fully and clearly, (4) to judge the significance of the experimental results by scientific criteria; and (5) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

National Toxicology Program Board of Scientific Counselors
Technical Reports Review Subcommittee

Dr. Jerry B. Hook (Chairperson)
Vice President, Preclinical Research and Development
Smith Kline & French Laboratories
Philadelphia, Pennsylvania

James Swenberg, Ph.D., D.V.M. (Principal Reviewer)
Chief of Pathology
Chemical Industry Institute of Toxicology
Research Triangle Park, North Carolina

Curtis Harper, Ph.D.
Associate Professor of Pharmacology
School of Medicine
University of North Carolina
Chapel Hill, North Carolina

AD HOC SUBCOMMITTEE PANEL OF EXPERTS

Louis S. Beliczky, M.S., M.P.H.
Director, Department of Industrial Hygiene
United Rubber Workers International Union
Akron, Ohio

Devra L. Davis, Ph.D.
Science Policy Director
Environmental Law Institute
Washington, D.C.

Robert M. Elashoff, Ph.D
University of California at Los Angeles
Jonsson Comprehensive Cancer Center
Los Angeles, California

Seymour L. Friess, Ph.D.
Arlington, Virginia

J. Michael Holland, Ph.D., D.V.M.
(Principal Reviewer)
Chevron Environmental Health Center
Richmond, California

Robert A. Scala, Ph.D. (Principal Reviewer)
Exxon Corporation
East Millstone, New Jersey

Tom Slaga, Ph.D.
University of Texas System Cancer Center
Science Park, Research Division
Smithville, Texas

John R. Van Ryzin, Ph.D. (Principal Reviewer)
Division of Biostatistics
School of Public Health
Columbia University
New York, New York

Stan D. Vesselinovitch, Ph.D.
Professor, Departments of Radiology
and Pathology
University of Chicago
Chicago, Illinois

Mary Vore, Ph.D.
Assistant Professor
Pharmacology Department
University of Kentucky
College of Medicine
Lexington, Kentucky

SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF TRIS(2-ETHYLHEXYL)PHOSPHATE

On October 28, 1983, the Technical Report on tris(2-ethylhexyl)phosphate received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Peer Review Panel. The review meeting began at 9:00 a.m. in the Conference Center, Building 101, South Campus, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. Swenberg, a principal reviewer for the Technical Report on the toxicology and carcinogenesis studies of tris(2-ethylhexyl)phosphate, agreed with the conclusions. He said that the lack of gastric irritation in the 2-year mouse studies was somewhat unusual, since this condition was found in prechronic studies. Dr. Swenberg requested that a statement be added to the effect that this chemical was not the same as the "Tris" used in children's sleepware, which was found to be carcinogenic in rodents.

As a second principal reviewer, Dr. Scala agreed in principle with the conclusions, although he questioned the bases for interpreting the occurrence of pheochromocytomas in male rats as *equivocal evidence of carcinogenicity* and the occurrence of hepatocellular carcinomas in female mice as *some evidence of carcinogenicity*. He said the "equivocal" designation apparently was based on a comparison with historical control animals and not concurrent control animals. Dr. H.B. Matthews, NTP Chemical Manager, replied that the category of *some evidence of carcinogenicity* was used for female mice because the strength of the evidence at the high dose was not overwhelming, the incidence of carcinomas was not significant at the low dose, and no significant increases were seen in male mice. He said that the *equivocal evidence of carcinogenicity* designation for male rats was based in part on comparison with historical controls, especially from the other two studies at the same laboratory. There followed considerable discussion about how and when historical controls should be used when comparisons are made. Dr. Van Ryzin expressed concern about the consistent or systematic use of historical controls. Dr. Scala stated that the rationale for the "equivocal" and "some evidence" designations should be included in the abstract. He commented that the subject of negative trends could be more fully discussed, especially with regard to the inverse relationship between malignant lymphomas and liver tumors in mice.

As a third principal reviewer, Dr. Holland also agreed with the conclusions. He inquired as to the reason for giving female rats doses half those given male rats. Dr. Matthews said he assumed that decreased weight gain in the 13-week studies was the determining factor. Dr. Holland commented that there needed to be a more informative way to look at and summarize weight gain data. Dr. Haseman replied that with the new toxicology data management system, formal statistical analysis of weight gain and other variables can be performed more easily, as data on individual animals will be readily available.

As a fourth principal reviewer, Dr. Van Ryzin said he agreed in principle with the conclusions except that there should be a statement in the abstract about the thyroid follicular cell tumors in male rats. Dr. Matthews said the thyroid tumor incidence was not statistically significant compared with controls. Dr. Van Ryzin also had reservations about the weight given to historical control values in designating the incidence of pheochromocytomas in male rats as *equivocal evidence of carcinogencity*. Dr. Holland observed that the relative lack of nonneoplastic effects in the adrenal glands of male rats tended to diminish the biologic significance of the pheochromocytomas and to support the "equivocal" designation. Dr. Davis requested that a comment be made about the increased incidences of liver cytoplasmic vacuolization in dosed female mice.

Dr. Swenberg moved that the Technical Report on the toxicology and carcinogenesis studies of tris(2-ethylhexyl)phosphate be accepted with inclusion in the abstract of the rationale for assigning the designations of *equivocal evidence* and *some evidence* as well as other additions and corrections. Dr. Scala seconded the motion, and the Technical Report was approved unanimously by the Peer Review Panel.

I. INTRODUCTION

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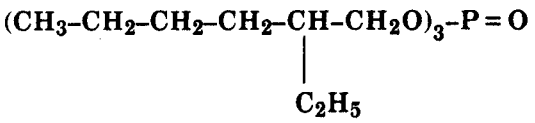

TRIS(2-ETHYLHEXYL)PHOSPHATE

CAS NO. 78-42-2

Specific gravity 0.93
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Vapor pressure 1.9 mm Hg at 200° C

Molecular formula $C_{24}H_{51}O_4P$
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Synonyms and Trade Names: TOF, trioctyl phosphate, phosphoric acid tri (2-ethylhexyl) ester, Flexol® TOF, Kronitex®

Use and Production

Tris(2-ethylhexyl)phosphate is one of a family of trialkyl phosphates that have been widely used as fire retardants and plasticizers. Another trialkyl phosphate, tris(2,3-dibromopropyl)phosphate (Tris-BP), once used as a flame retardant in children's sleepware, has been shown to be carcinogenic (NCI, 1978), but tris(2-ethylhexyl)phosphate has not been previously studied. Tris(2-ethylhexyl)phosphate, a clear, viscous liquid, is used as a component of vinyl stabilizers, grease additives, and flame-proofing compositions (Hawley, 1977); however, it is used primarily as a plasticizer for vinyl plastic and synthetic rubber compounds. In 1974, approximately 3 million pounds of tris(2-ethylhexyl)-phosphate was produced in the United States; imports during that year were negligible (Tox. Data Bank, 1983). Substantial human exposure probably occurs during production of tris(2-ethylhexyl)phosphate and during the manufacture and use of products containing it, but data on the magnitude of exposure are not available.

Metabolism

There are no studies of tris(2-ethylhexyl)phosphate disposition and metabolism per se, but it is reported to be transformed to at least one other compound in rats (MacFarland and Punte, 1966). The nature of this transformation was not reported.

Mutagenicity and Carcinogenicity

Tris(2-ethylhexyl)phosphate was not mutagenic or cytotoxic to *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 at any dose tested (100-10,000 µg/plate) in the presence or absence of induced rat or hamster liver S9 (Appendix G). There are no reports of previous studies of tris(2-ethylhexyl)phosphate carcinogenicity.

Toxicity

Tris(2-ethylhexyl)phosphate has been reported to be nontoxic in all species studied and is considered to be relatively inert physiologically (Treon, 1963). Oral LD_{50} values of more than 36.8 and approximately 46.0 g/kg have been reported for rats and rabbits, respectively (MacFarland and Punte, 1966). Tris(2-ethylhexyl)phosphate was similarly nontoxic when administered to rats and rabbits intravenously, intratracheally, or by inhalation. Placed in the eyes of rabbits at doses of 0.1-0.5 ml, tris(2-ethylhexyl)phosphate produced moderate conjunctivitis that cleared up in 24 hours. Tris(2-ethylhexyl)phosphate applied to clipped skin of rabbits produced moderate erythema that persisted for approximately 1 week. Tris(2-ethylhexyl)-phosphate, unlike some other organophosphates, does not produce neuropathologic effects on chickens or inhibit cholinesterase. Tris(2-ethylhexyl)phosphate did not have a significant

effect on the trained behavior of monkeys but did have a dose-related effect on the trained behavior of dogs (MacFarland and Punte, 1966).

Tris(2-ethylhexyl)phosphate was nominated for long-term toxicity testing by the U.S. Army to assure its suitability for use in Army training exercises. Tris(2-ethylhexyl)phosphate was selected for testing to support the needs of the U.S. Army and because of the large amount of this chemical produced and used in this country when it was nominated.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF TRIS(2-ETHYLHEXYL)PHOSPHATE

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Study Design
Source and Specifications of Test Animals
Animal Maintenance
Clinical Examinations and Pathology
Statistical Methods

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF TRIS(2-ETHYLHEXYL)PHOSPHATE

Tris(2-ethylhexyl)phosphate was obtained from the U.S. Army Chemical Systems Laboratory (Aberdeen Proving Grounds, Aberdeen, MD) in two lots that were assigned lot numbers by the analytical chemistry laboratory. Lot no. TP113077 (97%-98% pure) was used for the 14-day studies, 13-week studies, and the first 13 months of the 2-year studies. Lot no. TP121580 (98%-99% pure) was used for the remainder of the 2-year studies.

The cumulative analytical data (Appendix H) obtained for the first batch of the chemical (Lot No. TP113077) indicated a purity of approximately 97%-98%. The chemical was identified as tris(2-ethylhexyl)phosphate by spectroscopy. The infrared, ultraviolet/visible, and nuclear magnetic resonance spectra were consistent with those expected for the structure of the chemical. The overall purity estimate was based on elemental analyses, a value of $<0.1\%$ water by Karl Fischer titration, and chromatographic data. Results of elemental analyses for hydrogen and phosphorus agreed with the theoretical values, but those for carbon were high (determined/theoretical, 102.9%). Two trace impurities and a slight trace impurity were detected by thin-layer chromatography in one system and a trace impurity in a second system. Six impurities totaling 2.15% of the major peak area in one system and six impurities totaling 2.64% of the major peak in a second system were detected by gas chromatography. An impurity with an area of approximately 2% relative to the major peak area was detected by each gas chromatography system.

The second batch of chemical (Lot No. TP121580) was also identified as tris(2-ethylhexyl)phosphate by spectroscopy. The results were similar to those for the first batch. Cumulative data indicated that this batch was approximately 98%-99% pure. This conclusion was based on elemental analyses, a value for Karl Fischer titration of $<0.1\%$ water, and chromatographic data. Results of elemental analyses for carbon and phosphorus agreed with the theoretical values, but those for hydrogen were slightly high (determined/theoretical, 103.3%). A major spot only was detected in two systems by thin-layer chromatography. Five impurities totaling 0.45% relative to the major peak on one system and five impurities totaling 1.13% of the major peak on a second system were detected by gas chromatography.

Tris(2-ethylhexyl)phosphate was found by Midwest Research Institute to be stable when stored in a sealed container at temperatures up to 60° C for 2 weeks; gas chromatography was used to monitor the stability. The test material was stored in the dark at 4° C. Results of periodic reanalyses of both lots at Litton Bionetics, Inc. indicated there was no decomposition during the study.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

The analytical chemistry laboratory demonstrated that 20% (w/v) corn oil solutions of tris(2-ethylhexyl)phosphate were stable for at least 7 days at room temperature (Appendix I). The dosing solutions were prepared by the testing laboratory on a volume/volume basis and mixed by inversion of the container. The 200 mg/ml concentration was mixed with a Poly-tron® blender due to the large quantity used. The solutions were stored at room temperature for a maximum of 7 days (Table 1).

Analyses for tris(2-ethylhexyl)phosphate in the dose solutions were performed periodically by the testing and analytical chemistry laboratories to confirm that the correct doses were administered to the animals. Analyses were performed by extraction of the corn oil with methanol followed by gas chromatographic determination of the resultant extracts. Results of the periodic analyses of the dose solutions at the testing laboratory and referee analyses at the analytical laboratory indicated that the dose mixtures were properly formulated (Appendix K). A statistical summary of the analyses of the mixtures in the 2-year studies follows.

Target Conc. (mg/ml)					
	100	200	400	150.3	300.6
Experimental Mean (mg/ml)					
	104	206	415	153	310
Coefficient of Variation (percent)					
	8.7	4.7	7.1	6.1	6.9
No. of Samples					
	13	13	13	13	13
Range (mg/ml)					
	95.3-130	195-231	381-491	143-176	287-368

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF TRIS(2-ETHYLHEXYL)PHOSPHATE

	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN			
Testing Laboratory	Litton Bionetics, Inc.	Litton Bionetics, Inc.	Litton Bionetics, Inc.
Size of Test Groups	5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses	0, 375, 750, 1,500, 3,000, or 6,000 mg/kg tris(2-ethylhexyl) phosphate in corn oil by gavage (dose vol--3.33 ml/kg except high dose, 6.45 ml/kg)	Rats--0, 250, 500, 1,000, 2,000, or 4,000 mg/kg tris(2-ethylhexyl) phosphate in corn oil by gavage (dose vol: 10 ml/kg); mice--0, 500, 1,000, 2,000, 4,000, or 8,000 mg/kg in corn oil by gavage (dose vol--10 ml/kg)	Rats--male: 0, 2,000, or 4,000; female: 0, 1,000, or 2,000 mg/kg; tris(2-ethylhexyl)phosphate in corn oil by gavage; (dose vol: 10 ml/kg) mice--0, 500, or 1,000 mg/kg (dose vol--3.33 ml/kg)
Date of First Dose	Rats--6/16/78; mice--6/15/78	Rats--9/28/78; mice--9/29/78	Rats--1/3/80; mice--1/10/80
Date of Last Dose	Rats--6/29/78; mice--6/28/78	Rats--1/2/79; mice--1/1/79	Rats--12/28/81; mice--1/4/82
Duration of Dosing	14 consecutive days	5 d/wk for 97 d (rats) or 95 d (mice)	5 d/wk for 103 wk
Type and Frequency of Observation	Observed 1 × d for signs of moribundity and mortality; weighed on d 1 and d 14	Observed 2 × d for signs of moribundity and mortality; weighed and clinically examined 1 × wk	Observed 2 × d for signs of moribundity and mortality; weighed 1 × wk for 13 wk, 1 × 4 wk thereafter; clinical exam 1 × 4 wk
Necropsy and Histologic Examination	Necropsies on all animals; tissues examined: gross lesions, skin, mandibular lymph node, mammary gland, salivary gland, thigh muscle, sciatic nerve, sternebrae, vertebrae, or femur including marrow, costochondral junction, rib, thymus, larynx, trachea, lungs and bronchi, heart, thyroids, parathyroids, esophagus, stomach, duodenum, jejunum, ileum, colon, cecum, rectum, mesenteric lymph node, liver, pancreas, spleen, kidneys, adrenal glands, urinary bladder, seminal vesicles/prostate/testes or ovaries/uterus, nasal cavity, brain, pituitary, spinal cord, eyes	The following tissues were examined microscopically in vehicle controls, highest dose group, and all animals that died during the study: gross lesions and tissue masses, mandibular lymph node, salivary gland, sternebrae, including marrow, thyroid, parathyroids, small intestine, colon, liver, prostate/testes or ovaries/uterus, lungs and mainstem bronchi, mammary gland, skin, heart, esophagus, stomach, brain, thymus, trachea, pancreas, spleen, kidneys, adrenal glands, urinary bladder, pituitary, spinal cord if neurological signs were present, eyes if grossly abnormal, gallbladder (mice)	Necropsies and histopathologic exams performed on all animals; tissues examined same as the 13-wk studies

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE			
Strain and Species	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice
Animal Source	Harlan Industries, Inc. (Indianapolis, IN)	Same as 14-d studies	Rats--Charles River Labs (Portage, MI); mice--Charles River Labs (Kingston, NY)
Time Held Before Test	14 d	15 d	2 wk
Age When Placed on Study	Rats--5 wk; mice--8 wk	Rats--6 wk; mice--8 wk	Male rats--6-7 wk; female rats and mice--6-8 wk
Age When Killed	Rats--7 wk; mice--10 wk	Rats--8 wk; mice--10 wk	Rats--110-111 wk; mice--110-112 wk
Necropsy Dates	Rats--6/30/78; mice--6/29/78	Rats--1/4-1/5/79; mice--1/2-1/3/79	Rats--1/4-1/7/82; mice--1/11-1/14/82
Method of Animal Distribution	Assigned to groups so that cage weights of each group were approximately equal	Assigned to groups according to two tables of random numbers	Assigned to cages according to a table of randon numbers; cages then assigned to groups according to another table of random numbers
Feed	Purina Lab Chow® Meal (St. Louis, MO); freely available	Purina Lab Chow® Pellets (St. Louis, MO)	NIH 07 Open Formula Diet (Ziegler Bros., Gardners, PA)
Bedding	Absorb-Dri® heat-treated hardwood chips (Lab Products, Garfield, NJ)	Same as 14-d studies	Absorb-Dri® wood chips (Williams Feed and Bedding Co., Gaithersburg, MD) and Sani-Chips® (P.J. Murphey Forest Products, Rochelle, Park, NJ)
Water	Acidified to pH 2.5 with HCl; freely available	Same as 14-d studies	Same as 14-d studies
Cages	Polycarbonate (Lab Products, Inc.,Garfield, NJ, and Hazelton Systems, Aberdeen, MD)	Same as 14-d studies	Same as 14-d studies
Cage Filters		Nonwoven fiber	Nonwoven filter sheets (Snow Filtration, Cincinnati, OH)
Animals per Cage	5	Rats--2 or 3; mice--5	5
Animal Room Environment	Temp--23° ± 1°C humidity--30%-70% fluorescent light 12 h/d 12-15 room air changes/h	Temp--23° ± 1°C humidity--30%-70% fluorescent light 12 h/d 15 room air changes/h	Temp--23.5° ± 2.5°C humidity--30%-70% fluorescent light 12 h/d 12-15 room air changes/h
Other Chemicals on Test in Same Room	Dimethyl morpholino-phosphoramidate	None	None

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
CHEMISTRY			
Lot Numbers Used	TP113077	TP113077	TP113077;TP121580
Date of Initial Use of Subsequent Lot	N/A	N/A	2/17/81
Supplier	U.S. Army Chemical Systems Laboratories, Aberdeen Proving Grounds (Aberdeen, MD)	Same as 14-d studies	Same as 14-d studies
CHEMICAL/VEHICLE			
Preparation	Mixed (v/v) with corn oil in a urine cup; mixture stirred with glass rod	Mixed weekly (v/v) with corn oil in a graduated cylinder; solution thoroughly mixed by inversion	Same as 13-wk studies
Maximum Storage Time	1 wk	1 wk	1 wk
Storage Conditions	Room temperature	Room temperature	Room temperature

FOURTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries and held for 2 weeks before the study began. Groups of five males and five females of each species were administered 0, 375, 750, 1,500, 3,000, or 6,000 mg/kg tris(2-ethylhexyl)phosphate in corn oil by gavage for 14 consecutive days. Animals were housed five per cage and received water (acidified with hydrochloric acid to pH 2.5) and feed ad libitum. Further details of animal maintenance are presented in Table 1. The rats and mice were observed daily for mortality and were weighed on days 1 and 14. Necropsies were performed on all animals.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxicity of tris(2-ethylhexyl)-phosphate and to determine the doses to be used in the 2-year studies. Four-week-old male and female F344/N rats and 6-week-old B6C3F$_1$ mice were obtained from Harlan Industries, observed for 15 days, and then assigned to cages according to a table of random numbers. The cages then were assigned to dosed and control groups according to another table of random numbers. Rats were housed two or three per cage, and mice were housed five per cage in polycarbonate cages. Purina Lab Chow® and water (acidified with hydrochloric acid to pH 2.5 for bacterial control) were available ad libitum.

Groups of 10 rats of each sex were administered 0, 250, 500, 1,000, 2,000 or 4,000 mg/kg tris(2-ethylhexyl)phosphate, 5 days per week for 13 weeks. Groups of 10 mice of each sex were administered 0, 500, 1,000, 2,000, 4,000, or 8,000 mg/kg. Further experimental details are summarized in Table 1. Animals were checked twice daily for signs of moribundity and mortality; moribund animals were killed. Animal weights were recorded weekly. At the end of the 13-week studies, survivors were killed. Necropsies were performed on all animals, except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 1.

II. MATERIALS AND METHODS

TWO-YEAR STUDIES

Study Design

Groups of 50 male rats were administered 0, 2,000, or 4,000 mg/kg tris(2-ethylhexyl)phosphate in corn oil by gavage, 5 days per week for 103 weeks. Groups of 50 female rats were administered 0, 1,000, or 2,000 mg/kg on the same schedule. Groups of 50 mice of each sex were administered 0, 500, or 1,000 mg/kg on the same schedule.

Source and Specifications of Test Animals

The male and female F344/N rats and $B6C3F_1$ (C57BL/6N x C3H/HeN MTV^-) mice used in this study were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. Breeding starts for the foundation colony at the production facility originated at the National Institutes of Health Repository. Animals shipped for testing were progeny of defined microflora-associated parents that were transferred from isolators to barrier maintained rooms. Male rats were shipped to the testing laboratory at 4-5 weeks of age, and the female rats and male and female mice, at 4-6 weeks of age. The animals were quarantined at the testing facility for 2 weeks. Thereafter, a complete pathologic examination was performed on a selected number of animals to assess their health. The male rats were placed on study at 6-7 weeks of age, and the female rats and male and female mice, at 6-8 weeks. The health of the animals was monitored during the course of the study according to the protocols of the NTP Sentinel Animal Program (Appendix N).

A quality control skin grafting program has been in effect since early 1978 to monitor the genetic integrity of the inbred mice used to produce the hybrid $B6C3F_1$ test animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic integrity via isozyme and protein electrophoretograms that demonstrate phenotype expressions of known genetic loci.

The C57BL/6 mice were homogeneous at all loci tested. Eighty-five percent of the C3H mice monitored were variant at one to three loci, indicating some heterogeneity in the C3H line from this supplier. Nevertheless, the genome of this line is more homogeneous than that of randomly bred stocks.

Male mice from the C3H colony and female mice from the C57BL/6 colony were used as parents for the hybrid $B6C3F_1$ mice used in these studies. The influence of the potential genetic nonuniformity in the hybrid mice on these results is not known, but results of the studies are not affected because matched concurrent controls were included in each study.

Animal Maintenance

Rats and mice were housed five per cage in polycarbonate cages. Feed and water (acidified with hydrochloric acid to pH 2.5 for bacterial control) were available ad libitum. Details of animal maintenance are summarized in Table 1.

Clinical Examinations and Pathology

All animals were observed twice daily for signs of moribundity or mortality. Clinical signs were recorded once per week. Body weights by cage recorded once per week for the first 13 weeks of the study and once per month thereafter. Mean body weights were determined for each group. Moribund animals were killed, as were animals that survived to the end of the study. Necropsies were performed on all animals, including those found dead unless they were excessively autolyzed or cannibalized. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study in each group.

Examinations for grossly visible lesions were performed on major tissues or organs. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined microscopically are listed in Table 1.

When the pathology examination was completed, the slides, individual animal data

records, and summary tables were sent to an independent quality assurance laboratory. Individual animal records and tables were compared for accuracy, slides and tissue counts were verified; and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by the quality assurance pathologist. Slides of all target tissues and those about which the original and quality assurance pathologists disagreed were submitted to the Chairperson of the Pathology Working Group (PWG) for evaluation. Representative slides selected by the PWG chairperson were reviewed by the PWG pathologists, who reached a consensus and compared their findings with the original and quality assurance diagnoses. When diagnostic differences were found, the PWG sent the appropriate slides and comments to the original pathologist for review. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1984). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group.

Nonneoplastic lesions are not specifically examined routinely by the quality assurance pathologist or the PWG. Certain nonneoplastic findings are reviewed by the quality assurance pathologist and the PWG if they are considered part of the toxic response to a chemical or if they are deemed of special interest.

Statistical Methods

Data Recording: Data on this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969).

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found dead of other than natural causes or were found to be missing; animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) extensions of Cox's method for testing for a dose-related trend. All reported P values for the survival analysis are two-sided.

Calculation of Incidence: 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 to the number of animals in which that site was examined. In most instances, the denominators included only those animals for which the site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) prior to histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the number of animals on which necropsies were performed.

Analysis of Tumor Incidence: Three statistical methods are used to analyze tumor incidence data. The two that adjust for intercurrent mortality employ the classical method for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise comparisons of high dose and low dose groups with vehicle controls and tests for overall dose-response trends.
For studies in which compound administration has little effect on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death. All reported P values for tumor analyses are one-sided.

Life Table Analyses--The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals in each group examined during the time period. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-

Haenszel method to obtain an overall P value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975).

Incidental Tumor Analyses--The second method of analysis assumed that all tumors of a given type observed in animals that died before the end of the study were "incidental"; i.e., they were merely observed at necropsy in animals dying of an unrelated cause. According to this approach, the proportions of tumor-bearing animals in dosed and control groups were compared in each of five time intervals: 0-52 weeks, 53-78 weeks, 79-92 weeks, week 93 to the week before the terminal kill period, and the terminal kill period. The denominators of these proportions were the number of animals on which necropsies were actually performed during the time interval. The individual time interval comparisons were then combined by the previously described method to obtain a single overall result. (See Peto et al., 1980, for the computational details of both methods.)

Unadjusted Analyses--Primary survival-adjusted methods are used to evaluate tumor incidence. In addition, the results of the Fisher's exact test for pairwise comparisons and the Cochran-Armitage linear trend test (Armitage, 1971; Gart et al., 1979) are given in the appendix containing the analyses of primary tumor incidence. These two tests are based on the overall proportion of tumor-bearing animals and do not adjust for survival differences.

III. RESULTS

RATS

FOURTEEN-DAY STUDIES
THIRTEEN-WEEK STUDIES
TWO-YEAR STUDIES

Body Weights and Clinical Signs
Survival
Pathology and Statistical Analyses of Results

MICE

FOURTEEN-DAY STUDIES
THIRTEEN-WEEK STUDIES
TWO-YEAR STUDIES

Body Weights and Clinical Signs
Survival
Pathology and Statistical Analyses of Results

III. RESULTS: RATS

FOURTEEN-DAY STUDIES

No animals died (Table 2). Final mean body weights of males that received 1,500-6,000 mg/kg tris(2-ethylhexyl)phosphate and of females that received 3,000 or 6,000 mg/kg were lower than those of the vehicle controls. No compound-related effects were observed at necropsy.

TABLE 2. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FOURTEEN-DAY GAVAGE STUDIES OF TRIS(2-ETHYLHEXYL)PHOSPHATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial	Final	Change
MALE				
0	5/5	123	166	+43
375	5/5	123	166	+43
750	5/5	121	162	+41
1,500	5/5	119	153	+34
3,000	5/5	123	154	+31
6,000	5/5	122	151	+29
FEMALE				
0	5/5	98	115	+17
375	5/5	99	119	+20
750	5/5	100	120	+20
1,500	5/5	100	118	+18
3,000	5/5	102	112	+10
6,000	5/5	100	104	+ 4

(a) Number surviving/number per group

THIRTEEN-WEEK STUDIES

No compound-related deaths occurred (Table 3). Mean body weights relative to those of the vehicle controls were depressed 5% for males that received 4,000 mg/kg and 10% and 5% for females that received 2,000 mg/kg or 4,000 mg/kg, respectively. No compound-related histopathologic effects were observed.

Based on the results of the 13-week studies, doses selected for rats for the 2-year studies were 2,000 and 4,000 mg/kg tris(2-ethylhexyl)phosphate for males and 1,000 and 2,000 mg/kg for females. Doses were to be administered 5 days per week.

TABLE 3. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF TRIS(2-ETHYLHEXYL)PHOSPHATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial	Final	Change	Final Weight Relative to Vehicle Controls (b) (percent)
MALE					
0	(c) 9/10	105	285	+180	--
250	(c) 10/10	106	292	+186	+ 2.5
500	10/10	107	304	+197	+ 6.7
1,000	(c) 8/10	106	302	+196	+ 6.0
2,000	(c) 7/10	108	300	+192	+ 5.3
4,000	(c) 9/10	105	270	+165	- 5.3
FEMALE					
0	10/10	101	179	+ 78	--
250	10/10	100	178	+ 78	- 0.6
500	10/10	102	176	+ 74	- 1.7
1,000	10/10	100	177	+ 77	- 1.1
2,000	(c) 9/10	100	161	+ 61	-10.1
4,000	(c) 9/10	101	170	+ 69	- 5.0

(a) Number surviving/number per group

(b) Final weight relative to vehicle controls = $\frac{\text{Final Weight (Dosed Group)} - \text{Final Weight (Vehicle Control)}}{\text{Final Weight (Vehicle Control)}} \times 100$

(c) Deaths were a result of gavage error.

III. RESULTS: RATS

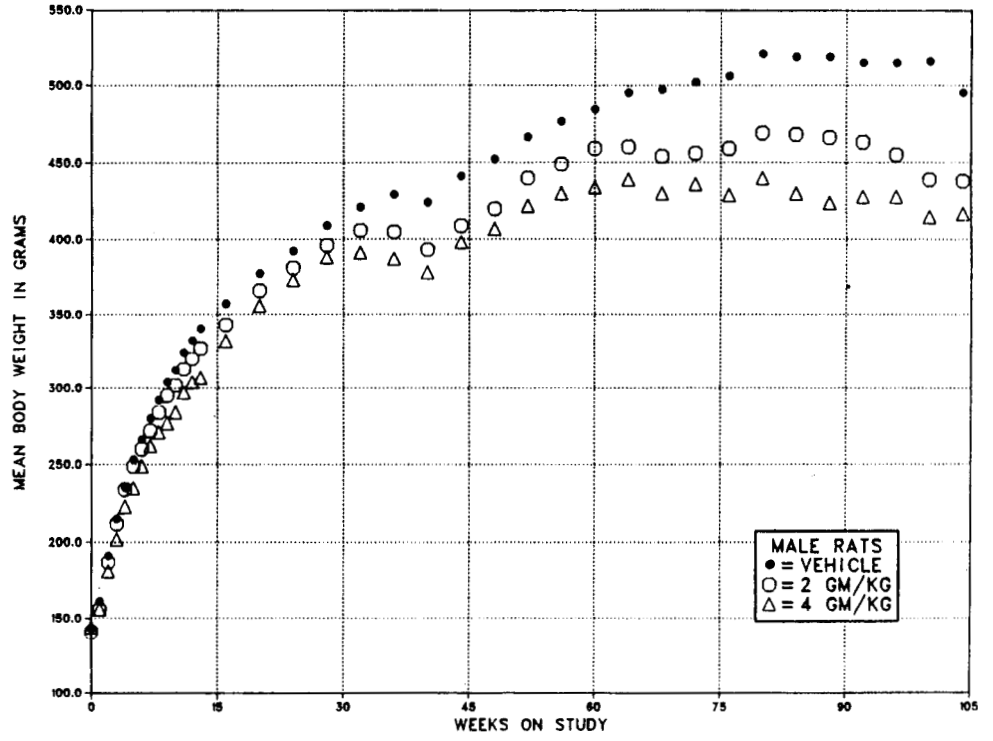
TWO-YEAR STUDIES

Body Weights and Clinical Signs

Throughout most of the study, mean body weights of dosed male rats were notably lower than those of the vehicle controls (Table 4 and Figure 1). Mean body weights of high dose female rats were only slightly lower than those of the vehicle controls. No compound-related clinical signs were observed.

TABLE 4. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF TRIS(2-ETHYLHEXYL)PHOSPHATE

Weeks on Study	Vehicle Control		Low Dose			High Dose		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE				2,000 mg/kg			4,000 mg/kg	
0	143	50	141	98.6	50	144	100.7	50
1	161	50	156	96.9	50	156	96.9	50
2	191	50	187	97.9	49	181	94.8	49
3	215	50	212	98.6	49	202	94.0	49
4	235	50	234	99.6	49	223	94.9	49
5	253	50	249	98.4	49	235	92.9	49
6	266	50	260	97.7	49	249	93.6	49
7	280	50	272	97.1	49	262	93.6	49
8	292	50	284	97.3	49	271	92.8	49
9	304	50	295	97.0	49	277	91.1	49
10	312	50	302	96.8	49	284	91.0	49
11	324	50	313	96.6	49	297	91.7	49
12	332	50	320	96.4	49	304	91.6	49
13	340	50	327	96.2	49	307	90.3	48
16	357	50	343	96.1	49	332	93.0	48
20	377	50	366	97.1	49	356	94.4	48
24	392	50	381	97.2	49	373	95.2	48
28	409	50	396	96.8	49	388	94.9	48
32	421	50	406	96.4	49	391	92.9	48
36	429	50	405	94.4	49	387	90.2	47
40	424	48	393	92.7	49	378	89.2	46
44	441	48	409	92.7	49	398	90.2	45
48	452	48	420	92.9	49	407	90.0	45
52	466	47	440	94.4	48	422	90.6	45
56	476	47	449	94.3	48	430	90.3	45
60	484	47	459	94.8	48	434	89.7	45
64	495	47	460	92.9	48	439	88.7	45
68	497	45	454	91.3	48	430	86.5	45
72	502	45	456	90.8	48	436	86.9	45
76	506	44	459	90.7	45	429	84.8	45
80	521	44	469	90.0	45	440	84.5	45
84	519	44	468	90.2	42	430	82.9	45
88	519	42	466	89.8	42	424	81.7	45
92	515	42	463	89.9	42	428	83.1	45
96	515	42	455	88.3	41	428	83.1	42
100	516	40	439	85.1	41	415	80.4	42
104	495	40	438	88.5	37	417	84.2	39
FEMALE				1,000 mg/kg			2,000 mg/kg	
0	114	50	115	100.9	50	113	99.1	50
1	126	50	124	98.4	50	120	95.2	49
2	140	49	140	100.0	49	134	95.7	49
3	151	49	152	100.7	49	149	98.7	49
4	160	49	161	100.6	49	159	99.4	49
5	169	49	171	101.2	49	167	98.8	49
6	174	49	177	101.7	49	172	98.9	49
7	179	49	183	102.2	49	177	98.9	49
8	183	49	187	102.2	49	181	98.9	49
9	187	49	191	102.1	49	184	98.4	49
10	189	49	194	102.6	49	189	100.0	49
11	195	49	200	102.6	49	192	98.5	49
12	197	49	202	102.5	49	194	98.5	49
13	200	49	204	102.0	49	196	98.0	49
16	204	49	208	102.0	47	203	99.5	49
20	214	49	217	101.4	47	211	98.6	49
24	220	49	223	101.4	47	217	98.6	49
28	226	49	229	101.3	47	221	97.8	49
32	231	49	234	101.3	47	226	97.8	49
36	233	49	234	100.4	47	225	96.6	49
40	229	48	229	100.0	47	220	96.1	49
44	237	48	238	100.4	46	223	94.1	48
48	240	48	245	102.1	46	229	95.4	48
52	249	47	253	101.6	46	240	96.4	48
56	250	47	254	101.6	45	242	96.8	46
60	257	47	261	101.6	45	247	96.1	46
64	263	47	266	101.1	44	253	96.2	45
68	266	47	266	100.0	44	253	95.1	43
72	272	46	274	100.7	43	261	96.0	42
76	280	46	281	100.4	41	269	96.1	40
80	292	46	298	102.1	41	287	98.3	40
84	299	44	303	101.3	40	286	95.7	40
88	301	44	307	102.0	39	291	96.7	38
92	305	44	312	102.3	38	290	95.1	34
96	311	40	310	99.7	37	297	95.5	32
100	313	38	307	98.1	34	294	93.9	31
104	306	36	304	99.3	34	298	97.4	30



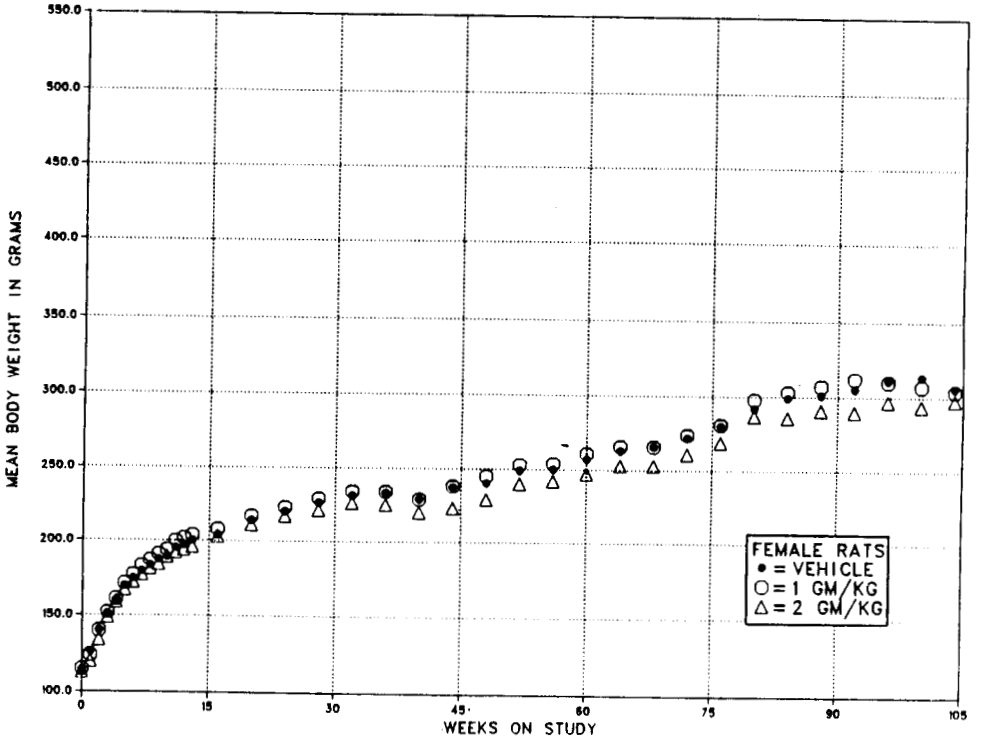


FIGURE 1. GROWTH CURVES FOR RATS ADMINISTERED TRIS(2-ETHYLHEXYL)PHOSPHATE IN CORN OIL BY GAVAGE FOR TWO YEARS

III. RESULTS: RATS

Survival

Estimates of the probabilities of the survival of male and female rats administered tris(2-ethylhexyl)phosphate at the doses used in these studies and those of the vehicle controls are shown in the Kaplan and Meier curves in Figure 2. No significant differences in survival were observed between any groups of either sex (Table 5).

TABLE 5. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF TRIS(2-ETHYHEXYL)PHOSPHATE

	Vehicle Control	2,000 mg/kg	4,000 mg/kg
MALE (a)			
Animals Initially in Study	50	50	50
Nonaccidental Deaths Before Termination (b)	8	9	7
Accidentally Killed	2	3	4
Killed at Termination	40	37	39
Died During Termination Period	0	1	0
Survival P Values (c)	0.883	0.815	0.989
	Vehicle Control	**1,000 mg/kg**	**2,000 mg/kg**
FEMALE (a)			
Animals Initially in Study	50	50	50
Nonaccidental Deaths Before Termination (b)	12	14	18
Accidentally Killed	2	2	2
Killed at Termination	36	34	30
Survival P Values (c)	0.169	0.662	0.194

(a) Terminal kill period: weeks 104-105
(b) Includes moribund animals that were killed
(c) Results of life table trend test are in the vehicle control column; those of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

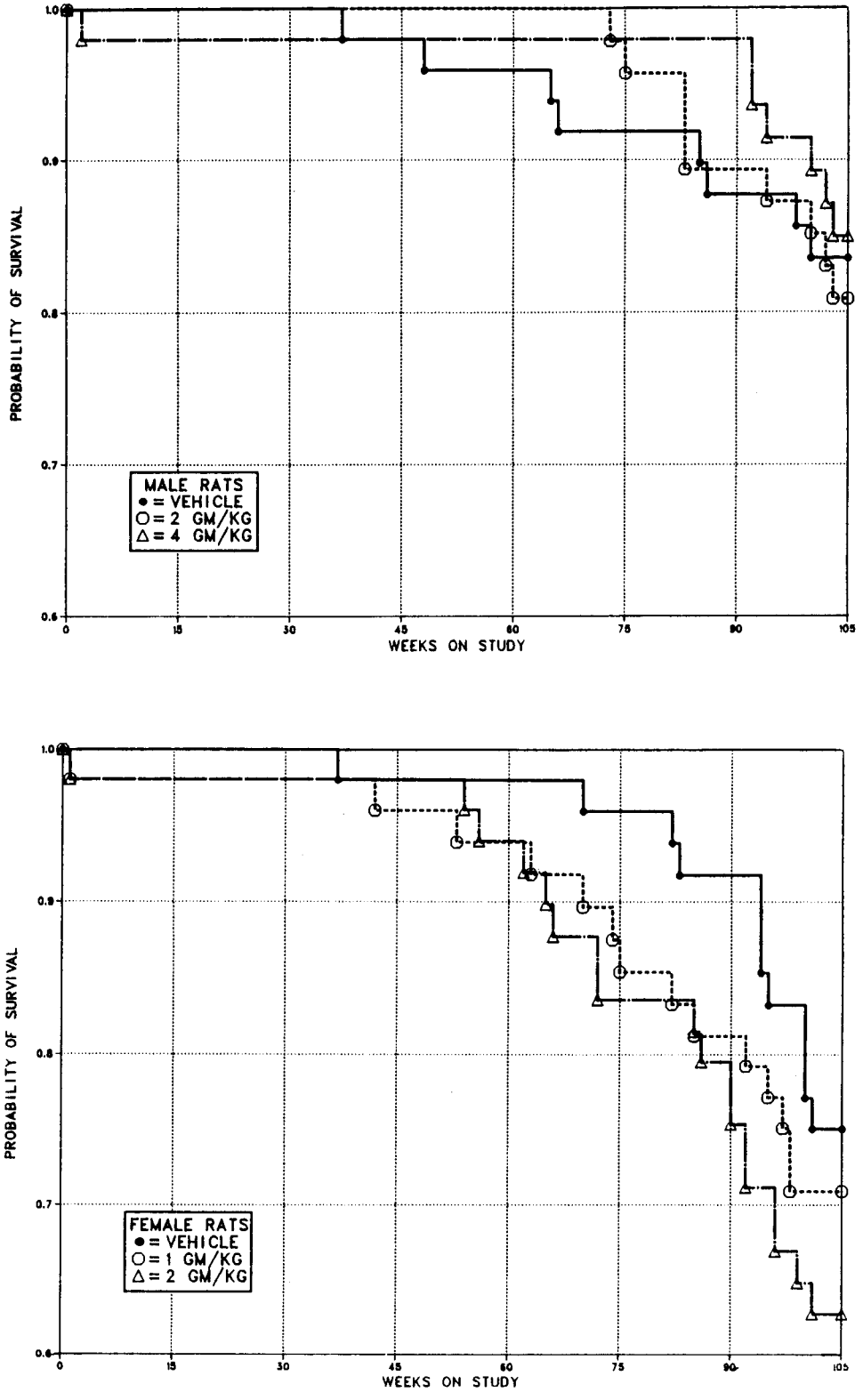


FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED TRIS(2-ETHYLHEXYL)PHOSPHATE IN CORN OIL BY GAVAGE FOR TWO YEARS

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidence of animals with neoplastic or nonneoplastic lesions. Histopathologic findings on neoplasms in rats are summarized in Appendix A, Tables A1 and A2; Tables A3 and A4 give the survival and tumor status for individual male and female rats. Findings on nonneoplastic lesions are summarized in Appendix C, Tables C1 and C2. Appendix E, Tables E1 and E2, contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes). Historical incidences of tumors in corn oil vehicle control animals are listed in Appendix F.

Adrenal: Pheochromocytomas in male rats occurred with a significant positive trend, and the incidences in the dosed groups were significantly higher than those in the vehicle controls (Table 6). Two malignant pheochromocytomas were observed in high dose male rats. Incidences of pheochromocytomas in dosed female rats were not significantly higher than that in the vehicle control (vehicle control, 2/50, 4%; low dose, 2/50, 4%; high dose, 1/49, 2%).

TABLE 6. ANALYSIS OF ADRENAL LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (a)

	Vehicle Control	2,000 mg/kg	4,000 mg/kg
Adrenal / Medulla Hyperplasia			
Overall Rates	1/50 (2%)	6/50 (12%)	3/50 (6%)
Pheochromocytoma			
Overall Rates	2/50 (4%)	9/50 (18%)	(b) 12/50 (24%)
Adjusted Rates	5.0%	22.3%	29.9%
Terminal Rates	2/40 (5%)	7/38 (18%)	11/39 (28%)
Life Table Tests	P=0.004	P=0.025	P=0.004
Incidental Tumor Tests	P=0.005	P=0.035	P=0.005

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) Two other male rats had malignant pheochromocytomas.

Thyroid: Follicular cell adenomas, cystadenomas, or carcinomas (combined) in male rats occurred with a significant positive trend, but the incidences in the dosed groups were not significantly higher than that in the vehicle controls (Table 7).

Salivary Gland: A malignant mixed tumor was observed in the salivary gland of one high dose male rat. The tumor metastasized to the lung and liver.

Pancreas: Acinar cell adenomas in male rats occurred with a significant negative trend, and the incidences in the dosed groups were significantly lower than that in the vehicle controls (Table 8).

TABLE 7. ANALYSIS OF THYROID LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE

	Vehicle Control	2,000 mg/kg	4,000 mg/kg
Follicular Cell Hyperplasia			
Overall Rates	2/46 (4%)	1/49 (2%)	0/49 (0%)
Follicular Cell Adenoma, Cystadenoma, or Carcinoma			
Overall Rates	(a) 1/46 (2%)	(b) 2/49 (4%)	(c) 6/49 (12%)
Adjusted Rates	2.6%	5.3%	15.2%
Terminal Rates	1/39 (3%)	2/38 (5%)	5/38 (13%)
Life Table Tests	P=0.028	P=0.491	P=0.057
Incidental Tumor Tests	P=0.032	P=0.491	P=0.071

(a) Follicular cell carcinoma
(b) One follicular cell adenoma or cystadenoma, one follicular cell carcinoma
(c) Three follicular cell adenomas or cystadenomas, three follicular cell carcinomas

TABLE 8. ANALYSIS OF PANCREATIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE

	Vehicle Control	2,000 mg/kg	4,000 mg/kg
Acinar Cell Hyperplasia			
Overall Rates	9/50 (18%)	9/48 (19%)	6/49 (12%)
Acinar Cell Adenoma			
Overall Rates	14/50 (28%)	5/48 (10%)	2/49 (4%)
Adjusted Rates	35.0%	13.2%	5.1%
Terminal Rates	14/40 (35%)	5/38 (13%)	2/39 (5%)
Life Table Tests	P<0.001N	P=0.024N	P=0.001N
Incidental Tumor Tests	P<0.001N	P=0.024N	P=0.001N

Subcutaneous Tissue: Lipomas in male rats occurred with a significant negative trend, but the incidences in the dosed groups were not significantly lower than that in the vehicle controls (vehicle control, 3/50, 6%; low dose, 0/50, 0%; high dose, 0/50, 0%).

Mammary Gland: The incidence of low dose female rats with fibroadenomas was significantly lower than for the vehicle controls (Table 9).

TABLE 9. ANALYSIS OF MAMMARY GLAND TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE

	Vehicle Control	1,000 mg/kg	2,000 mg/kg
Fibroadenoma			
Overall Rates	11/50 (22%)	2/50 (4%)	7/50 (14%)
Adjusted Rates	28.8%	5.4%	19.5%
Terminal Rates	9/36 (25%)	1/34 (3%)	3/30 (10%)
Life Table Tests	P=0.248N	P=0.013N	P=0.359N
Incidental Tumor Tests	P=0.189N	P=0.015N	P=0.308N

FOURTEEN-DAY STUDIES

All animals survived to the end of the dosing period (Table 10). Mice administered 6,000 mg/kg tris(2-ethylhexyl)phosphate had decreased activity and rough coats. No compound-related effects were observed at necropsy.

TABLE 10. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOURTEEN-DAY GAVAGE STUDIES OF TRIS(2-ETHYLHEXYL)PHOSPHATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams)		
		Initial	Final	Change
MALE				
0	5/5	19	23	+4
375	5/5	20	22	+2
750	5/5	20	20	0
1,500	5/5	20	22	+2
3,000	5/5	20	22	+2
6,000	5/5	20	22	+2
FEMALE				
0	5/5	17	20	+3
375	5/5	17	18	+1
750	5/5	17	19	+2
1,500	5/5	17	19	+2
3,000	5/5	17	18	+1
6,000	5/5	17	18	+1

(a) Number surviving/number per group

III. RESULTS: MICE

THIRTEEN-WEEK STUDIES

No compound-related deaths occurred (Table 11). Final mean body weight relative to that of the controls was depressed 7.1% for males that received 8,000 mg/kg and 4.5% for females that received 4,000 or 8,000 mg/kg. Inflammatory lesions in the gastric mucosa were observed in all groups, with increased severity in the higher dose groups. Ulceration was observed in the forestomach of 1/10 males that received 2,000 mg/kg, 1/10 females that received 4,000 mg/kg, and 1/10 males and 3/10 females that received 8,000 mg/kg.

Based on the results of the 13-week studies, doses selected for mice for the 2-year studies were 500 and 1,000 mg/kg tris(2-ethylhexyl)-phosphate, to be administered 5 days per week.

TABLE 11. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF TRIS(2-ETHYLHEXYL)PHOSPHATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial	Final	Change	Final Weight Relative to Vehicle Controls (b) (percent)
MALE					
0	10/10	20	28	+ 8	--
500	10/10	20	30	+ 10	+7.1
1,000	10/10	20	29	+ 9	+3.6
2,000	10/10	20	28	+ 8	0
4,000	10/10	20	29	+ 9	+3.6
8,000	10/10	20	26	+ 6	−7.1
FEMALE					
0	10/10	17	22	+ 5	--
500	10/10	17	23	+ 6	+4.5
1,000	(c) 9/10	17	22	+ 5	0
2,000	(c) 7/10	17	22	+ 5	0
4,000	10/10	17	21	+ 4	−4.5
8,000	10/10	16	21	+ 5	−4.5

(a) Number surviving/number per group

(b) Final weight relative to vehicle controls =

$$\frac{\text{Final Weight (Dosed Group)} - \text{Final Weight (Vehicle Control)}}{\text{Final Weight (Vehicle Control)}} \times 100$$

(c) Deaths were not considered to be compound related. All deaths occurred during week 1.

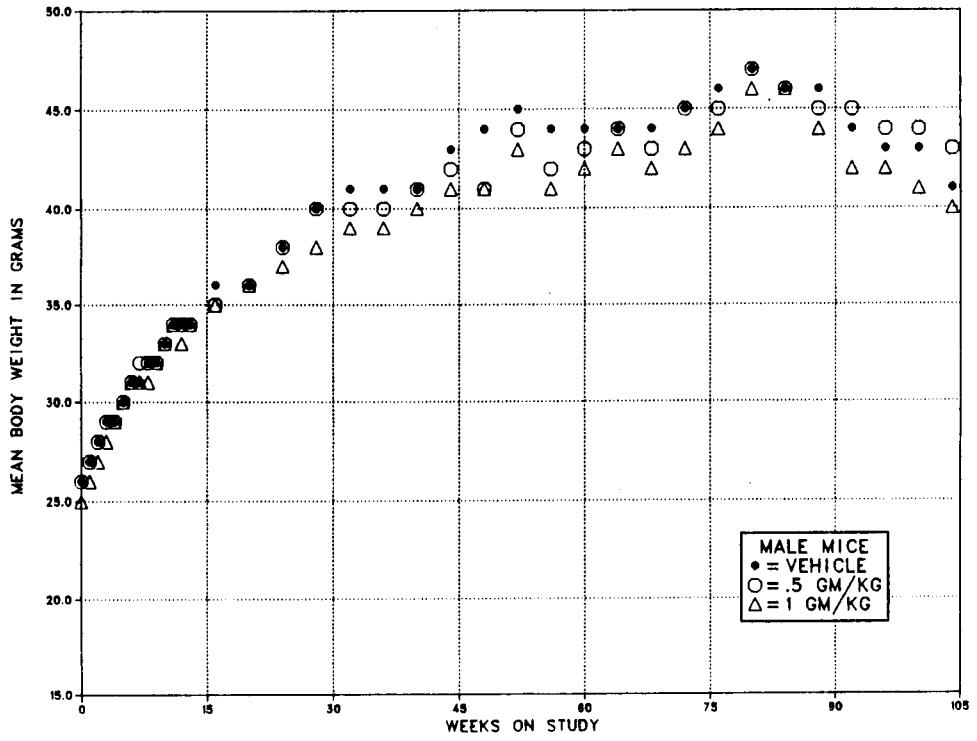
TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights for dosed male and female mice were within 10% of those of vehicle controls at all time points (Table 12 and Figure 3).

TABLE 12. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF TRIS(2-ETHYLHEXYL)PHOSPHATE

Weeks on Study	Vehicle Control		500 mg/kg			1,000 mg/kg		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
0	26.3	50	25.7	97.7	50	25.1	95.4	50
1	26.7	50	26.5	99.3	50	25.6	95.9	49
2	27.5	50	27.5	100.0	50	27.1	98.5	48
3	28.6	50	28.6	100.0	50	28.3	99.0	48
4	29.3	50	29.4	100.3	50	29.3	100.0	48
5	29.9	50	30.2	101.0	50	30.2	101.0	48
6	30.5	50	31.1	102.0	50	30.7	100.7	48
7	31.3	50	31.7	101.3	50	31.2	99.7	48
8	31.6	50	31.5	99.7	50	31.2	98.7	48
9	32.2	50	31.9	99.1	50	32.0	99.4	48
10	32.8	50	32.7	99.7	49	32.8	100.0	48
11	33.8	50	33.5	99.1	49	33.7	99.7	48
12	33.6	50	33.9	100.9	49	33.4	99.4	48
13	34.0	49	34.2	100.6	49	33.7	99.1	47
16	36.0	49	35.4	98.3	48	34.9	96.9	47
20	36.3	49	36.3	100.0	47	36.2	99.7	47
24	38.0	49	37.8	99.5	46	37.1	97.6	47
28	39.8	49	39.5	99.2	45	38.5	96.7	47
32	40.6	49	39.8	98.0	45	39.0	96.1	47
36	41.1	49	40.2	97.8	44	39.5	96.1	46
40	41.5	48	40.8	98.3	44	40.1	96.6	46
44	43.2	48	42.0	97.2	43	41.4	95.8	46
48	43.5	48	41.1	94.5	43	41.4	95.2	45
52	44.6	48	43.5	97.5	42	42.7	95.7	45
56	43.6	48	42.1	96.6	42	41.2	94.5	44
60	43.5	48	42.8	98.4	42	42.3	97.2	43
64	43.7	48	43.8	100.2	42	43.0	98.4	43
68	44.0	47	43.1	98.0	42	42.3	96.1	43
72	45.4	47	45.0	99.1	42	43.4	95.6	43
76	46.3	47	45.4	98.1	42	44.1	95.2	42
80	47.3	47	47.2	99.8	40	46.1	97.5	42
84	46.3	46	46.2	99.8	38	45.5	98.3	42
88	45.6	41	45.4	99.6	36	44.2	96.9	42
92	44.3	38	44.8	101.1	33	42.5	95.9	40
96	43.5	37	44.4	102.1	32	41.8	96.1	40
100	42.5	36	44.1	103.8	29	41.3	97.2	39
104	40.9	34	42.7	104.4	27	40.2	98.3	38
FEMALE								
0	20.2	50	19.6	97.0	50	20.2	100.0	50
1	20.0	50	19.9	99.5	50	20.5	102.5	50
2	20.9	48	21.2	101.4	50	21.4	102.4	50
3	21.9	48	22.1	100.9	50	22.3	101.8	50
4	22.3	48	22.4	100.4	50	22.8	102.2	50
5	22.9	48	22.8	99.6	50	23.5	102.6	50
6	23.3	48	23.4	100.4	50	23.7	101.7	50
7	23.8	48	23.6	99.2	50	24.0	100.8	50
8	23.8	48	23.5	98.7	50	24.1	101.3	50
9	24.9	48	24.1	96.8	50	24.3	97.6	50
10	24.6	48	24.4	99.2	49	24.9	101.2	50
11	24.6	48	25.0	101.6	49	25.3	102.8	50
12	24.3	48	24.7	101.6	49	25.0	102.9	50
13	25.1	48	25.0	99.6	48	25.9	103.2	50
16	26.5	46	26.5	100.0	48	27.0	101.9	50
20	27.7	44	27.5	99.3	48	27.9	100.7	50
24	28.7	43	27.8	96.9	47	28.6	99.7	50
28	29.9	43	29.5	98.7	47	29.6	99.0	50
32	30.8	43	29.7	96.4	47	30.3	98.4	50
36	31.5	43	30.2	95.9	47	30.9	98.1	50
40	32.2	43	31.2	96.9	47	32.5	100.9	50
44	33.0	43	31.4	95.2	47	32.6	98.8	50
48	33.0	43	31.8	96.4	47	32.7	99.1	49
52	34.6	43	32.7	94.5	47	34.3	99.1	49
56	34.1	43	32.2	94.4	47	33.4	97.9	49
60	35.4	43	34.1	96.3	47	34.4	97.2	49
64	36.0	43	34.9	96.9	47	36.5	101.4	48
68	36.5	43	35.2	96.4	47	36.1	98.9	48
72	38.8	43	36.8	94.8	46	37.1	95.6	48
76	40.4	43	38.5	95.3	46	38.3	94.8	48
80	42.2	42	39.5	93.6	46	40.7	96.4	47
84	42.6	40	39.7	93.2	45	39.6	93.0	46
88	42.2	40	39.4	93.4	44	39.1	92.7	46
92	40.6	38	38.2	94.1	43	36.9	90.9	43
96	38.9	37	37.4	96.1	43	36.9	94.9	42
100	37.1	37	37.0	99.7	42	36.0	97.0	40
104	36.0	32	36.0	100.0	42	35.8	99.4	40



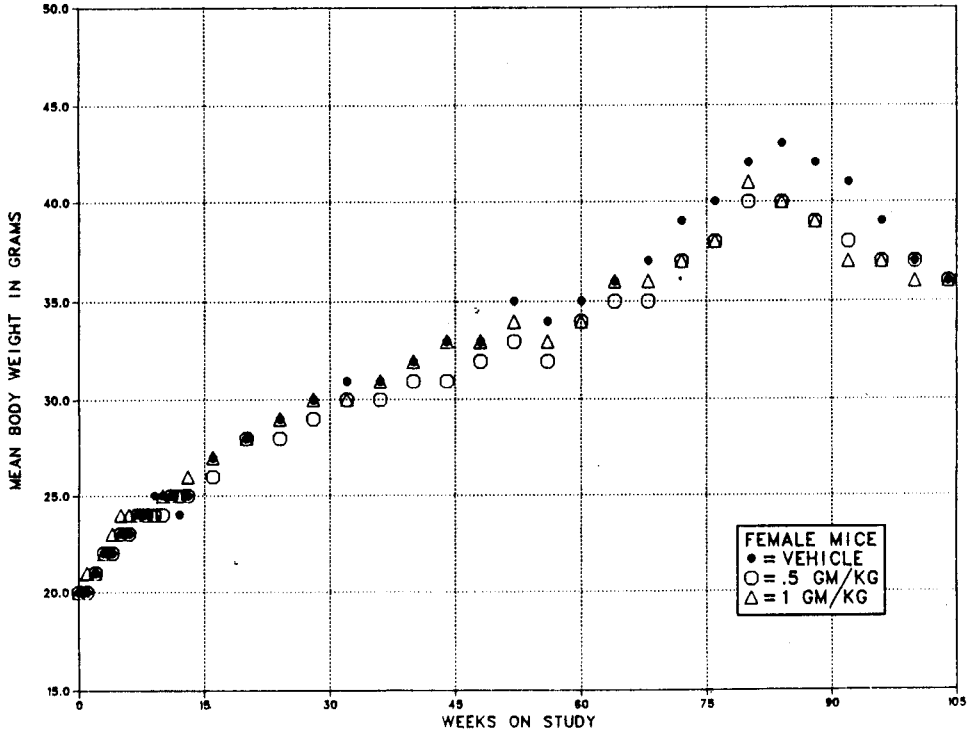


FIGURE 3. GROWTH CURVES FOR MICE ADMINISTERED TRIS(2-ETHYLHEXYL)PHOSPHATE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival of male and female mice administered tris(2-ethylhexyl)phosphate at the doses used in these studies and those of the vehicle controls are shown by the Kaplan and Meier curves in Figure 4. In mice, the survival of dosed groups was not significantly different from that of the vehicle controls, but the survival of the males in the low dose group was significantly less than that of the males in the high dose group ($P = 0.034$). Additional survival data are summarized in Table 13.

TABLE 13. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF TRIS(2-ETHYLHEXYL)PHOSPHATE

	Vehicle Control	500 mg/kg	1,000 mg/kg
MALE (a)			
Animals Initially in Study	50	50	50
Nonaccidental Deaths Before Termination (b)	15	21	10
Animals Missing	0	0	1
Accidentally Killed	1	1	1
Killed at Termination	32	27	37
Died During Termination Period	2	1	1
Survival P Values (c)	0.449	0.202	0.439
FEMALE (a)			
Animals Initially in Study	50	50	50
Nonaccidental Deaths Before Termination (b)	15	7	10
Accidentally Killed	3	1	0
Killed at Termination	32	42	40
Survival P Values (c)	0.216	0.084	0.278

(a) Terminal kill period: weeks 104-105
(b) Includes moribund animals that were killed
(c) Results of the life table trend test are in the vehicle control column; those of the the life table pairwise comparisons with the vehicle controls are in the dosed columns.

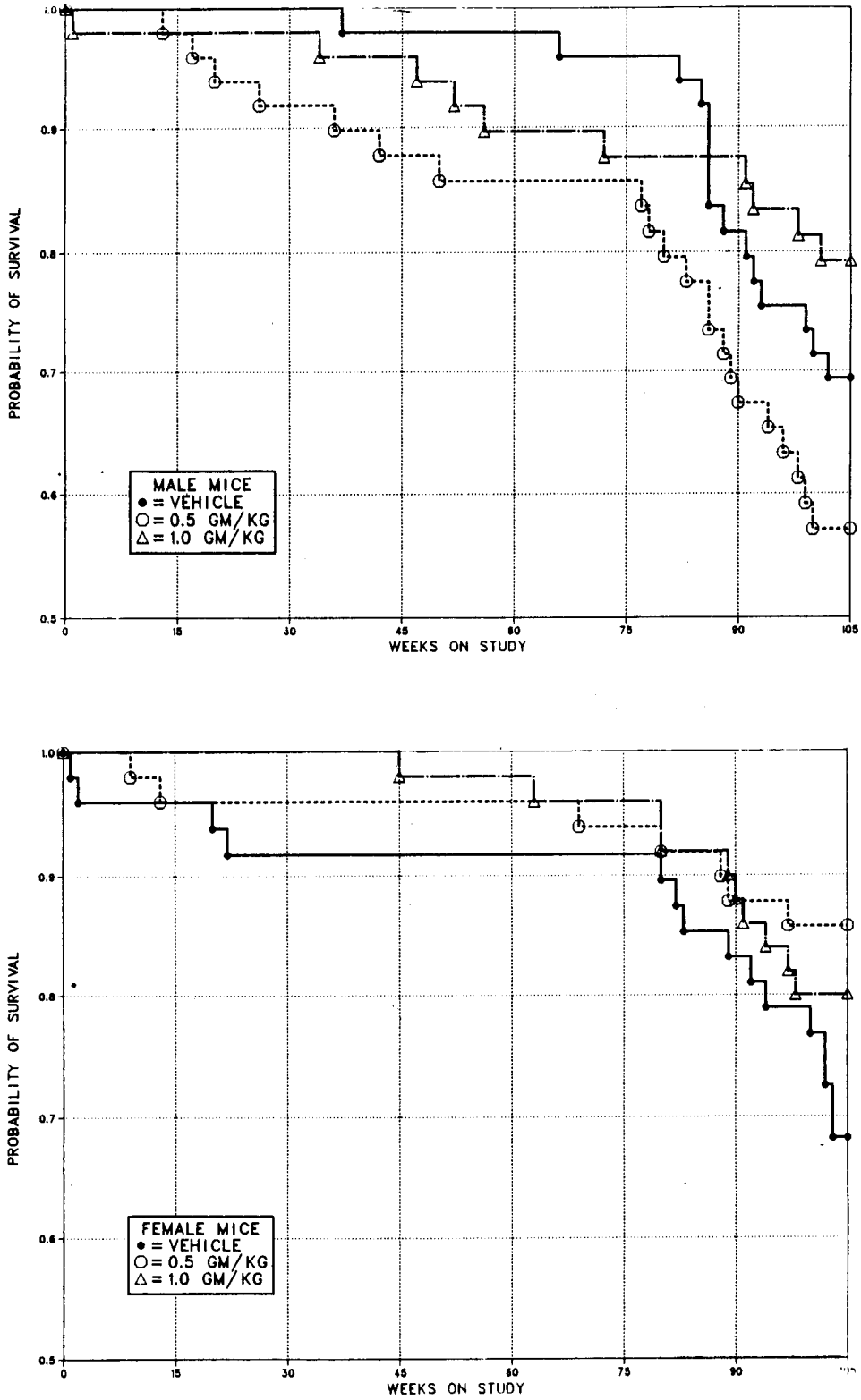


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED TRIS(2-ETHYLHEXYL)PHOSPHATE IN CORN OIL BY GAVAGE FOR TWO YEARS

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidence of animals with neoplastic or nonneoplastic lesions. Histopathologic findings on neoplasms in mice are summarized in Appendix B, Tables B1 and B2; Tables B3 and B4 give the survival and tumor status for individual male and female mice. Findings on nonneoplastic lesions are summarized in Appendix D, Tables D1 and D2. Appendix E, Tables E3 and E4, contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes). Historical incidences of tumors in corn oil vehicle control animals are listed in Appendix F.

Liver: Hepatocellular carcinomas in female mice occurred with significant positive trends, and the incidence in the high dose group was significantly higher than that in the vehicle controls (Table 14). Combining adenomas and carcinomas did not eliminate the significance at this dose level. Carcinomas alone or in combination with adenomas were not significant at the lower dose. In male mice, hepatocellular carcinomas occurred in 9/50 vehicle controls, 12/50 low dose, and 12/49 high dose animals; no statistically significant compound-related trend was observed.

Cytoplasmic vacuolization of the liver was observed at increased incidences in dosed female mice (vehicle control, 10/48, 21%; low dose, 16/50, 32%; high dose, 18/50, 36%).

TABLE 14. ANALYSIS OF LIVER TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (a)

	Vehicle Control	500 mg/kg	1,000 mg/kg (b)
Adenoma			
Overall Rates	2/48 (4%)	4/50 (8%)	3/50 (6%)
Adjusted Rates	5.5%	9.5%	7.5%
Terminal Rates	1/32 (3%)	4/42 (10%)	3/40 (7%)
Life Table Tests	P=0.517	P=0.453	P=0.591
Incidental Tumor Tests	P=0.510	P=0.404	P=0.581
Carcinoma			
Overall Rates	0/48 (0%)	4/50 (8%)	7/50 (14%)
Adjusted Rates	0.0%	9.5%	16.7%
Terminal Rates	0/32 (0%)	4/42 (10%)	5/40 (13%)
Life Table Tests	P=0.012	P=0.103	P=0.019
Incidental Tumor Tests	P=0.006	P=0.103	P=0.007
Adenoma or Carcinoma			
Overall Rates	2/48 (4%)	8/50 (16%)	10/50 (20%)
Adjusted Rates	5.5%	19.0%	23.8%
Terminal Rates	1/32 (3%)	8/42 (19%)	8/40 (20%)
Life Table Tests	P=0.031	P=0.105	P=0.039
Incidental Tumor Tests	P=0.020	P=0.087	P=0.020

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) One cholangiocarcinoma was observed in the high dose group.

Thyroid: Follicular cell hyperplasia was observed at increased incidences in dosed male and dosed female mice (males: vehicle control, 0/49; low dose, 12/48, 25%; high dose, 24/47, 51%; females: vehicle control, 1/44, 2%; low dose, 13/47, 28%; high dose, 12/46, 26%). Follicular cell adenomas were found in one high dose male and in two low dose females but in none of the vehicle controls.

Circulatory System: Hemangiosarcomas in male mice occurred with a significant negative trend, and the incidences in the dosed groups were significantly lower than that in the vehicle controls (Table 15).

Hematopoietic System: Malignant lymphomas in female mice occurred with a significant negative trend, and the incidence in the high dose group was significantly lower than that in the vehicle controls (Table 16).

Pituitary: Pituitary adenomas in female mice occurred with a significant negative trend, and the incidence in the high dose group was significantly lower than that in the vehicle controls (Table 17).

TABLE 15. ANALYSIS OF CIRCULATORY SYSTEM TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE

	Vehicle Control	500 mg/kg	1,000 mg/kg
Hemangiosarcoma			
Overall Rates	7/50 (14%)	0/50 (0%)	1/49 (2%)
Adjusted Rates	17.8%	0.0%	2.6%
Terminal Rates	4/34 (12%)	0/28 (0%)	1/38 (3%)
Life Table Tests	P=0.008N	P=0.020N	P=0.030N
Incidental Tumor Tests	P=0.008N	P=0.011N	P=0.041N

TABLE 16. ANALYSIS OF HEMATOPOIETIC SYSTEM TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE

	Vehicle Control	500 mg/kg	1,000 mg/kg
Lymphoma, All Malignant			
Overall Rates	14/49 (29%)	10/50 (20%)	6/50 (12%)
Adjusted Rates	35.5%	23.3%	13.8%
Terminal Rates	7/32 (22%)	9/42 (21%)	4/40 (10%)
Life Table Tests	P=0.012N	P=0.103N	P=0.020N
Incidental Tumor Tests	P=0.024N	P=0.461N	P=0.021N

TABLE 17. ANALYSIS OF PITUITARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE

	Vehicle Control	500 mg/kg	1,000 mg/kg
Adenoma			
Overall Rates	6/41 (15%)	8/47 (17%)	2/47 (4%)
Adjusted Rates	22.2%	20.0%	5.0%
Terminal Rates	6/27 (22%)	8/40 (20%)	2/40 (5%)
Life Table Tests	P=0.030N	P=0.534N	P=0.041N
Incidental Tumor Tests	P=0.030N	P=0.534N	P=0.041N

IV. DISCUSSION AND CONCLUSIONS

IV. DISCUSSION AND CONCLUSIONS

Fourteen-day and 13-week studies were conducted in F344/N rats and B6C3F$_1$ mice to determine toxicity and target organs and to aid in selecting the doses for the 2-year studies. In the 14-day tests, groups of five animals of each sex and species were administered doses of 0, 375, 750, 1,500, 3,000, or 6,000 mg/kg tris(2-ethylhexyl)phosphate daily by gavage in corn oil. In these studies, the final body weights of rats receiving the higher doses were depressed, but survival was good and no compound-related effects were observed at necropsy. In the 13-week studies, groups of 10 rats of each sex received doses of 0, 250, 500, 1,000, 2,000, or 4,000 mg/kg tris(2-ethylhexyl)phosphate 5 days per week for 13 weeks. Similar groups of mice received doses of 0, 500, 1,000, 2,000, 4,000, or 8,000 mg/kg on the same schedule. All doses were administered by gavage in corn oil. Mild weight depression was observed in some of the higher dose groups of each species, but no compound-related deaths were observed in either sex or species in the 13-week studies (Tables 3 and 11). Weight depression in female rats was greater than in males and was considered in setting doses. In these studies, dose-related inflammatory lesions were observed in the gastric mucosa of mice, but no other compound-related effects were observed in either species at necropsy.

Based on these prechronic studies, doses for the 2-year studies were set at 0, 2,000, and 4,000 mg/kg for male rats, 0, 1,000, and 2,000 mg/kg for female rats, and 0, 500, and 1,000 mg/kg for mice of each sex. Groups of 50 animals of each sex and species were administered the respective doses by gavage in corn oil 5 days per week for 103 weeks. No compound-related clinical toxicity was observed in either sex of either species. Significant depressions in body weights in dosed animals were limited to male rats: low dose, 11.5%; high dose, 15.8% (Table 4). Decreased body weight in the 2-year studies was not considered life threatening and did not affect survival.

Corn oil is high in caloric content relative to the NIH 07 diet used in these studies (corn oil = 9 calories/g; NIH 07 = approximately 3.8 calories/g; Appendix L). A 200-g vehicle control male rat eating 15 g of diet per day would have a daily intake of 57 calories from the diet and 16.5 calories from corn oil. All animals within a species/dose group received the same volume (rats, 10 ml/kg; mice, 3.3 ml/kg); therefore, dosed animals, because of the volume of chemical administered, received 16%-43% less corn oil and fewer calories per dose than did the respective controls. This could account for the mildly depressed body weights of dosed male rats.

The present study is the first to be completed using the completely defined NIH 07 diet (Appendix L). The nutrients in this diet are equivalent to those in the diet used in previous studies. Formerly, the diet was assumed to be well balanced and free of contaminants. In the present study, the nutritive value and purity of the diet were confirmed at regular intervals. The only appreciable exposure to a known carcinogen for animals occurred during a 3-month period when concentrations of nitrosamines (115-280 ppb) exceeded levels usually present (Table L3). Since the levels of nitrosamines were not high and dosed and vehicle control animals ingested approximately the same amount, the nitrosamines are not considered to adversely affect the results of this study.

Some rats died from gavage accidents or undetermined causes in the 2-year studies. Male mice died primarily from infections incurred after fighting, and some female mice were lost from accidental or undetermined causes; however, survival of all dosed groups was comparable with that of the vehicle controls. Overall survival was good and was considered adequate for statistical analyses of tumor incidences.

At the end of the 2-year studies, neoplasms of the adrenal gland and thyroid gland were observed at higher incidences in dosed male rats than in vehicle controls. The incidences of adrenal pheochromocytomas were dose related and significantly higher in dosed male rats than in vehicle controls (2/50; 9/50; 12/50) (Table 6). Two additional high dose male rats had malignant pheochromocytomas of the adrenal glands (total, 14/50; 28%). However, the 4% incidence of pheochromocytomas in male vehicle control rats equaled the lowest ever reported (Appendix F, Table F1) and was significantly below the incidences of 24% and 26% observed in vehicle control animals of two previous gavage studies at this laboratory or the 18% overall vehicle control historical incidence observed in the Program (Appendix F, Table F1). A review of adrenal

medullary tissue in vehicle control rats in the present study indicated that this low incidence of pheochromocytomas was not due to sampling techniques (Appendix M). The incidence of these neoplasms in dosed groups was similar to historical control incidences; therefore, this increase was not regarded as being clearly related to administration of tris(2-ethylhexyl)phosphate. There was a significant positive trend for increased incidence of thyroid follicular cell tumors in male rats. However, the incidences of thyroid follicular cell neoplasms in the dosed groups were not significantly higher than that in vehicle controls (Table 7), and both the original and NTP reviewing pathologists who evaluated the study were not convinced that the increased incidence of thyroid neoplasia was a dose-related effect. Therefore, it was not considered a positive effect.

Follicular cell hyperplasia of the thyroid gland was observed at increased incidences in dosed male and female mice. Thyroid follicular cell hyperplasia was characterized by a focal increase in cellularity which affected one or several follicles. No dose-related increases in thyroid neoplasms occurred in male or female mice. Follicular cell adenomas were found in one high dose male and in two low dose female mice. A rare, malignant, mixed salivary gland tumor was observed in one high dose male rat. (Only one has been reported in over 2,000 vehicle controls.) Since only one tumor was seen, its significance cannot be determined.

Two tumors were observed at lower incidences in dosed rats than in vehicle controls. Pancreatic acinar cell adenomas in dosed male rats occurred with a significant negative trend ($P < 0.001$), and the incidences in low dose and high dose rats were significantly lower than that in vehicle controls (Table 8). However, the incidence of acinar cell adenomas in the vehicle controls (14/50) was the greatest ever recorded for historical vehicle control animals. Only one acinar cell adenoma was observed in two previous studies at the same laboratory (Appendix F, Table F3). The incidence of pancreatic acinar cell adenomas in the historical vehicle controls is approximately 3.3% and has ranged from 0% to 22% in previous studies. Therefore, the decreased incidences observed in the low dose and high dose groups are probably not biologically relevant. In female rats, the incidence of fibroadenomas in the mammary gland was significantly lower in the low dose group than in the vehicle controls (Table 9). The incidence of mammary gland fibroadenomas has been reported to decrease with dose when a significant decreased weight gain also occurs (Haseman, 1983). The decreased incidence of fibroadenomas observed here, however, was not associated with a significant decreased weight gain.

The use of a dose volume of 10 ml/kg corn oil for rats may complicate the comparison of results from the present study because the dose volume of corn oil in previous studies never exceeded 5 ml/kg. There were no obvious effects attributable to the use of the 10 ml/kg dose. Two observations unique to this study, however, were the low incidence of adrenal pheochromocytomas and the high incidence of pancreatic acinar cell adenomas in vehicle control male rats. The dose-related effects of tris(2-ethylhexyl)phosphate on these organs were significant when compared with incidences in concurrent vehicle controls but were similar to historical vehicle control incidences. Therefore, it is not possible to determine if the observed results are attributable to administration of tris(2-ethylhexyl)-phosphate, to the smaller volume of corn oil received by dosed animals, or to chance. The absence of similar results in female rats could be attributed to differences in sensitivity or differences in metabolism; or the absorption of corn oil by dosed and vehicle control animals may have been so similar that the effects, if any, were not significantly different.

Neoplasms that occurred at increased frequencies in dosed mice were restricted to the livers of dosed females (Table 14). Hepatocellular carcinomas occurred in female mice with a significant positive trend and were present in significantly greater numbers in high dose animals than in vehicle controls. Classification of evidence of carcinogenicity according to the "Note to the Reader" on page 2 of this report was "some" rather than "clear" because the increased incidence of hepatocellular carcinomas was significant and only moderately increased at the high dose. Cytoplasmic vacuolization of the liver in female mice and follicular cell hyperplasia of the thyroid in male and female mice occurred at increased incidences in the 2-year studies. The contents of the vacuoles in the

liver is unknown, and, in his narrative, the original pathologist did not consider the cytoplasmic vacuolization a compound-related change in liver.

Other neoplastic lesions occurred with significant negative trends in dosed mice. Hemangiosarcomas occurred with a significant negative trend in male mice, and the incidences in the low dose and high dose groups were significantly lower than that in the vehicle controls (Table 15); however, the incidence of hemangiosarcomas in the concurrent vehicle controls was higher than that seen in historical vehicle controls, and the biologic relevance of the negative trends is questionable. Incidences of malignant lymphomas in dosed female mice occurred with a significant negative trend, and the incidence in the high dose group was lower than that in both the concurrent and historical vehicle controls. The decreased incidence of malignant lymphomas in female mice supports the observation that a decreased incidence of this tumor is frequently associated with an increase in liver tumors (Haseman, 1983).

The metabolism of tris(2-ethylhexyl)phosphate has not been studied, but the major metabolites of trialkyl phosphates are generally bis- and monoalkyl phosphates plus the respective alcohols (Nomeir et al., 1981; Nomeir and Matthews, 1983). The alcohol metabolite of tris(2-ethylhexyl)phosphate would be 2-ethylhexanol. Like tris(2-ethylhexyl)phosphate, 2-ethylhexanol has been reported to cause moderate gastric irritation when administered in corn oil by gavage at high doses (Scala and Burtis, 1973). Otherwise, 2-ethylhexanol is a relatively nontoxic, nongenotoxic chemical (in Chinese hamster ovary cells) that is readily metabolized by rats and mice (Treon, 1963; Scala and Burtis, 1973; Albro, 1975; Phillips et al., 1982). 2-Ethylhexanol has not been the subject of a 2-year toxicology and carcinogenesis study, but it is a major metabolite of two chemicals that have undergone long-term toxicity testing (Albro et al., 1973). Di(2-ethylhexyl)adipate (NTP, 1982a) was administered in the diet at 12,000 or 25,000 ppm to rats and mice, and di(2-ethylhexyl)phthalate (NTP 1982b) was administered in the diet at 6,000 or 12,000 ppm to F344/N rats and at 3,000 or 6,000 ppm to $B6C3F_1$ mice. Under the conditions of these tests, administration of each chemical produced significantly increased incidences of hepatocellular carcinomas in female mice and a significantly decreased incidence of mammary gland fibroadenomas in female F344/N rats, effects also found in the present study. Decreased incidences of lymphomas in female mice were observed in the studies of di(2-ethylhexyl)-adipate and tris(2-ethylhexyl)phosphate. In each study, significant positive and negative trends were not associated with decreased survival of dosed animals relative to that of the vehicle controls. The biologic significance of the correlation of the positive and negative trends in the incidences of neoplasms associated with exposure to tris(2-ethylhexyl)phosphate, di(2-ethylhexyl)adipate, and di(2-ethylhexyl)-phthalate is not yet known. It is clear, however, that the effects observed with tris(2-ethylhexyl)-phosphate have been observed with other chemicals that are metabolized to 2-ethylhexanol. That common link has yet to be established, but these correlations do imply that the positive and negative effects are compound related.

Under the conditions of these studies, a comparison of concurrent and historical controls indicated that there was *equivocal evidence of carcinogenicity** in male F344/N rats receiving 2,000 and 4,000 mg/kg tris(2-ethylhexyl)phosphate, as evidenced by increased incidences of pheochromocytomas of the adrenal glands. There was *no evidence of carcinogenicity* in female F344/N rats or in male $B6C3F_1$ mice receiving tris(2-ethylhexyl)phosphate. There was *some evidence of carcinogenicity* in female $B6C3F_1$ mice that received 1,000 mg/kg tris(2-ethylhexyl)phosphate, as shown by an increased incidence of hepatocellular carcinoma. Tris(2-ethylhexyl)phosphate was associated with increased incidences of follicular cell hyperplasias of the thyroid gland in male and female $B6C3F_1$ mice.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.

V. REFERENCES

V. REFERENCES

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF TRIS(2-ETHYLHEXYL)PHOSPHATE

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)	4 (8%)	1 (2%)
KERATOACANTHOMA	1 (2%)	1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)
FIBROMA	2 (4%)	2 (4%)	
LIPOMA	3 (6%)		
HIBERNOMA			1 (2%)
NEUROFIBROMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)		
MIXED TUMOR, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
LYMPHOCYTIC LEUKEMIA		1 (2%)	
LEUKEMIA,MONONUCLEAR CELL	2 (4%)	6 (12%)	6 (12%)
#MANDIBULAR L. NODE	(47)	(47)	(47)
MIXED TUMOR, METASTATIC			1 (2%)
CIRCULATORY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)		
#SPLEEN	(50)	(49)	(50)
HEMANGIOSARCOMA		1 (2%)	
#LIVER	(50)	(50)	(50)
HEMANGIOSARCOMA, METASTATIC		1 (2%)	
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(48)	(49)	(50)
MIXED TUMOR, MALIGNANT			1 (2%)
NEURILEMOMA, INVASIVE			1 (2%)
#LIVER	(50)	(50)	(50)
NEOPLASTIC NODULE		1 (2%)	
MIXED TUMOR, METASTATIC			1 (2%)
#PANCREAS	(50)	(48)	(49)
ACINAR-CELL ADENOMA	14 (28%)	5 (10%)	2 (4%)
#SMALL INTESTINE	(49)	(46)	(47)
LEIOMYOSARCOMA		1 (2%)	
#DUODENUM	(49)	(46)	(47)
ADENOCARCINOMA, NOS		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
TUBULAR-CELL ADENOMA		1 (2%)	

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(50)	(50)
CHROMOPHOBE ADENOMA	7 (14%)	9 (18%)	7 (14%)
CHROMOPHOBE CARCINOMA	2 (4%)		1 (2%)
#ADRENAL	(50)	(50)	(50)
CORTICAL ADENOMA	1 (2%)	1 (2%)	
PHEOCHROMOCYTOMA	2 (4%)	9 (18%)	12 (24%)
PHEOCHROMOCYTOMA, MALIGNANT			2 (4%)
#THYROID	(46)	(49)	(49)
FOLLICULAR-CELL ADENOMA		1 (2%)	2 (4%)
FOLLICULAR-CELL CARCINOMA	1 (2%)	1 (2%)	3 (6%)
C-CELL ADENOMA	4 (9%)	3 (6%)	1 (2%)
C-CELL CARCINOMA	2 (4%)	2 (4%)	3 (6%)
#THYROID FOLLICLE	(46)	(49)	(49)
CYSTADENOMA, NOS			1 (2%)
#PANCREATIC ISLETS	(50)	(48)	(49)
ISLET-CELL ADENOMA	1 (2%)	3 (6%)	2 (4%)
ISLET-CELL CARCINOMA			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
FIBROADENOMA	2 (4%)	1 (2%)	3 (6%)
*PREPUTIAL GLAND	(50)	(50)	(50)
CARCINOMA, NOS		1 (2%)	
#PROSTATE	(47)	(47)	(50)
ADENOMA, NOS	5 (11%)	7 (15%)	5 (10%)
#TESTIS	(50)	(50)	(50)
INTERSTITIAL-CELL TUMOR	42 (84%)	41 (82%)	43 (86%)
*EPIDIDYMIS	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)		
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
GRANULAR-CELL TUMOR, NOS			1 (2%)
SPECIAL SENSE ORGANS			
*EAR	(50)	(50)	(50)
FIBROMA	1 (2%)		
*ZYMBAL'S GLAND	(50)	(50)	(50)
SEBACEOUS ADENOCARCINOMA			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*TUNICA VAGINALIS	(50)	(50)	(50)
MESOTHELIOMA, NOS	2 (4%)		1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
MESOTHELIOMA, NOS		1 (2%)	
TAIL			
SQUAMOUS CELL PAPILLOMA			1

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

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	4	8	4
MORIBUND SACRIFICE	4	2	3
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	40	37	39
DOSING ACCIDENT	1	2	1
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS	1	1	3
ANIMAL MISSING			
ANIMAL MISSEXED			
OTHER CASES			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	44	47	45
TOTAL PRIMARY TUMORS	98	104	103
TOTAL ANIMALS WITH BENIGN TUMORS	43	47	45
TOTAL BENIGN TUMORS	86	88	82
TOTAL ANIMALS WITH MALIGNANT TUMORS	9	13	16
TOTAL MALIGNANT TUMORS	10	14	19
TOTAL ANIMALS WITH SECONDARY TUMORS##		1	2
TOTAL SECONDARY TUMORS		1	4
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 IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
FIBROMA	1 (2%)		
LIPOMA			1 (2%)
NEURILEMOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(49)	(50)
FIBROSARCOMA			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
LEUKEMIA, NOS	2 (4%)		1 (2%)
LYMPHOCYTIC LEUKEMIA	1 (2%)		
LEUKEMIA,MONONUCLEAR CELL	5 (10%)	5 (10%)	8 (16%)
#MEDIASTINAL L. NODE	(49)	(47)	(47)
FIBROSARCOMA, METASTATIC			1 (2%)
CIRCULATORY SYSTEM			
#BRAIN	(50)	(50)	(50)
HEMANGIOMA		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
NEOPLASTIC NODULE	1 (2%)		
#BILE DUCT	(50)	(50)	(50)
CYSTADENOMA, NOS	1 (2%)		
#PANCREAS	(49)	(50)	(50)
ACINAR-CELL ADENOMA	2 (4%)		1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(49)	(49)
CHROMOPHOBE ADENOMA	18 (36%)	20 (41%)	11 (22%)
CHROMOPHOBE CARCINOMA	1 (2%)	1 (2%)	3 (6%)
#ADRENAL	(50)	(50)	(49)
CORTICAL ADENOMA	1 (2%)		
PHEOCHROMOCYTOMA	2 (4%)	2 (4%)	1 (2%)
#THYROID	(46)	(50)	(47)
FOLLICULAR-CELL CARCINOMA	1 (2%)	3 (6%)	
C-CELL ADENOMA	5 (11%)	3 (6%)	2 (4%)
C-CELL CARCINOMA	1 (2%)	3 (6%)	
#THYROID FOLLICLE	(46)	(50)	(47)
CYSTADENOMA, NOS	1 (2%)	1 (2%)	3 (6%)

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS	1 (2%)	1 (2%)	2 (4%)
FIBROADENOMA	11 (22%)	2 (4%)	7 (14%)
*PREPUTIAL GLAND	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)		1 (2%)
#UTERUS	(50)	(50)	(49)
ENDOMETRIAL STROMAL POLYP	9 (18%)	15 (30%)	9 (18%)
ENDOMETRIAL STROMAL SARCOMA		1 (2%)	
#CERVIX UTERI	(50)	(50)	(49)
ENDOMETRIAL STROMAL POLYP		1 (2%)	
#UTERUS/ENDOMETRIUM	(50)	(50)	(49)
ADENOCARCINOMA, NOS		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
CHROMOPHOBE CARCINOMA, INVASIVE	1 (2%)		
PINEALOMA		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*MUSCLE OF NECK	(50)	(50)	(50)
FOLLICULAR-CELL CARCINOMA, INVAS		1 (2%)	
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
FIBROSARCOMA, METASTATIC			1 (2%)
NEURILEMOMA, MALIGNANT		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC		1 (2%)	

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

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	7	8	9
MORIBUND SACRIFICE	5	6	9
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	36	34	30
DOSING ACCIDENT	2	2	1
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS			1
ANIMAL MISSING			
ANIMAL MISSEXED			
OTHER CASES			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	37	38	31
TOTAL PRIMARY TUMORS	65	63	51
TOTAL ANIMALS WITH BENIGN TUMORS	32	32	25
TOTAL BENIGN TUMORS	52	46	36
TOTAL ANIMALS WITH MALIGNANT TUMORS	12	13	13
TOTAL MALIGNANT TUMORS	12	16	15
TOTAL ANIMALS WITH SECONDARY TUMORS##	1	2	1
TOTAL SECONDARY TUMORS	1	2	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	1	
TOTAL UNCERTAIN TUMORS	1	1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE: VEHICLE CONTROL

ANIMAL NUMBER	0 0 1 1	0 0 1 2	0 0 1 3	0 0 1 4	0 0 1 5	0 0 1 6	0 0 1 7	0 0 1 8	0 0 1 9	0 0 2 0	0 0 2 1	0 0 2 2	0 0 2 3	0 0 2 4	0 0 2 5	0 0 2 6	0 0 2 7	0 0 2 8	0 0 2 9	0 0 3 0	0 0 3 1	0 0 3 2	0 0 3 3	0 0 3 4	0 0 3 5
WEEKS ON STUDY	0 0	0 4	0 4	0 4	0 4	0 4	0 3	0 4	0 4	0 4	0 4	0 4	0 4	0 4	0 4	0 4	0 4	0 4	0 4	0 4	0 4	0 4	0 4	0 4	0 4
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																									
KERATOACANTHOMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA				X																					
LIPOMA																									
HEMANGIOSARCOMA	X																								
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	-	-	+	+	+	-	+	-	-	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ACINAR-CELL ADENOMA									X					X	X		X				X		X	X	
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CHROMOPHOBE ADENOMA		X											X					X							
CHROMOPHOBE CARCINOMA			X																						
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																					X				
PHEOCHROMOCYTOMA		X																		X					
THYROID	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA																									
C-CELL ADENOMA																						X			
C-CELL CARCINOMA										X															
PARATHYROID	+	-	+	-	+	-	-	-	+	+	-	+	-	+	+	+	+	+	-	+	+	+	-	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+
FIBROADENOMA																									
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X		X	X				X	X	X	X	X	X	X	X	X	X	X	X	X
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS		X															X				X			
EPIDIDYMIS	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
SARCOMA, NOS																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
EAR	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
FIBROMA																									
BODY CAVITIES																									
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MESOTHELIOMA, NOS													X												
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
LEUKEMIA, MONONUCLEAR CELL										X															

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
M: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	085	095	095	095	095	095	095	095	095	095	095	095	095	095	086	095	095	095	065	066	095	037	085	095	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
SQUAMOUS CELL PAPILLOMA																										1
KERATOACANTHOMA								X																		1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
FIBROMA																			X							2
LIPOMA								X			X					X										3
HEMANGIOSARCOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•	+	•	•	50
ALVEOLAR/BRONCHIOLAR CARCINOMA																		X								1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	47
THYMUS	+	-	+	+	+	+	+	+	+	+	-	-	+	+	+	+	-	+	+	+	-	+	+	+	+	46
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ACINAR-CELL ADENOMA			X	X											X		X		X			X			X	14
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	48
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•	+	+	+	•	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	•	+	+	+	+	+	•	•	•	+	+	•	•	•	+	+	-	+	+	•	+	•	•	+	49
CHROMOPHOBE ADENOMA	X								X													X			X	7
CHROMOPHOBE CARCINOMA																X										2
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA																										1
PHEOCHROMOCYTOMA																										2
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	46
FOLLICULAR-CELL CARCINOMA											X															1
C-CELL ADENOMA								X		X												X				4
C-CELL CARCINOMA									X																	2
PARATHYROID	+	-	+	+	-	+	+	+	+	-	+	-	+	-	-	-	-	+	+	+	-	-	+	+	+	38
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ISLET-CELL ADENOMA			X																							1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	50M
FIBROADENOMA							X			X																2
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		X		X	X	42
PROSTATE	+	+	+	+	+	+	-	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	47
ADENOMA, NOS	X		X																							5
EPIDIDYMIS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
SARCOMA, NOS																	X									1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
EAR	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	50M
FIBROMA																		X								1
BODY CAVITIES																										
TUNICA VAGINALIS	+	•	•	+	+	•	+	•	+	•	+	•	•	+	•	•	+	•	+	+	+	•	•	+	+	50M
MESOTHELIOMA, NOS																						X				2
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
LEUKEMIA, MONONUCLEAR CELL								X																		2

• ANIMALS NECROPSIED

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE: LOW DOSE

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025	0026	0027	0028	0029	0030	0031	0032	0033	0034	0035
WEEKS ON STUDY	104	104	104	104	83	104	104	85	104	100	83	104	104	104	73	104	104	104	82	83	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																							X		
KERATOACANTHOMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA															X										
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	-	+	+	-	-	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	-	+	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE																									
HEMANGIOSARCOMA, METASTATIC															X										
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ACINAR-CELL ADENOMA	X																								X
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
ADENOCARCINOMA, NOS																									
LEIOMYOSARCOMA																									
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TUBULAR-CELL ADENOMA																					X				
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CHROMOPHOBE ADENOMA		X			X				X	X				X							X				
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																									
PHEOCHROMOCYTOMA		X		X										X					X						X
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																									
FOLLICULAR-CELL CARCINOMA																							X		
C-CELL ADENOMA		X				X																			
C-CELL CARCINOMA																									
PARATHYROID	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	-	-	+	+
PANCREATIC ISLETS	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																					X				X
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	N	+
FIBROADENOMA																									
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR	X	X	X	X		X	X		X			X		X	X	X	X		X	X		X	X	X	
PROSTATE	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																	X								
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA, NOS													X												
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MESOTHELIOMA, NOS																									
LYMPHOCYTIC LEUKEMIA																									
LEUKEMIA, MONONUCLEAR CELL										X												X	X		

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	0 2 4	0 2 7	0 2 8	0 2 9	0 3 0	0 3 1	0 3 2	0 3 3	0 3 4	0 3 5	0 3 6	0 3 7	0 3 8	0 3 9	0 4 0	0 4 1	0 4 2	0 4 3	0 4 4	0 4 5	0 4 6	0 4 7	0 4 8	0 4 9	0 5 0	TOTAL TISSUES TUMORS
WEEKS ON STUDY	1 0 5	1 0 5	1 0 5	1 0 5	1 0 2	1 0 5	1 0 4	1 0 5	1 0 5	1 0 5	1 0 5	1 0 2	1 0 5	1 0 5	1 0 3	1 0 5	1 0 5	1 0 5	1 0 4	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
SQUAMOUS CELL PAPILLOMA					X																	X	X			4
KERATOACANTHOMA	X																									1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
FIBROMA									X								X									2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRACHEA	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMANGIOSARCOMA																										1
LYMPH NODES	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	47
THYMUS	+	+	-	-	+	+	+	+	+	+	-	+	+	-	+	-	+	+	+	-	-	+	+	-	-	34
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE																						X				1
HEMANGIOSARCOMA, METASTATIC																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ACINAR-CELL ADENOMA								X			X											X				5
ESOPHAGUS	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SMALL INTESTINE	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	46
ADENOCARCINOMA, NOS							X																			1
LEIOMYOSARCOMA																				X						1
LARGE INTESTINE	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TUBULAR-CELL ADENOMA																										1
URINARY BLADDER	•	•	+	+	+	+	+	+	+	•	+	+	•	+	+	+	+	+	+	+	+	+	+	•	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•	+	+	50
CHROMOPHOBE ADENOMA				X																X				X		
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA					X																					1
PHEOCHROMOCYTOMA	X														X							X		X		3
THYROID	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL ADENOMA																		X								1
FOLLICULAR-CELL CARCINOMA																										1
C-CELL ADENOMA							X																			1
C-CELL CARCINOMA	X													X												3
PARATHYROID	•	-	•	•	-	•	+	-	+	-	+	-	+	+	+	-	-	•	+	-	+	-	-	+	-	34
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ISLET-CELL ADENOMA																				X						1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	M	+	+	+	+	+	+	+	+	M	+	M	M	+	+	+	+	+	M	+	+	+	+	M	M	50M
FIBROADENOMA														X												1
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	41
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	47
ADENOMA, NOS	X		X	X	X						X											X				7
PREPUTIAL/CLITORAL GLAND	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
CARCINOMA, NOS																										1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
MESOTHELIOMA, NOS																									X	1
LYMPHOCYTIC LEUKEMIA					X																					1
LEUKEMIA, MONONUCLEAR CELL											X					X				X						1

* ANIMALS NECROPSIED

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE: HIGH DOSE

ANIMAL NUMBER	0 0 1 1	0 0 1 2	0 0 1 3	0 0 1 4	0 0 1 5	0 0 1 6	0 0 1 7	0 0 1 8	0 0 1 9	0 0 2 0	0 0 2 1	0 0 2 2	0 0 2 3	0 0 2 4	0 0 2 5	0 0 2 6	0 0 2 7	0 0 2 8	0 0 2 9	0 0 3 0	0 0 3 1	0 0 3 2	0 0 3 3	0 0 3 4	0 0 3 5	0 0 3 6	0 0 3 7	0 0 3 8	0 0 3 9	0 0 4 0	0 0 4 1
WEEKS ON STUDY	0 4	1 4	1 4	1 4	1 2	1 4	2 2	3 1	4 1	4 1	4 1	4 1	4 1	4 1	5 1	5 1	5 1	6 1	6 1	6 1	6 1	6 1	6 1	6 1	6 1	6 1	6 1	6 1	6 1	6 1
INTEGUMENTARY SYSTEM																														
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																														
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
HIBERNOMA																				X										
NEUROFIBROMA																					X									
NEURILEMOMA, MALIGNANT																														
RESPIRATORY SYSTEM																														
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MIXED TUMOR, METASTATIC																														
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																														
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEURILEMOMA, INVASIVE																					X									
THYMUS	-	-	-	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	-	-	-	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																														
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																														
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MIXED TUMOR, MALIGNANT																					X									
NEURILEMOMA, INVASIVE																														
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MIXED TUMOR, METASTATIC																														
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ACINAR-CELL ADENOMA																														
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																														
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																														
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CHROMOPHOBE ADENOMA		X			X						X														X					
CHROMOPHOBE CARCINOMA																														
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA	X									X				X				X		X										
PHEOCHROMOCYTOMA, MALIGNANT						X																					X			
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA													X																	
FOLLICULAR-CELL CARCINOMA			X																											
C-CELL ADENOMA					X																									
C-CELL CARCINOMA											X		X																	
CYSTADENOMA, NOS																								X						
PARATHYROID	-	-	+	-	+	-	+	+	-	-	+	+	+	-	+	+	+	+	-	-	-	+	+	+	+	+	+	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																										X				
ISLET-CELL CARCINOMA																														
REPRODUCTIVE SYSTEM																														
MAMMARY GLAND	+	M	+	M	+	M	+	+	M	+	+	M	+	+	+	+	X	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROADENOMA																														
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X	X		X	X	X	X	X	X	X					X	X	X	X	X	X	X	X			
PROSTATE	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS		X	X																	X						X				
NERVOUS SYSTEM																														
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GRANULAR-CELL TUMOR, NOS					X																									
SPECIAL SENSE ORGANS																														
ZYMBAL GLAND	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
SEBACEOUS ADENOCARCINOMA							X																							
BODY CAVITIES																														
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MESOTHELIOMA, NOS																				X										
ALL OTHER SYSTEMS																														
MULTIPLE ORGANS NOS	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
LEUKEMIA, MONONUCLEAR CELL						X				X	X							X												
TAIL																														
SQUAMOUS CELL PAPILLOMA																														

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	106	106	106	092	105	105	105	105	105	105	105	105	105	092	105	105	105	105	105	105	105	105	105	100	105	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
SQUAMOUS CELL PAPILLOMA								X																		1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
HIBERNOMA																								X		1
NEUROFIBROMA																										1
NEURILEMOMA, MALIGNANT																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MIXED TUMOR, METASTATIC				X																						1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
NEURILEMOMA, INVASIVE																										1
THYMUS	+	●	+	+	+	-	+	+	●	●	+	-	●	+	●	+	+	-	-	●	●	●	+	-	●	37
CIRCULATORY SYSTEM																										
HEART	+	●	+	+	●	+	+	+	+	+	+	+	●	●	+	+	●	+	+	+	+	+	+	●	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MIXED TUMOR, MALIGNANT				X																						1
NEURILEMOMA, INVASIVE																										1
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MIXED TUMOR, METASTATIC				X																						1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ACINAR-CELL ADENOMA												X										X				2
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	47
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CHROMOPHOBE ADENOMA					X		X						X													7
CHROMOPHOBE CARCINOMA																								X		1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA		X			X			X					X			X			X					X		12
PHEOCHROMOCYTOMA, MALIGNANT																										2
THYROID	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL ADENOMA																								X		2
FOLLICULAR-CELL CARCINOMA							X															X				3
C-CELL ADENOMA																										1
C-CELL CARCINOMA											X															3
CYSTADENOMA, NOS																										1
PARATHYROID	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	38
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL ADENOMA																X						X				2
ISLET-CELL CARCINOMA																										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	●	●	+	●	N	●	●	N	●	+	●	+	N	+	●	+	+	●	●	●	+	+	●	+	50*
FIBROADENOMA															X										X	3
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR	X	X	X	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	43
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOMA, NOS																					X					5
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GRANULAR-CELL TUMOR, NOS																										1
SPECIAL SENSE ORGANS																										
ZYMBAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
SEBACEOUS ADENOCARCINOMA																										1
BODY CAVITIES																										
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
MESOTHELIOMA, NOS																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
LEUKEMIA, MONONUCLEAR CELL											X											X				6
TAIL																										
SQUAMOUS CELL PAPILLOMA			X																							1

* ANIMALS NECROPSIED

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE: VEHICLE CONTROL

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0110	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	0041	0041	0047	0041	0041	0821	0511	0041	0041	0041	0041	0041	0041	0041	0041	0041	0041	0041	0991	0831	0991	0041	0041	0991	0041
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA	X																								
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CYSTADENOMA, NOS											X														
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ACINAR-CELL ADENOMA			X																						
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CHROMOPHOBE ADENOMA		X							X	X	X		X	X		X		X				X	X	X	X
CHROMOPHOBE CARCINOMA						X																			
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA												X													
PHEOCHROMOCYTOMA														X											
THYROID	-	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA																		X							X
C-CELL ADENOMA																									
C-CELL CARCINOMA																									
CYSTADENOMA, NOS																									
PARATHYROID	+	-	+	-	+	-	+	+	+	+	-	-	+	+	-	+	-	+	-	-	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
ADENOCARCINOMA, NOS																							X		
FIBROADENOMA		X				X							X			X		X					X	X	
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																									
UTERUS	+	+	•	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP					X												X						X		
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CHROMOPHOBE CARCINOMA, INVASIVE						X																			
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
LEUKEMIA,NOS																			X						
LYMPHOCYTIC LEUKEMIA																									
LEUKEMIA,MONONUCLEAR CELL				X													X								

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER / WEEKS ON STUDY	0261 011	0274 094	0288 095	0299 095	0300 100	0311 100	0322 097	0331 095	0344 095	0355 095	0366 095	0377 095	0388 095	0399 095	0401 095	0411 095	0422 095	0433 092	0444 095	0455 095	0466 100	0477 095	0488 095	0491 095	0501 095	TOTAL TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
FIBROMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRACHEA	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	47
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE				X																						1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CYSTADENOMA, NOS																										1
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ACINAR-CELL ADENOMA														X												2
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CHROMOPHOBE ADENOMA	X			X		X				X				X		X										18
CHROMOPHOBE CARCINOMA																										1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA																										1
PHEOCHROMOCYTOMA								X																		2
THYROID	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
FOLLICULAR-CELL CARCINOMA																						X				1
C-CELL ADENOMA	X									X										X						5
C-CELL CARCINOMA																									X	1
CYSTADENOMA, NOS				X																						1
PARATHYROID	+	-	+	+	+	+	+	-	-	+	-	+	-	+	-	+	+	+	+	+	+	+	+	-	+	34
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
ADENOCARCINOMA, NOS																										1
FIBROADENOMA	X								X	X															X	11
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
ADENOMA, NOS							X																			1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOMETRIAL STROMAL POLYP				X								X				X				X		X	X			9
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CHROMOPHOBE CARCINOMA, INVASIVE																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
LEUKEMIA, NOS		X																								2
LYMPHOCYTIC LEUKEMIA					X																					1
LEUKEMIA, MONONUCLEAR CELL				X											X							X				5

M ANIMALS NECROPSIED

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE: LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	104	104	104	104	104	104	042	043	043	043	043	043	095	043	053	055	085	070	043	043	043	043	053	043	097
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEURILEMOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+
THYMUS	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	-	+	+	-	+	+	+	+	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CHROMOPHOBE ADENOMA		X		X				X	X	X				X	X	X	X			X		X			
CHROMOPHOBE CARCINOMA	X																								
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA											X														
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA								X	X		X														
C-CELL ADENOMA					X								X												
C-CELL CARCINOMA																									
CYSTADENOMA, NOS																X									
PARATHYROID	+	+	+	+	+	+	+	-	-	-	+	+	+	+	-	+	-	-	+	+	-	+	-	-	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+
ADENOCARCINOMA, NOS																	X								X
FIBROADENOMA																									
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS				X	X											X			X	X		X			
ENDOMETRIAL STROMAL POLYP																									
ENDOMETRIAL STROMAL SARCOMA														X											
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOMA																									
PINEALOMA																									
MUSCULOSKELETAL SYSTEM																									
MUSCLE	M	M	M	M	M	M	M	M	N	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
FOLLICULAR-CELL CARCINOMA, INVASI									X																
BODY CAVITIES																									
MEDIASTINUM	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
NEURILEMOMA, MALIGNANT							X																		
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
ADENOCARCINOMA, NOS, METASTATIC									X																X
LEUKEMIA, MONONUCLEAR CELL																									

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	0262	0277	0288	0299	0310	0311	0312	0313	0314	0315	0316	0317	0318	0319	0320	0321	0322	0323	0324	0325	0326	0327	0328	0329	0330	TOTAL
WEEKS ON STUDY	1004	1001	1005	1005	1005	1005	1005	1001	1004	0882	0975	1005	1005	0998	0998	1005	1005	1005	0974	1005	1005	1005	1005	1005	1005	0992	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
NEURILEMOMA																											1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
TRACHEA	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
THYMUS	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	41
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	49
CHROMOPHOBE ADENOMA			X	X	X				X								X			X		X		X	X	20
CHROMOPHOBE CARCINOMA																											1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA						X																					2
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL CARCINOMA																											3
C-CELL ADENOMA																								X			3
C-CELL CARCINOMA																	X					X	X				3
CYSTADENOMA, NOS																											1
PARATHYROID	+	-	+	+	+	+	+	-	+	-	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	36
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
ADENOCARCINOMA, NOS																											1
FIBROADENOMA					X																						2
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS													X														1
ENDOMETRIAL STROMAL POLYP	X									X	X	X					X	X	X	X	X			X			16
ENDOMETRIAL STROMAL SARCOMA																											1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOMA						X																					1
PINEALOMA									X																		1
MUSCULOSKELETAL SYSTEM																										
MUSCLE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
FOLLICULAR-CELL CARCINOMA, INVASI																											1
BODY CAVITIES																										
MEDIASTINUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
NEURILEMOMA, MALIGNANT																											1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
ADENOCARCINOMA, NOS, METASTATIC													X														1
LEUKEMIA,MONONUCLEAR CELL										X				X											X		5

M ANIMALS NECROPSIED

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE: HIGH DOSE

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0110	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	1104	1104	1104	0856	1104	1104	1104	1104	1104	1104	0011	0354	0774	1104	1109	0092	0966	1104	0969	0921	1041	1041	1041	0858	0959
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIPOMA																								X	
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROSARCOMA																				X					
TRACHEA	-	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROSARCOMA, METASTATIC																				X					
THYMUS	+	+	+	+	+	+	+	+	-	+	-	-	+	+	+	+	-	-	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ACINAR-CELL ADENOMA																									
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CHROMOPHOBE ADENOMA	X	X		X											X				X					X	
CHROMOPHOBE CARCINOMA																									
ADRENAL	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA																									X
THYROID	-	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-CELL ADENOMA							X																		
CYSTADENOMA, NOS																									
PARATHYROID	-	+	-	+	+	-	+	-	-	+	-	+	+	-	+	+	-	-	-	-	-	+	+	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																									
FIBROADENOMA				X														X							
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS	X																								
UTERUS	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP						X		X	X														X		X
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BODY CAVITIES																									
MEDIASTINUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
FIBROSARCOMA, METASTATIC																				X					
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
LEUKEMIA, NOS																X	X								
LEUKEMIA, MONONUCLEAR CELL	X																		X						

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	0262	0271	0281	0291	0310	0311	0312	0331	0345	0353	0362	0375	0389	0399	0401	0411	0422	0435	0443	0455	0461	0477	0481	0491	0501	TOTAL
WEEKS ON STUDY	1051	0721	1151	0151	0151	0151	0151	0431	0951	0262	0665	0961	0991	0911	0051	0551	0561	0451	0551	0451	0551	0551	0991	0151	0172	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
LIPOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FIBROSARCOMA																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	47
FIBROSARCOMA, METASTATIC																										1
THYMUS	-	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	-	+	-	+	+	+	+	40
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ACINAR-CELL ADENOMA																					X					1
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LARGE INTESTINE	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CHROMOPHOBE ADENOMA				X					X				X					X						X		11
CHROMOPHOBE CARCINOMA	X	X				X																				3
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PHEOCHROMOCYTOMA																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
C-CELL ADENOMA																					X					2
CYSTADENOMA, NOS							X		X				X													3
PARATHYROID	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	-	+	-	34
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
ADENOCARCINOMA, NOS	X																							X		2
FIBROADENOMA		X				X	X						X	X												7
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
ADENOMA, NOS																										1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOMETRIAL STROMAL POLYP	X															X			X			X				3
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BODY CAVITIES																										
MEDIASTINUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
FIBROSARCOMA, METASTATIC																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	X	N	N	N	N	N	N	N	N	N	N	50M
LEUKEMIA, NOS																										1
LEUKEMIA, MONONUCLEAR CELL				X							X			X										X		5

* ANIMALS NECROPSIED

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF TRIS(2-ETHYLHEXYL)PHOSPHATE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(49)
BASAL-CELL TUMOR	1 (2%)		
SARCOMA, NOS	1 (2%)		
FIBROMA	1 (2%)		
FIBROSARCOMA	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(49)
SARCOMA, NOS	2 (4%)	4 (8%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(49)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)	1 (2%)	2 (4%)
ALVEOLAR/BRONCHIOLAR ADENOMA	5 (10%)	2 (4%)	6 (12%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	2 (4%)	1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(49)
MALIGNANT LYMPHOMA, NOS	6 (12%)	2 (4%)	4 (8%)
#LIVER	(50)	(50)	(49)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
CIRCULATORY SYSTEM			
#SPLEEN	(50)	(50)	(48)
HEMANGIOSARCOMA	3 (6%)		1 (2%)
#LIVER	(50)	(50)	(49)
HEMANGIOSARCOMA	3 (6%)		
#URINARY BLADDER	(48)	(50)	(47)
HEMANGIOSARCOMA	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(49)
HEPATOCELLULAR ADENOMA	7 (14%)	10 (20%)	6 (12%)
HEPATOCELLULAR CARCINOMA	9 (18%)	12 (24%)	12 (24%)
#STOMACH	(50)	(49)	(47)
SQUAMOUS CELL PAPILLOMA	1 (2%)		
#FORESTOMACH	(50)	(49)	(47)
SQUAMOUS CELL PAPILLOMA			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(44)	(47)	(43)
ADENOMA, NOS	1 (2%)		
#ADRENAL	(48)	(48)	(45)
CORTICAL ADENOMA	1 (2%)		
PHEOCHROMOCYTOMA	1 (2%)		
#THYROID	(49)	(48)	(47)
FOLLICULAR-CELL ADENOMA			1 (2%)
#PANCREATIC ISLETS	(50)	(50)	(48)
ISLET-CELL ADENOMA			1 (2%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
#TESTIS	(50)	(50)	(48)
INTERSTITIAL-CELL TUMOR	1 (2%)	3 (6%)	1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(49)
ADENOMA, NOS	2 (4%)	1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*THORAX	(50)	(50)	(49)
SARCOMA, NOS		1 (2%)	
*MESENTERY	(50)	(50)	(49)
SARCOMA, NOS	1 (2%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(49)
SARCOMA, NOS, METASTATIC	1 (2%)	1 (2%)	
TAIL			
FIBROMA			1
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	16	17	11
MORIBUND SACRIFICE	1	5	
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	32	27	37
DOSING ACCIDENT	1	1	1
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS			
ANIMAL MISSING			1
ANIMAL MISSEXED			
OTHER CASES			

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	33	30	25
TOTAL PRIMARY TUMORS	51	36	35
TOTAL ANIMALS WITH BENIGN TUMORS	16	14	12
TOTAL BENIGN TUMORS	21	16	17
TOTAL ANIMALS WITH MALIGNANT TUMORS	24	19	15
TOTAL MALIGNANT TUMORS	30	20	18
TOTAL ANIMALS WITH SECONDARY TUMORS##	2	2	2
TOTAL SECONDARY TUMORS	2	2	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(49)	(50)	(50)
PAPILLOMA, NOS			1 (2%)
SARCOMA, NOS	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(48)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)	1 (2%)	3 (6%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(49)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	13 (27%)	7 (14%)	3 (6%)
#SPLEEN	(48)	(49)	(50)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
#LIVER	(48)	(50)	(50)
MALIGNANT LYMPHOMA, NOS			1 (2%)
#SMALL INTESTINE	(42)	(47)	(46)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
#DUODENUM	(42)	(47)	(46)
MALIGNANT LYMPHOMA, NOS			2 (4%)
#JEJUNUM	(42)	(47)	(46)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
#THYMUS	(36)	(41)	(41)
MALIGNANT LYMPHOMA, NOS	1 (3%)		
CIRCULATORY SYSTEM			
#SPLEEN	(48)	(49)	(50)
HEMANGIOSARCOMA	2 (4%)		
#URINARY BLADDER	(46)	(47)	(46)
HEMANGIOSARCOMA	1 (2%)		
#UTERUS	(49)	(50)	(50)
HEMANGIOSARCOMA			1 (2%)
DIGESTIVE SYSTEM			
*TONGUE	(49)	(50)	(50)
PAPILLOMA, NOS		1 (2%)	
#LIVER	(48)	(50)	(50)
BILE DUCT CARCINOMA			1 (2%)
HEPATOCELLULAR ADENOMA	2 (4%)	4 (8%)	3 (6%)
HEPATOCELLULAR CARCINOMA		4 (8%)	7 (14%)
URINARY SYSTEM			
NONE			

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(41)	(47)	(47)
ADENOMA, NOS	6 (15%)	8 (17%)	2 (4%)
#ADRENAL	(44)	(46)	(47)
CORTICAL ADENOMA		1 (2%)	
PHEOCHROMOCYTOMA	1 (2%)		
#THYROID	(44)	(47)	(46)
FOLLICULAR-CELL ADENOMA		2 (4%)	
#PANCREATIC ISLETS	(47)	(50)	(49)
ISLET-CELL ADENOMA			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(49)	(50)	(50)
ADENOCARCINOMA, NOS			1 (2%)
#UTERUS	(49)	(50)	(50)
LEIOMYOSARCOMA		1 (2%)	
ENDOMETRIAL STROMAL POLYP	1 (2%)		
#OVARY	(49)	(49)	(47)
PAPILLARY CYSTADENOMA, NOS			1 (2%)
TERATOMA, NOS	1 (2%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(49)	(50)	(50)
ADENOMA, NOS		1 (2%)	2 (4%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(49)	(50)	(50)
BILE DUCT CARCINOMA, METASTATIC			1 (2%)
ALVEOLAR/BRONCHIOLAR CA, METASTA		1 (2%)	

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

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	12	7	8
MORIBUND SACRIFICE	3		2
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	32	42	40
DOSING ACCIDENT	2		
ACCIDENTALLY KILLED, NDA	1		
ACCIDENTALLY KILLED, NOS		1	
ANIMAL MISSING			
ANIMAL MISSEXED			
OTHER CASES			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	24	25	25
TOTAL PRIMARY TUMORS	31	34	30
TOTAL ANIMALS WITH BENIGN TUMORS	9	15	12
TOTAL BENIGN TUMORS	12	18	13
TOTAL ANIMALS WITH MALIGNANT TUMORS	17	15	15
TOTAL MALIGNANT TUMORS	18	16	17
TOTAL ANIMALS WITH SECONDARY TUMORS##		1	1
TOTAL SECONDARY TUMORS		1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1		
TOTAL UNCERTAIN TUMORS	1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE: VEHICLE CONTROL

ANIMAL NUMBER	0011	0021	0031	0041	0051	0061	0071	0081	0091	0101	0111	0121	0131	0141	0151	0161	0171	0181	0191	0201	0211	0221	0231	0241	0251
WEEKS ON STUDY	1 0 4	1 0 4	1 0 6	1 0 9	1 1 4	1 3 7	1 4 5	1 4 6	1 4 8	1 4 8	1 4 9	1 9 9	1 9 2	1 4 4	1 4 4	1 4 4	1 5 5	1 5 5	1 5 5	1 5 3	1 5 5	1 5 1	1 5 1	1 5 1	1 5 5
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BASAL-CELL TUMOR													X												
SARCOMA, NOS																		X							
FIBROMA													X												
FIBROSARCOMA		X																							
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA										X															
ALVEOLAR/BRONCHIOLAR ADENOMA					X		X													X			X		
ALVEOLAR/BRONCHIOLAR CARCINOMA																			X						
TRACHEA	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	-	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	-	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA														X					X						
LYMPH NODES	-	+	-	-	+	+	+	+	+	-	+	+	-	-	-	+	+	-	-	+	+	+	-	+	-
THYMUS	+	+	+	-	+	-	+	+	+	-	-	-	+	+	+	+	+	+	+	-	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA	X	X																					X		
HEPATOCELLULAR CARCINOMA					X					X	X							X	X						
HEMANGIOSARCOMA			X																	X					
MALIGNANT LYMPHOMA, NOS																								X	
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	M	+	M	M	+	M	+	+	M	+	+	+	+	+	+	+	+	M	+	M	M	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																					X				
SMALL INTESTINE	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
HEMANGIOSARCOMA											X														
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	-	+	+	+	+	+	-	+	+	-	+	+	+	+	+	-	-	+	+	+	+	+
ADENOMA, NOS																X									
ADRENAL	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA	X																								
PHEOCHROMOCYTOMA										X															
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PARATHYROID	-	-	+	-	+	+	-	+	+	-	+	+	+	+	+	-	-	-	-	-	-	+	+	-	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR																									
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
ADENOMA, NOS										X															
BODY CAVITIES																									
MESENTERY	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
SARCOMA, NOS					X																				
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
SARCOMA, NOS, METASTATIC																									
MALIGNANT LYMPHOMA, NOS				X																X					

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
M: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	01 22 46	01 22 47	01 22 48	01 22 49	01 23 10	01 23 11	01 23 12	01 23 13	01 23 14	01 23 15	01 23 16	01 23 17	01 23 18	01 23 19	01 24 00	01 24 01	01 24 02	01 24 03	01 24 04	01 24 05	01 24 06	01 24 07	01 24 08	01 24 09	01 24 10	TOTAL TISSUES TUMORS
WEEKS ON STUDY	01 51	01 51	01 51	01 51	01 51	01 51	01 51	01 51	01 51	01 51	01 51	01 51	01 51	01 51	01 51	01 51	01 52	01 52	01 52	01 52	01 52	01 52	01 52	01 52	01 52	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
BASAL-CELL TUMOR																										1
SARCOMA, NOS																										1
FIBROMA																										1
FIBROSARCOMA																										1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
SARCOMA, NOS							X							X												2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA, METASTA																										1
ALVEOLAR/BRONCHIOLAR ADENOMA			X																			X				5
ALVEOLAR/BRONCHIOLAR CARCINOMA																	X									2
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	48
HEMATOPOIETIC SYSTEM																										
BONE MARROW	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	41
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOSARCOMA					X																					1
LYMPH NODES	+	-	-	+	+	+	+	-	-	+	+	+	+	-	-	+	+	+	+	-	+	+	+	+	+	32
THYMUS	+	+	-	+	+	+	+	-	+	+	+	-	-	-	+	-	+	+	+	+	+	+	+	+	+	38
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA		X	X		X																		X			7
HEPATOCELLULAR CARCINOMA	X	X															X		X							9
HEMANGIOSARCOMA																		X								3
MALIGNANT LYMPHOMA, NOS																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	N	+	+	+	+	+	N	+	+	N	N	+	+	+	+	N	+	N	+	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA																										1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	-	+	+	45
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMANGIOSARCOMA																										1
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	44
ADENOMA, NOS																										1
ADRENAL	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
CORTICAL ADENOMA																										1
PHEOCHROMOCYTOMA																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	49
PARATHYROID	-	+	-	-	-	+	+	-	+	+	+	+	+	-	-	-	+	+	+	+	-	-	-	-	+	25
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	50M
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR																		X								1
PROSTATE	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
ADENOMA, NOS				X																						2
BODY CAVITIES																										
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
SARCOMA, NOS																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
SARCOMA, NOS, METASTATIC												X					X									1
MALIGNANT LYMPHOMA, NOS																	X	X	X							5

M ANIMALS NECROPSIED

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE: LOW DOSE

ANIMAL NUMBER	001	001	001	001	001	001	001	001	001	001	001	001	001	001	001	001	001	001	001	001	001	001	001	001	001
	112	123	134	145	156	167	178	189	190	101	112	123	134	145	156	167	178	189	201	212	223	234	245	256	267
WEEKS ON STUDY	104	104	101	098	104	104	091	104	104	104	104	105	100	099	097	096	105	105	104	104	103	104	105	098	105
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS							X						X												
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA														X											
ALVEOLAR/BRONCHIOLAR ADENOMA																									
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	-	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	-	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	-	+
THYMUS	+	+	+	-	+	+	-	+	+	+	-	+	-	-	+	-	+	-	-	+	+	-	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA							X						X				X					X	X		
HEPATOCELLULAR CARCINOMA			X		X									X			X	X		X				X	X
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	M	+	M	M	+	+	+	+	M	M	M	M	+	+	M	M	+	+	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	-	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
THYROID	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PARATHYROID	+	+	+	-	-	-	-	-	-	-	-	+	+	+	-	+	-	+	-	-	+	-	+	-	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	+	N	N	N	N	N	N	N	N	N	N	N	+	N	+	N	N	N	N	N	+	N	
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR																									
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																					X				
BODY CAVITIES																									
PLEURA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SARCOMA, NOS				X																					
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SARCOMA, NOS, METASTATIC										X															
MALIGNANT LYMPHOMA, NOS																									

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	0212	0217	0218	0219	0310	0311	0312	0313	0314	0315	0316	0317	0318	0319	0320	0411	0412	0413	0414	0415	0416	0417	0418	0419	0420	TOTAL
WEEKS ON STUDY	081	210	117	015	026	086	105	095	095	095	095	095	099	095	095	095	095	091	131	041	095	095	095	094	095	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
SARCOMA, NOS	X																							X		4
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA, METASTA																										1
ALVEOLAR/BRONCHIOLAR ADENOMA				X					X																	2
ALVEOLAR/BRONCHIOLAR CARCINOMA											X															1
TRACHEA	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
HEMATOPOIETIC SYSTEM																										
BONE MARROW	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	45
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	-	-	+	-	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	40
THYMUS	-	-	+	+	-	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	-	-	+	+	34
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA												X		X							X	X				10
HEPATOCELLULAR CARCINOMA								X	X								X	X					X			12
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	-	-	+	-	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	42
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ADRENAL	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
PARATHYROID	-	+	-	+	-	+	+	+	+	+	+	-	+	-	-	-	+	-	+	+	-	+	+	-	+	26
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	+	M	M	M	M	M	M	M	50M
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR												X	X										X			3
PROSTATE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	47
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
ADENOMA, NOS																										1
BODY CAVITIES																										
PLEURA	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
SARCOMA, NOS																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	M	M	M	M	+M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
SARCOMA, NOS, METASTATIC																								X		1
MALIGNANT LYMPHOMA, NOS																			X							2

M ANIMALS NECROPSIED

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE: HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	098	104	106	106	104	104	106	104	106	104	104	105	092	105	105	105	091	105	105	105	105	072	105	105	105
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA						X													X						
ALVEOLAR/BRONCHIOLAR ADENOMA	X			X				X			X														X
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	-	+	-	-	+	-
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA																	X								
LYMPH NODES	+	+	-	+	-	+	-	+	+	+	+	+	+	+	-	+	+	+	-	-	-	+	-	-	+
THYMUS	-	+	+	+	-	-	+	+	-	+	-	+	-	+	+	+	+	+	-	+	-	+	-	+	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA	X							X															X		
HEPATOCELLULAR CARCINOMA		X				X	X			X		X					X		X			X			X
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	M	+	M	M	+	+	+	+	M	+	M	+	M	+	+	+	M	+	+	+	+	M	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																								X	
SMALL INTESTINE	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+
LARGE INTESTINE	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
FOLLICULAR-CELL ADENOMA*																									
PARATHYROID	-	-	+	+	+	+	+	+	+	-	+	+	-	-	+	+	-	+	-	+	-	-	-	-	-
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
ISLET-CELL ADENOMA				X																					
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR																							X		
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
MALIGNANT LYMPHOMA, NOS													X				X		X						
TAIL																									
FIBROMA																									

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	103	105	105	105	105	105	047	012	105	105	105	101	052	105	011	105	105	105	105	056	103	101	105	
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
HEPATOCELLULAR CARCINOMA, METASTA																										2
ALVEOLAR/BRONCHIOLAR ADENOMA		X																								6
ALVEOLAR/BRONCHIOLAR CARCINOMA														X												1
TRACHEA	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	M	+	+	45
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	42
SPLEEN	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
HEMANGIOSARCOMA																										1
LYMPH NODES	-	-	+	+	-	-	+	+	-	-	-	-	-	+	+	-	+	+	+	+	+	-	M	-	+	28
THYMUS	+	+	-	+	-	-	+	+	-	+	-	-	-	-	-	-	-	-	-	+	-	+	M	+	-	24
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	M	+	+	48
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
HEPATOCELLULAR ADENOMA						X															X					6
HEPATOCELLULAR CARCINOMA			X														X								X	12
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	N	+	M	+	+		49M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+		48
ESOPHAGUS	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	M	+	+		46
STOMACH	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	M	+	+		47
SQUAMOUS CELL PAPILLOMA																										1
SMALL INTESTINE	+	+	+	+	+	+	+	+	-	+	+	+	+	-	-	+	+	+	+	+	+	M	+	+		42
LARGE INTESTINE	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	M	+	+		45
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+		49
URINARY BLADDER	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+		47
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	M	+	-		43
ADRENAL	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+		45
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	M	+	+		47
FOLLICULAR-CELL ADENOMA																		X								1
PARATHYROID	-	-	-	+	+	-	+	+	-	+	-	+	-	-	+	-	-	+	-	+	+	M	-	-		24
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+		48
ISLET-CELL ADENOMA																										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	M	N	N	49M
TESTIS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+		48
INTERSTITIAL-CELL TUMOR																										1
PROSTATE	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+		48
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+		49
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	M	N	N	49M
MALIGNANT LYMPHOMA, NOS			X																							4
TAIL																							M			
FIBROMA																						X				1

M ANIMALS NECROPSIED

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE: VEHICLE CONTROL

ANIMAL NUMBER	0 0 1	0 0 2	0 0 3	0 0 4	0 0 5	0 0 6	0 0 7	0 0 8	0 0 9	0 1 0	0 1 1	0 1 2	0 1 3	0 1 4	0 1 5	0 1 6	0 1 7	0 1 8	0 1 9	0 2 0	0 2 1	0 2 2	0 2 3	0 2 4
WEEKS ON STUDY	0 4	0 4	0 4	0 8	0 8	0 8	0	1	1	0 2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	1	1	1	3	3	4	3	4	0	4	4	4	5	5	5	5	5	7	8	9	1	1	2
	6	1	1	1	1	1	1	6	1	4	1	1	1	1	1	1	1	1	1	1	1	9	1	1
INTEGUMENTARY SYSTEM																								
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+
SARCOMA, NOS										X														
RESPIRATORY SYSTEM																								
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	B	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA			X											X										
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	B	-	+	+	+
HEMATOPOIETIC SYSTEM																								
BONE MARROW	-	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	B	-	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B	-	+	+	+
HEMANGIOSARCOMA						X				X																
LYMPH NODES	-	-	+	+	+	-	+	+	+	-	+	+	+	+	+	-	+	+	+	+	B	+	-	+	+	
THYMUS	+	-	-	-	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	B	-	-	+	+	
MALIGNANT LYMPHOMA, NOS																				X						
CIRCULATORY SYSTEM																								
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+	
DIGESTIVE SYSTEM																								
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+	
LIVER	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+	
HEPATOCELLULAR ADENOMA			X			X																				
BILE DUCT	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+	
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	N	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	B	N	+	+	+	
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+	
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	B	+	+	+	+	
STOMACH	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	B	+	+	+	+	
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	B	-	+	+	+	
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	B	-	+	+	+	
URINARY SYSTEM																								
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+	
URINARY BLADDER	+	+	+	+	-	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+	
HEMANGIOSARCOMA																										
ENDOCRINE SYSTEM																								
PITUITARY	+	+	+	+	+	+	+	-	+	+	+	X	+	X	+	+	+	-	-	+	B	+	+	+	+	X
ADENOMA, NOS																										
ADRENAL	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	B	+	+	+	+	
PHEOCHROMOCYTOMA																										
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	B	+	+	+	
PARATHYROID	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	-	-	+	B	-	+	+	
REPRODUCTIVE SYSTEM																								
MAMMARY GLAND	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+
UTERUS	+	+	‡	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+
ENDOMETRIAL STROMAL POLYP																										
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+
TERATOMA, NOS																										
NERVOUS SYSTEM																								
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B	+	+	+	+
ALL OTHER SYSTEMS																								
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	B	N	N	N	N
MALIGNANT LYMPHOMA, NOS	X	X	X											X				X					X		X	

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0212	0227	0238	0249	0330	0341	0352	0363	0374	0385	0396	0407	0418	0429	0430	0441	0452	0463	0474	0485	0496	0507	0518	0529	0530	TOTAL TISSUES TUMORS
WEEKS ON STUDY	1 0 5	1 2 5	1 0 5	1 0 5	1 0 5	1 0 1	1 0 5	1 0 5	1 0 5	1 0 2	1 0 5	1 0 2	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 2	1 0 5	1 0 2	1 0 5	1 0 5	1 0 5	1 0 5	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49M
SARCOMA, NOS																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ALVEOLAR/BRONCHIOLAR ADENOMA																										2
TRACHEA	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	-	+	-	+	+	-	-	+	-	+	+	+	+	-	+	+	+	+	-	38
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMANGIOSARCOMA																										2
LYMPH NODES	+	-	+	+	+	+	+	+	-	-	+	-	+	+	+	+	+	+	-	+	+	-	+	+	+	37
THYMUS	-	-	+	-	+	+	+	+	+	+	+	-	+	-	+	-	+	+	+	+	+	+	+	+	+	36
MALIGNANT LYMPHOMA, NOS																										1
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	-	-	-	+	+	+	+	+	44
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEPATOCELLULAR ADENOMA																										2
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
GALLBLADDER & COMMON BILE DUCT	+	M	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	M	M	+	+	+	+	+	+	49M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	47
ESOPHAGUS	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	45
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	-	+	-	+	+	+	+	42
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	44
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
HEMANGIOSARCOMA				X																						1
ENDOCRINE SYSTEM																										
PITUITARY	-	+	+	+	+	+	+	+	-	+	-	+	-	+	-	+	+	+	+	+	+	+	+	+	+	41
ADENOMA, NOS										X										X				X		5
ADRENAL	+	+	+	+	+	+	+	+	+	+	-	+	-	+	-	+	+	+	+	+	+	-	+	+	+	44
PHEOCHROMOCYTOMA										X																1
THYROID	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	44
PARATHYROID	+	-	-	+	+	+	+	-	-	-	+	-	-	-	+	-	+	-	-	-	-	-	-	-	-	26
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	M	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	49M
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOMETRIAL STROMAL POLYP								X																		1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
TERATOMA, NOS		X																								1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49M
MALIGNANT LYMPHOMA, NOS					X			X				X					X		X			X				13

M ANIMALS NECROPSIED

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE: LOW DOSE

ANIMAL NUMBER	0 0 1	0 0 2	0 0 3	0 0 4	0 0 5	0 0 6	0 0 7	0 0 8	0 0 9	0 1 0	0 1 1	0 1 2	0 1 3	0 1 4	0 1 5	0 1 6	0 1 7	0 1 8	0 1 9	0 2 0	0 2 1	0 2 2	0 2 3	0 2 4	0 2 5
WEEKS ON STUDY	0 8 0	1 0 4	1 0 4	1 0 4	1 2 3	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 5	1 0 5	1 0 5	1 1 1	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 6 9
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA	X																								
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	-	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	-	-	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MALIGNANT LYMPHOMA, NOS																									
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	-	+	-
THYMUS	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
ORAL CAVITY	N	N	N	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	M
PAPILLOMA, NOS										X															
SALIVARY GLAND	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA											X							X				X			
HEPATOCELLULAR CARCINOMA										X															
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MALIGNANT LYMPHOMA, NOS																						X			
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS									X	X		X								X	X				
ADRENAL	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
CORTICAL ADENOMA																									
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
FOLLICULAR-CELL ADENOMA																									
PARATHYROID	+	+	+	+	-	+	-	-	-	-	-	-	+	+	-	+	-	+	-	+	+	-	-	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	+
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LEIOMYOSARCOMA																									
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	M
ADENOMA, NOS											X														
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	M	M	N	N	N	N	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	M
ALVEOLAR/BRONCHIOLAR CA, METASTAT	X													X											
MALIGNANT LYMPHOMA, NOS																									

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	0226	0227	0228	0229	0230	0231	0232	0233	0234	0235	0236	0237	0238	0239	0240	0241	0242	0243	0244	0245	0246	0247	0248	0249	0250	TOTAL
WEEKS ON STUDY	105	105	105	091	105	105	105	105	089	088	105	105	105	105	105	105	105	105	105	097	105	105	105	105	105	TISSUES TUMORS
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA																										1
ALVEOLAR/BRONCHIOLAR CARCINOMA																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	43
SPLEEN	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	X	+	+	+	+	+	+	49
MALIGNANT LYMPHOMA, NOS																										1
LYMPH NODES	+	+	-	-	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	42
THYMUS	+	+	+	+	+	-	+	+	-	+	-	+	+	-	+	+	+	-	+	+	+	-	+	+	+	41
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
ORAL CAVITY	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
PAPILLOMA, NOS																										1
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA			X										X		X				X							4
HEPATOCELLULAR CARCINOMA																										4
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	50N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	47
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
MALIGNANT LYMPHOMA, NOS																		X								2
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
PITUITARY	-	+	+	+	+	+	+	+	X	+	+	X	+	+	+	+	X	+	+	+	+	-	+	+	+	47
ADENOMA, NOS																										8
ADRENAL	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	46
CORTICAL ADENOMA	X																									1
THYROID	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	47
FOLLICULAR-CELL ADENOMA																		X			X					2
PARATHYROID	-	-	-	-	-	-	+	-	+	+	-	-	+	+	+	-	+	+	+	+	-	-	-	+	-	24
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LEIOMYOSARCOMA									X																	1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
ADENOMA, NOS																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
ALVEOLAR/BRONCHIOLAR CA, METASTAT	X	X									X											X	X		X	1
MALIGNANT LYMPHOMA, NOS																										7

M ANIMALS NECROPSIED

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE: HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	041	041	041	041	041	041	041	041	041	041	051	051	051	051	051	051	051	051	051	089	051	051	051	089	089
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PAPILLOMA, NOS				X																					
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																							X		
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	-	+	+	-	+	+	+	-	+	+	+	+	-	+	+	+	-	-	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	-	+	-	+	-	+	+	+	+	+
THYMUS	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT CARCINOMA																								X	
HEPATOCELLULAR ADENOMA		X							X																
HEPATOCELLULAR CARCINOMA											X	X											X	X	
MALIGNANT LYMPHOMA, NOS																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MALIGNANT LYMPHOMA, NOS																									
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																									
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-
PARATHYROID	-	-	+	+	-	+	+	-	-	-	-	+	+	+	+	-	+	+	-	-	-	+	+	-	-
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																									X
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																				X					
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA																			X						
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+
PAPILLARY CYSTADENOMA, NOS																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
ADENOMA, NOS																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
BILE DUCT CARCINOMA, METASTATIC																								X	
MALIGNANT LYMPHOMA, NOS																									

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	0212	0217	0218	0229	0310	0311	0313	0315	0334	0335	0336	0337	0338	0339	0340	0341	0342	0343	0344	0345	0346	0347	0348	0349	0350	TOTAL
WEEKS ON STUDY	1005	1005	0631	0445	0805	1005	1005	1005	0907	0901	1005	1005	1005	1005	1005	1005	1005	1005	1005	1005	1005	1005	0805	1005	1005	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PAPILLOMA, NOS																										M 1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA																		X							X	3
ALVEOLAR/BRONCHIOLAR CARCINOMA	X																									1
TRACHEA	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	-	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	-	40
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	-	+	+	+	+	-	+	-	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	40
THYMUS	+	+	+	+	+	+	-	+	-	+	+	-	+	+	+	+	+	+	+	+	-	-	+	+		41
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	47
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BILE DUCT CARCINOMA																										1
HEPATOCELLULAR ADENOMA							X														X					3
HEPATOCELLULAR CARCINOMA	X								X			X														7
MALIGNANT LYMPHOMA, NOS																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	50N
PANCREAS	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
MALIGNANT LYMPHOMA, NOS							X											X								2
LARGE INTESTINE	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	46
ENDOCRINE SYSTEM																										
PITUITARY	+	+	-	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ADENOMA, NOS												X	X													2
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	-	+	+	+	+	+	+	47
THYROID	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
PARATHYROID	+	-	-	-	-	+	-	-	-	-	+	-	+	-	+	-	+	+	+	+	-	-	+	-	-	22
PANCREATIC ISLETS	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL ADENOMA																										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50N
ADENOCARCINOMA, NOS																										1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOSARCOMA																										1
OVARY	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
PAPILLARY CYSTADENOMA, NOS					X																					1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50N
ADENOMA, NOS		X										X														2
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50N
BILE DUCT CARCINOMA, METASTATIC																										1
MALIGNANT LYMPHOMA, NOS			X			X				X																3

N ANIMALS NECROPSIED

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF TRIS(2-ETHYLHEXYL)PHOSPHATE

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	2 (4%)
ABSCESS, NOS	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
HYPERPLASIA, BASAL CELL			1 (2%)
HYPERKERATOSIS		1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
*NASAL CAVITY	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		
INFLAMMATION, ACUTE			1 (2%)
#TRACHEA	(49)	(48)	(49)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
METAPLASIA, SQUAMOUS			1 (2%)
#LUNG/BRONCHIOLE	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
#LUNG	(50)	(50)	(50)
CONGESTION, NOS	2 (4%)	2 (4%)	1 (2%)
EDEMA, NOS		1 (2%)	
HEMORRHAGE		2 (4%)	2 (4%)
PNEUMONIA, ASPIRATION			1 (2%)
BRONCHOPNEUMONIA, ACUTE			1 (2%)
INFLAMMATION, ACUTE	1 (2%)		1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	1 (2%)	2 (4%)
PNEUMONIA, CHRONIC MURINE		1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)	1 (2%)	1 (2%)
BRONCHOPNEUMONIA, CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
INFLAMMATION, GRANULOMATOUS			1 (2%)
GRANULOMA, NOS	1 (2%)		
SCAR			1 (2%)
CHOLESTEROL DEPOSIT	1 (2%)		
PIGMENTATION, NOS			2 (4%)
HYPERPLASIA, ADENOMATOUS	4 (8%)	4 (8%)	10 (20%)
HISTIOCYTOSIS	5 (10%)	2 (4%)	4 (8%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(50)	(49)	(50)
MYELOFIBROSIS			1 (2%)
HYPERPLASIA, HEMATOPOIETIC			1 (2%)
#SPLEEN	(50)	(49)	(50)
ACCESSORY STRUCTURE	2 (4%)		
INFARCT, NOS			1 (2%)
#MANDIBULAR L. NODE	(47)	(47)	(47)
PLASMACYTOSIS		1 (2%)	
#HEPATIC LYMPH NODE	(47)	(47)	(47)
HYPERPLASIA, LYMPHOID		1 (2%)	
#PANCREATIC L. NODE	(47)	(47)	(47)
HEMORRHAGE			1 (2%)
#LUNG	(50)	(50)	(50)
SIDEROCYTES			6 (12%)
#ADRENAL	(50)	(50)	(50)
HEMATOPOIESIS	1 (2%)		

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#THYMUS	(40)	(34)	(37)
INFLAMMATION, ACUTE			1 (3%)
ABSCESS, NOS	1 (3%)		
CIRCULATORY SYSTEM			
#HEART	(50)	(50)	(50)
ENDOCARDITIS, BACTERIAL		1 (2%)	
#MYOCARDIUM	(50)	(50)	(50)
INFLAMMATION, CHRONIC	35 (70%)	30 (60%)	29 (58%)
FIBROSIS	1 (2%)	1 (2%)	
DEGENERATION, NOS	2 (4%)	2 (4%)	1 (2%)
CALCIFICATION, FOCAL		1 (2%)	
*BLOOD VESSEL	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
*HEPATIC VEIN	(50)	(50)	(50)
THROMBOSIS, NOS		1 (2%)	
#PANCREAS	(50)	(48)	(49)
PERIARTERITIS		1 (2%)	
*MESENTERY	(50)	(50)	(50)
PERIARTERITIS			1 (2%)
#ADRENAL/CAPSULE	(50)	(50)	(50)
THROMBOSIS, NOS		1 (2%)	
#THYMUS	(40)	(34)	(37)
THROMBOSIS, NOS	1 (3%)		
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(48)	(49)	(50)
INFLAMMATION ACTIVE CHRONIC		1 (2%)	1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
DEGENERATION, NOS			1 (2%)
ATROPHY, NOS	1 (2%)		
#LIVER	(50)	(50)	(50)
HERNIA, NOS	1 (2%)	3 (6%)	1 (2%)
CYST, NOS	1 (2%)		
CONGESTION, NOS	2 (4%)	1 (2%)	1 (2%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
NECROSIS, FOCAL		1 (2%)	
METAMORPHOSIS FATTY	16 (32%)	13 (26%)	16 (32%)
BASOPHILIC CYTO CHANGE	4 (8%)	5 (10%)	6 (12%)
EOSINOPHILIC CYTO CHANGE	2 (4%)	1 (2%)	
CYTOLOGIC ALTERATION, NOS			1 (2%)
ANGIECTASIS			1 (2%)
#HEPATIC CAPSULE	(50)	(50)	(50)
CONGESTION, NOS		1 (2%)	2 (4%)
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
CONGESTION, NOS		1 (2%)	1 (2%)
DEGENERATION, NOS		1 (2%)	
METAMORPHOSIS FATTY	2 (4%)		
#LIVER/PERIPORTAL	(50)	(50)	(50)
METAMORPHOSIS FATTY	1 (2%)		
#BILE DUCT	(50)	(50)	(50)
CYST, NOS	2 (4%)	1 (2%)	
HYPERPLASIA, NOS	24 (48%)	13 (26%)	17 (34%)
HYPERPLASIA, FOCAL			2 (4%)
#PANCREAS	(50)	(48)	(49)
ECTOPIA	1 (2%)		
CYST, NOS		1 (2%)	1 (2%)
CYSTIC DUCTS	1 (2%)		
INFLAMMATION, CHRONIC FOCAL		1 (2%)	

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#PANCREATIC ACINUS	(50)	(48)	(49)
ATROPHY, NOS	8 (16%)	6 (13%)	11 (22%)
ATROPHY, FOCAL		1 (2%)	
HYPERPLASIA, FOCAL	9 (18%)	9 (19%)	6 (12%)
#ESOPHAGUS	(50)	(49)	(50)
HEMORRHAGE		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
#PERIESOPHAGEAL TISSUE	(50)	(49)	(50)
FOREIGN BODY, NOS			1 (2%)
INFLAMMATION, SUPPURATIVE			1 (2%)
INFECTION, BACTERIAL			1 (2%)
#STOMACH	(48)	(48)	(50)
ULCER, ACUTE	1 (2%)	1 (2%)	
CALCIFICATION, FOCAL			1 (2%)
#FORESTOMACH	(48)	(48)	(50)
INFLAMMATION, ACUTE	1 (2%)		1 (2%)
ABSCESS, NOS	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
HYDRONEPHROSIS	1 (2%)		
PYELONEPHRITIS, ACUTE		1 (2%)	
PYELONEPHRITIS, ACUTE/CHRONIC	1 (2%)		
NEPHROPATHY	22 (44%)	28 (56%)	29 (58%)
NEPHROSIS, NOS	1 (2%)		4 (8%)
CALCIFICATION, FOCAL			1 (2%)
#KIDNEY/CORTEX	(50)	(50)	(50)
CYST, NOS	2 (4%)		
#KIDNEY/MEDULLA	(50)	(50)	(50)
CALCIFICATION, FOCAL	1 (2%)		
#RENAL PYRAMID	(50)	(50)	(50)
CALCIFICATION, FOCAL	1 (2%)		
#KIDNEY/GLOMERULUS	(50)	(50)	(50)
NEPHROSIS, NOS			1 (2%)
#KIDNEY/TUBULE	(50)	(50)	(50)
DILATATION, NOS			3 (6%)
INFLAMMATION, ACUTE FOCAL	1 (2%)	1 (2%)	2 (4%)
PIGMENTATION, NOS			1 (2%)
#KIDNEY/PELVIS	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		
CALCIFICATION, FOCAL	2 (4%)		
HYPERPLASIA, EPITHELIAL	1 (2%)		
#URINARY BLADDER	(48)	(50)	(50)
CALCIFICATION, FOCAL			1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(50)	(50)
CYST, NOS	5 (10%)	2 (4%)	3 (6%)
HEMOSIDEROSIS			2 (4%)
HYPERPLASIA, CHROMOPHOBE-CELL	6 (12%)	2 (4%)	5 (10%)
ANGIECTASIS	2 (4%)		6 (12%)
#ADRENAL	(50)	(50)	(50)
CONGESTION, NOS	1 (2%)		
HEMORRHAGE		1 (2%)	
INFLAMMATION, SUPPURATIVE		1 (2%)	
ANGIECTASIS			2 (4%)
#ADRENAL/CAPSULE	(50)	(50)	(50)
HERNIA, NOS			1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#ADRENAL CORTEX	(50)	(50)	(50)
CONGESTION, NOS	1 (2%)		
HEMORRHAGE		1 (2%)	1 (2%)
DEGENERATION, LIPOID	1 (2%)	2 (4%)	2 (4%)
HYPERPLASIA, FOCAL		1 (2%)	
#ADRENAL MEDULLA	(50)	(50)	(50)
HYPERPLASIA, FOCAL	1 (2%)	6 (12%)	3 (6%)
#THYROID	(46)	(49)	(49)
ULTIMOBRANCHIAL CYST	1 (2%)	1 (2%)	1 (2%)
CYSTIC FOLLICLES			1 (2%)
FOLLICULAR CYST, NOS			1 (2%)
CALCIFICATION, FOCAL	1 (2%)		
HYPERPLASIA, FOCAL		1 (2%)	
HYPERPLASIA, C-CELL	10 (22%)	2 (4%)	1 (2%)
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)		
#THYROID FOLLICLE	(46)	(49)	(49)
HYPERPLASIA, CYSTIC	1 (2%)	1 (2%)	
#PANCREATIC ISLETS	(50)	(48)	(49)
HYPERPLASIA, NOS	2 (4%)		1 (2%)
HYPERPLASIA, FOCAL		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
DILATATION/DUCTS	8 (16%)	6 (12%)	6 (12%)
GALACTOCELE	2 (4%)	2 (4%)	
HEMATOMA, NOS		1 (2%)	
HYPERPLASIA, NOS		1 (2%)	
*MAMMARY LOBULE	(50)	(50)	(50)
HYPERPLASIA, NOS	2 (4%)		
*PREPUTIAL GLAND	(50)	(50)	(50)
DILATATION/DUCTS		1 (2%)	
ABSCESS, NOS			1 (2%)
INFLAMMATION, PYOGRANULOMATOUS		1 (2%)	
#PROSTATE	(47)	(47)	(50)
INFLAMMATION, ACUTE/CHRONIC	2 (4%)	1 (2%)	2 (4%)
INFLAMMATION, CHRONIC	2 (4%)		1 (2%)
CALCIFICATION, FOCAL	1 (2%)		
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, EPITHELIAL	1 (2%)		3 (6%)
HYPERPLASIA, FOCAL	5 (11%)	12 (26%)	6 (12%)
METAPLASIA, SQUAMOUS	1 (2%)		
#TESTIS	(50)	(50)	(50)
CALCIFICATION, FOCAL	1 (2%)		
ATROPHY, NOS	3 (6%)	5 (10%)	
HYPERPLASIA, INTERSTITIAL CELL	4 (8%)	1 (2%)	
#TESTIS/TUBULE	(50)	(50)	(50)
CALCIFICATION, FOCAL	1 (2%)		
*EPIDIDYMIS	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC FOCAL			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
HEMORRHAGE		2 (4%)	
INFARCT, NOS		1 (2%)	
CALCIFICATION, FOCAL	1 (2%)		
#CEREBELLUM	(50)	(50)	(50)
CALCIFICATION, FOCAL			1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
INFLAMMATION, ACUTE			1 (2%)
CATARACT	13 (26%)	8 (16%)	7 (14%)
MULTINUCLEATE GIANT-CELL	1 (2%)		
ATROPHY, NOS	2 (4%)		
METAPLASIA, OSSEOUS	1 (2%)		
*EYE/SCLERA	(50)	(50)	(50)
CALCIFICATION, FOCAL	2 (4%)		1 (2%)
*EYE/CORNEA	(50)	(50)	(50)
INFLAMMATION, ACUTE		1 (2%)	
*EYEBALL TUNICA VASCU	(50)	(50)	(50)
INFLAMMATION, ACUTE	1 (2%)		
*EYE/RETINA	(50)	(50)	(50)
ATROPHY, NOS	12 (24%)	8 (16%)	6 (12%)
MUSCULOSKELETAL SYSTEM			
*MUSCLE OF THORAX	(50)	(50)	(50)
HEMATOMA, NOS			1 (2%)
ABSCESS, NOS			1 (2%)
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
HEMORRHAGE	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
*ABDOMINAL CAVITY	(50)	(50)	(50)
NECROSIS, FAT	1 (2%)		
*PLEURA	(50)	(50)	(50)
HEMORRHAGE			1 (2%)
INFLAMMATION, FIBRINOUS			1 (2%)
FIBROSIS, FOCAL	1 (2%)		
*PERICARDIUM	(50)	(50)	(50)
INFLAMMATION, FIBRINOUS			1 (2%)
INFLAMMATION, CHRONIC	1 (2%)		
*MESENTERY	(50)	(50)	(50)
INFLAMMATION GRANULOMATOUS FOCAL			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
BACTERIAL SEPTICEMIA		1 (2%)	
ADIPOSE TISSUE			
HEMORRHAGE			1
INFLAMMATION, CHRONIC NECROTIZIN	1		
INFLAMMATION, GRANULOMATOUS	4	3	
INFLAMMATION GRANULOMATOUS FOCAL		1	
INFARCT, FOCAL			1
CALCIFICATION, FOCAL	1		
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		1	

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

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)
RESPIRATORY SYSTEM			
*LARYNX	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
#TRACHEA	(48)	(49)	(47)
HEMORRHAGE			1 (2%)
INFLAMMATION, SUPPURATIVE	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
INFLAMMATION, CHRONIC	1 (2%)		
#LUNG	(50)	(49)	(50)
ASPIRATION, FOREIGN BODY			1 (2%)
CONGESTION, NOS	2 (4%)		3 (6%)
EDEMA, NOS	1 (2%)		
HEMORRHAGE	1 (2%)	1 (2%)	1 (2%)
INFLAMMATION, ACUTE	1 (2%)		
ABSCESS, NOS	1 (2%)		1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
PNEUMONIA, CHRONIC MURINE		3 (6%)	1 (2%)
INFLAMMATION, CHRONIC	1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (2%)		1 (2%)
INFLAMMATION, GRANULOMATOUS	2 (4%)	2 (4%)	
GRANULOMA, FOREIGN BODY		1 (2%)	
HEMOSIDEROSIS		1 (2%)	
HYPERPLASIA, ADENOMATOUS	2 (4%)	2 (4%)	7 (14%)
HISTIOCYTOSIS	2 (4%)	7 (14%)	6 (12%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(49)	(50)	(49)
ACCESSORY STRUCTURE		1 (2%)	
FIBROSIS			1 (2%)
INFARCT, NOS			1 (2%)
INFARCT, ACUTE			1 (2%)
HEMOSIDEROSIS	1 (2%)		
HEMATOPOIESIS	3 (6%)		1 (2%)
#SPLENIC CAPSULE	(49)	(50)	(49)
HEMATOMA, ORGANIZED	1 (2%)		
FIBROSIS	1 (2%)		
#SPLENIC FOLLICLES	(49)	(50)	(49)
ATROPHY, NOS		1 (2%)	
#LYMPH NODE	(49)	(47)	(47)
NECROSIS, NOS	1 (2%)		
#MANDIBULAR L. NODE	(49)	(47)	(47)
NECROSIS, NOS	1 (2%)		
HYPERPLASIA, LYMPHOID			1 (2%)
#CERVICAL LYMPH NODE	(49)	(47)	(47)
HYPERPLASIA, NOS		1 (2%)	
#PANCREATIC L. NODE	(49)	(47)	(47)
HEMORRHAGE			1 (2%)
#LUNG	(50)	(49)	(50)
SIDEROCYTES			1 (2%)
#LIVER	(50)	(50)	(50)
HEMATOPOIESIS			1 (2%)

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#ADRENAL	(50)	(50)	(49)
HEMATOPOIESIS	1 (2%)		
#THYMUS	(47)	(41)	(40)
CYST, NOS	1 (2%)		
HEMORRHAGE	1 (2%)		1 (3%)
HEMATOMA, NOS	1 (2%)		
ABSCESS, NOS	1 (2%)		
FIBROSIS, FOCAL			1 (3%)
CIRCULATORY SYSTEM			
#HEART	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		1 (2%)
FIBROSIS	1 (2%)		
PERIVASCULITIS			1 (2%)
DEGENERATION, NOS		1 (2%)	
NECROSIS, NOS			1 (2%)
HYPERPLASIA, NOS			1 (2%)
#MYOCARDIUM	(50)	(50)	(50)
INFLAMMATION, CHRONIC	20 (40%)	10 (20%)	13 (26%)
FIBROSIS		1 (2%)	1 (2%)
DEGENERATION, NOS	1 (2%)	1 (2%)	2 (4%)
#LIVER	(50)	(50)	(50)
THROMBUS, ORGANIZED			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(50)	(50)
INFLAMMATION ACTIVE CHRONIC	1 (2%)		1 (2%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
DEGENERATION, NOS		1 (2%)	
ATROPHY, NOS	1 (2%)		
ATROPHY, FOCAL		1 (2%)	
#PAROTID GLAND	(50)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
#LIVER	(50)	(50)	(50)
HERNIA, NOS	2 (4%)	3 (6%)	2 (4%)
DILATATION/SINUS			1 (2%)
BILE STASIS			1 (2%)
CONGESTION, CHRONIC PASSIVE	1 (2%)		
INFLAMMATION, ACUTE NECROTIZING			1 (2%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
INFLAMMATION, GRANULOMATOUS			1 (2%)
GRANULOMA, NOS	1 (2%)		
NECROSIS, NOS	1 (2%)		
NECROSIS, FOCAL		1 (2%)	
METAMORPHOSIS FATTY	4 (8%)	3 (6%)	3 (6%)
BASOPHILIC CYTO CHANGE	16 (32%)	7 (14%)	8 (16%)
#HEPATIC CAPSULE	(50)	(50)	(50)
CONGESTION, NOS	1 (2%)		
#PORTAL TRACT	(50)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
NECROSIS, NOS		1 (2%)	
#BILE DUCT	(50)	(50)	(50)
CYST, NOS		1 (2%)	
HYPERPLASIA, NOS	13 (26%)	10 (20%)	9 (18%)
#PANCREAS	(49)	(50)	(50)
CYST, NOS	1 (2%)		2 (4%)
CYSTIC DUCTS			1 (2%)
#PANCREATIC ACINUS	(49)	(50)	(50)
ATROPHY, NOS	13 (27%)	5 (10%)	9 (18%)
HYPERPLASIA, FOCAL	1 (2%)		

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#PANCREATIC INTERSTIT	(49)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
#PERIPANCREATIC TISSUE	(49)	(50)	(50)
INFLAMMATION, NECRO GRANULOMATOUS	1 (2%)		
#ESOPHAGUS	(50)	(49)	(50)
HEMORRHAGE		1 (2%)	
INFLAMMATION ACTIVE CHRONIC		1 (2%)	
GRANULOMA, NOS			1 (2%)
HYPERKERATOSIS		1 (2%)	
#STOMACH	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL			1 (2%)
#FORESTOMACH	(50)	(50)	(50)
ULCER, NOS	1 (2%)		1 (2%)
INFLAMMATION, ACUTE	1 (2%)		2 (4%)
INFLAMMATION, ACUTE/CHRONIC	2 (4%)	1 (2%)	
FIBROSIS, FOCAL		1 (2%)	
HYPERPLASIA, EPITHELIAL	1 (2%)	1 (2%)	
#COLON	(49)	(50)	(49)
PARASITISM		1 (2%)	
CALCIFICATION, NOS	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
MINERALIZATION		1 (2%)	
HYDRONEPHROSIS			1 (2%)
PYELONEPHRITIS, ACUTE		1 (2%)	1 (2%)
NEPHROPATHY	18 (36%)	17 (34%)	19 (38%)
NEPHROSIS, NOS			1 (2%)
CALCIFICATION, FOCAL	1 (2%)		
#KIDNEY/CORTEX	(50)	(50)	(50)
CYST, NOS		1 (2%)	
#KIDNEY/TUBULE	(50)	(50)	(50)
DILATATION, NOS		7 (14%)	1 (2%)
CAST, NOS	1 (2%)		
INFLAMMATION, ACUTE		1 (2%)	
PIGMENTATION, NOS			1 (2%)
CYTOPLASMIC VACUOLIZATION	1 (2%)		
#KIDNEY/PELVIS	(50)	(50)	(50)
CALCIFICATION, FOCAL	1 (2%)	1 (2%)	1 (2%)
HYPERPLASIA, EPITHELIAL			1 (2%)
#URINARY BLADDER	(48)	(49)	(49)
MINERALIZATION		1 (2%)	
INFLAMMATION, ACUTE NECROTIZING			1 (2%)
INFLAMMATION ACTIVE CHRONIC		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
HYPERPLASIA, EPITHELIAL		1 (2%)	
#U.BLADDER/SEROSA	(48)	(49)	(49)
HYPERPLASIA, NOS			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(49)	(49)
DILATATION, NOS		1 (2%)	
DILATATION/SINUS	1 (2%)		2 (4%)
CYST, NOS	10 (20%)	14 (29%)	12 (24%)
HYPERPLASIA, CHROMOPHOBE-CELL	1 (2%)		1 (2%)
ANGIECTASIS			2 (4%)
#ADRENAL	(50)	(50)	(49)
DEGENERATION, LIPOID	1 (2%)		
NECROSIS, NOS	1 (2%)		
ANGIECTASIS		1 (2%)	

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#ADRENAL CORTEX	(50)	(50)	(49)
DEGENERATION, LIPOID	1 (2%)	1 (2%)	3 (6%)
HYPERPLASIA, FOCAL	1 (2%)	3 (6%)	1 (2%)
#ADRENAL MEDULLA	(50)	(50)	(49)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, FOCAL		2 (4%)	1 (2%)
#THYROID	(46)	(50)	(47)
ULTIMOBRANCHIAL CYST	1 (2%)	2 (4%)	
CYSTIC FOLLICLES		1 (2%)	1 (2%)
HYPERPLASIA, C-CELL	6 (13%)	10 (20%)	7 (15%)
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)		
#THYROID FOLLICLE	(46)	(50)	(47)
HYPERPLASIA, CYSTIC	1 (2%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
DILATATION/DUCTS	13 (26%)	9 (18%)	3 (6%)
GALACTOCELE	3 (6%)	1 (2%)	
CYSTIC DUCTS	1 (2%)		2 (4%)
PIGMENTATION, NOS			1 (2%)
*MAMMARY LOBULE	(50)	(50)	(50)
FIBROSIS		1 (2%)	
HYPERPLASIA, NOS	11 (22%)	14 (28%)	11 (22%)
HYPERPLASIA, EPITHELIAL		1 (2%)	
#UTERUS	(50)	(50)	(49)
CYST, NOS	1 (2%)	1 (2%)	
HEMORRHAGE	2 (4%)		
INFLAMMATION, ACUTE			1 (2%)
#CERVIX UTERI	(50)	(50)	(49)
CYST, NOS		1 (2%)	
ABSCESS, NOS		1 (2%)	
#UTERUS/ENDOMETRIUM	(50)	(50)	(49)
CYST, NOS	3 (6%)	7 (14%)	2 (4%)
INFLAMMATION, ACUTE		1 (2%)	
HYPERPLASIA, CYSTIC	3 (6%)	4 (8%)	5 (10%)
#OVARY/PAROVARIAN	(50)	(50)	(50)
INFLAMMATION, ACUTE NECROTIZING	1 (2%)		
INFLAMMATION, GRANULOMATOUS	2 (4%)	1 (2%)	
INFLAMMATION GRANULOMATOUS FOCAL		1 (2%)	1 (2%)
INFLAMMATION, CALC GRANULOMATOUS		1 (2%)	
#OVARY	(50)	(50)	(50)
CYST, NOS	4 (8%)	3 (6%)	6 (12%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
#MESOVARIUM	(50)	(50)	(50)
INFLAMMATION GRANULOMATOUS FOCAL		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
HYDROCEPHALUS, NOS		1 (2%)	
HEMORRHAGE	1 (2%)		
INFARCT, FOCAL			1 (2%)
CALCIFICATION, FOCAL		1 (2%)	

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
INFLAMMATION, ACUTE	1 (2%)		
INFLAMMATION, CHRONIC SUPPURATIV			1 (2%)
CATARACT	10 (20%)	7 (14%)	8 (16%)
ATROPHY, NOS		2 (4%)	
*EYE/CORNEA	(50)	(50)	(50)
INFLAMMATION, ACUTE	1 (2%)		1 (2%)
*EYEBALL TUNICA VASCU	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
*EYE/RETINA	(50)	(50)	(50)
ATROPHY, NOS	10 (20%)	4 (8%)	8 (16%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
HEMORRHAGE			1 (2%)
INFLAMMATION, FIBRINOUS		1 (2%)	
INFLAMMATION, NECROTIZING			1 (2%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
INFECTION, BACTERIAL		1 (2%)	
*ABDOMINAL CAVITY	(50)	(50)	(50)
HEMATOMA, NOS			1 (2%)
INFLAMMATION, GRANULOMATOUS			1 (2%)
*PLEURA	(50)	(50)	(50)
FOREIGN BODY, NOS		1 (2%)	
INFLAMMATION, FIBRINOUS		1 (2%)	
ABSCESS, CHRONIC			1 (2%)
INFECTION, BACTERIAL		1 (2%)	
*EPICARDIUM	(50)	(50)	(50)
INFLAMMATION, FIBRINOUS	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
INFECTION, BACTERIAL		1 (2%)	
*MESENTERY	(50)	(50)	(50)
INFLAMMATION, GRANULOMATOUS	1 (2%)	2 (4%)	
INFLAMMATION GRANULOMATOUS FOCAL		1 (2%)	
NECROSIS, FAT		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
ADIPOSE TISSUE			
CONGESTION, NOS			1
INFLAMMATION, GRANULOMATOUS		1	
INFLAMMATION GRANULOMATOUS FOCAL			1
SPECIAL MORPHOLOGY SUMMARY			
NONE			

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF TRIS(2-ETHYHEXYL)PHOSPHATE

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(49)
INFLAMMATION, NECROTIZING		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)	1 (2%)	
GRANULATION, TISSUE		1 (2%)	
FIBROSIS		1 (2%)	
ACANTHOSIS	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(49)
ABSCESS, NOS		1 (2%)	
INFLAMMATION, GRANULOMATOUS			1 (2%)
NECROSIS, FAT			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(49)
HEMORRHAGE	1 (2%)	1 (2%)	
INFLAMMATION, INTERSTITIAL	1 (2%)		
INFLAMMATION, SUPPURATIVE	1 (2%)		
BRONCHOPNEUMONIA, ACUTE			2 (4%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)
PNEUMONIA INTERSTITIAL CHRONIC			2 (4%)
HYPERPLASIA, FOCAL			2 (4%)
HISTIOCYTOSIS		2 (4%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(49)
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)
MYELOPOIESIS	2 (4%)		1 (2%)
#BONE MARROW	(41)	(45)	(42)
MYELOPOIESIS	1 (2%)		2 (5%)
#SPLEEN	(50)	(50)	(48)
PLASMACYTOSIS		1 (2%)	
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)	
HEMATOPOIESIS	3 (6%)	5 (10%)	5 (10%)
#LYMPH NODE	(32)	(40)	(28)
HEMOSIDEROSIS	1 (3%)		
HYPERPLASIA, LYMPHOID			1 (4%)
#MEDIASTINAL L. NODE	(32)	(40)	(28)
HEMORRHAGE			1 (4%)
PLASMACYTOSIS			1 (4%)
#MESENTERIC L. NODE	(32)	(40)	(28)
HEMORRHAGE	2 (6%)	1 (3%)	1 (4%)
INFLAMMATION, SUPPURATIVE			1 (4%)
HYPERPLASIA, LYMPHOID		1 (3%)	1 (4%)
HEMATOPOIESIS			1 (4%)
#RENAL LYMPH NODE	(32)	(40)	(28)
HEMORRHAGE		1 (3%)	
#SACRAL LYMPH NODE	(32)	(40)	(28)
INFLAMMATION, CHRONIC			1 (4%)
PLASMACYTOSIS	1 (3%)		
HYPERPLASIA, LYMPHOID	1 (3%)		
#AXILLARY LYMPH NODE	(32)	(40)	(28)
HYPERPLASIA, LYMPHOID		1 (3%)	1 (4%)
#LUNG	(50)	(50)	(49)
LEUKOCYTOSIS, NOS		2 (4%)	

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#LIVER	(50)	(50)	(49)
HEMATOPOIESIS		2 (4%)	
MYELOPOIESIS	1 (2%)	1 (2%)	2 (4%)
#KIDNEY	(50)	(50)	(49)
PLASMACYTOSIS		1 (2%)	
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(49)
PERIARTERITIS		1 (2%)	
#MESENTERIC L. NODE	(32)	(40)	(28)
THROMBUS, ORGANIZED	1 (3%)		
#HEART	(50)	(50)	(48)
MINERALIZATION	1 (2%)		
#HEART/ATRIUM	(50)	(50)	(48)
THROMBUS, ORGANIZED			1 (2%)
*AORTA	(50)	(50)	(49)
MINERALIZATION	1 (2%)		
*PULMONARY VEIN	(50)	(50)	(49)
THROMBOSIS, NOS	1 (2%)		
#PROSTATE	(49)	(47)	(48)
PERIARTERITIS		1 (2%)	
*SEMINAL VESICLE	(50)	(50)	(49)
PERIARTERITIS	1 (2%)		
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(50)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR	6 (12%)	4 (8%)	12 (24%)
INFLAMMATION, SUPPURATIVE		1 (2%)	
FIBROSIS			1 (2%)
CALCINOSIS CIRCUMSCRIPTA			1 (2%)
#LIVER	(50)	(50)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
FIBROSIS, FOCAL	1 (2%)		
NECROSIS, NOS	1 (2%)	1 (2%)	
NUCLEAR-SIZE ALTERATION	2 (4%)	1 (2%)	1 (2%)
NUCLEAR-SHAPE ALTERATION		1 (2%)	
CYTOPLASMIC VACUOLIZATION	6 (12%)	9 (18%)	7 (14%)
BASOPHILIC CYTO CHANGE		1 (2%)	
FOCAL CELLULAR CHANGE			1 (2%)
EOSINOPHILIC CYTO CHANGE	1 (2%)	1 (2%)	1 (2%)
CLEAR-CELL CHANGE		2 (4%)	2 (4%)
ATROPHY, FOCAL			1 (2%)
HYPERTROPHY, FOCAL		1 (2%)	
#LIVER/CENTRILOBULAR	(50)	(50)	(49)
CYTOPLASMIC VACUOLIZATION			1 (2%)
*GALLBLADDER	(50)	(50)	(49)
INFLAMMATION, CHRONIC		1 (2%)	
#BILE DUCT	(50)	(50)	(49)
HYPERPLASIA, NOS	1 (2%)		
#PANCREAS	(50)	(50)	(48)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)	1 (2%)	2 (4%)
INFLAMMATION, CHRONIC			1 (2%)
#ESOPHAGUS	(48)	(50)	(46)
PERFORATION, INFLAMMATORY			1 (2%)
#ESOPHAGEAL ADVENTITI	(48)	(50)	(46)
HEMORRHAGE		1 (2%)	

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#STOMACH	(50)	(49)	(47)
MINERALIZATION	1 (2%)		
ULCER, NOS	1 (2%)	1 (2%)	1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (4%)	2 (4%)	2 (4%)
INFLAMMATION, SUPPURATIVE			2 (4%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
EOSINOPHILIC INFILTRATE			1 (2%)
#SMALL INTESTINE	(45)	(42)	(42)
HYPERPLASIA, ADENOMATOUS			1 (2%)
#JEJUNUM	(45)	(42)	(42)
HYPERPLASIA, ADENOMATOUS	1 (2%)		
*RECTUM	(50)	(50)	(49)
EPIDERMAL INCLUSION CYST		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(49)
MINERALIZATION	7 (14%)	3 (6%)	1 (2%)
HYDRONEPHROSIS	2 (4%)	1 (2%)	
CYST, NOS	2 (4%)	2 (4%)	
GLOMERULONEPHRITIS, NOS	4 (8%)	4 (8%)	6 (12%)
LYMPHOCYTIC INFLAMMATORY INFILTR	22 (44%)	17 (34%)	22 (45%)
INFLAMMATION, SUPPURATIVE	1 (2%)		
ATROPHY, NOS	2 (4%)	2 (4%)	3 (6%)
#KIDNEY/TUBULE	(50)	(50)	(49)
PIGMENTATION, NOS			1 (2%)
#KIDNEY/PELVIS	(50)	(50)	(49)
INFLAMMATION, SUPPURATIVE	1 (2%)	1 (2%)	1 (2%)
INFLAMMATION, CHRONIC SUPPURATIV			1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)	
#URINARY BLADDER	(48)	(50)	(47)
CALCULUS,GROSS OBSERVATION ONLY		1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	12 (25%)	6 (12%)	15 (32%)
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFLAMMATION, CHRONIC		2 (4%)	1 (2%)
INFLAMMATION, CHRONIC SUPPURATIV	1 (2%)		
HYPERPLASIA, EPITHELIAL		1 (2%)	
#U.BLADDER/SEROSA	(48)	(50)	(47)
INFLAMMATION, SUPPURATIVE	1 (2%)		
*URETHRA	(50)	(50)	(49)
CALCULUS,GROSS OBSERVATION ONLY			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(44)	(47)	(43)
CYST, NOS			1 (2%)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)		2 (5%)
#ADRENAL	(48)	(48)	(45)
ATROPHY, BROWN		2 (4%)	
#ADRENAL CORTEX	(48)	(48)	(45)
LIPOIDOSIS		3 (6%)	
HYPERTROPHY, FOCAL	1 (2%)		2 (4%)
#ADRENAL MEDULLA	(48)	(48)	(45)
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)	1 (2%)
#THYROID	(49)	(48)	(47)
CYST, NOS		1 (2%)	1 (2%)
HYPERPLASIA, FOLLICULAR-CELL		12 (25%)	24 (51%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*PENIS	(50)	(50)	(49)
HEMORRHAGE		1 (2%)	
INFLAMMATION, NECROTIZING		1 (2%)	
*PREPUCE	(50)	(50)	(49)
EPIDERMAL INCLUSION CYST		1 (2%)	
INFLAMMATION, NECROTIZING		1 (2%)	
INFLAMMATION, ACUTE NECROTIZING		1 (2%)	
*PREPUTIAL GLAND	(50)	(50)	(49)
DILATATION/DUCTS		2 (4%)	
CYST, NOS	1 (2%)		
INFLAMMATION, SUPPURATIVE	1 (2%)		
ABSCESS, NOS	2 (4%)		5 (10%)
INFLAMMATION, CHRONIC SUPPURATIVE	1 (2%)		
INFLAMMATION, GRANULOMATOUS	1 (2%)		1 (2%)
INFLAMMATION, PYOGRANULOMATOUS		1 (2%)	
#PROSTATE	(49)	(47)	(48)
LYMPHOCYTIC INFLAMMATORY INFILTR	6 (12%)	2 (4%)	2 (4%)
INFLAMMATION, SUPPURATIVE	2 (4%)	2 (4%)	1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC		1 (2%)	
*SEMINAL VESICLE	(50)	(50)	(49)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC		1 (2%)	
#TESTIS	(50)	(50)	(48)
MINERALIZATION	10 (20%)	9 (18%)	10 (21%)
ATROPHY, NOS		3 (6%)	5 (10%)
*EPIDIDYMIS	(50)	(50)	(49)
MINERALIZATION			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	3 (6%)		5 (10%)
GRANULOMA, SPERMATIC	1 (2%)		3 (6%)
*SCROTUM	(50)	(50)	(49)
NECROSIS, FAT		3 (6%)	1 (2%)
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*STERNUM	(50)	(50)	(49)
INFLAMMATION, PYOGRANULOMATOUS		1 (2%)	
OSTEOSCLEROSIS	1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(49)
HEMORRHAGE		1 (2%)	
INFLAMMATION, FIBRINOUS	1 (2%)	1 (2%)	
INFLAMMATION, PYOGRANULOMATOUS		1 (2%)	
FIBROSIDEROTIC NODULE		1 (2%)	
*ABDOMINAL CAVITY	(50)	(50)	(49)
STEATITIS	1 (2%)		
NECROSIS, FAT	1 (2%)		1 (2%)
*INGUINAL REGION	(50)	(50)	(49)
NECROSIS, FAT	1 (2%)		
*PLEURA	(50)	(50)	(49)
INFLAMMATION, CHRONIC SUPPURATIVE			1 (2%)
*PERICARDIUM	(50)	(50)	(49)
INFLAMMATION, PYOGRANULOMATOUS		1 (2%)	
*EPICARDIUM	(50)	(50)	(49)
INFLAMMATION, FIBRINOUS	1 (2%)		
INFLAMMATION, CHRONIC			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(49)
CONGESTION, NOS			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	14 (28%)	14 (28%)	11 (22%)
INFLAMMATION, SUPPURATIVE		2 (4%)	1 (2%)
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		1	1
ANIMAL MISSING/NO NECROPSY			1

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

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(49)	(50)	(50)
HYPERPLASIA, FOCAL		1 (2%)	
RESPIRATORY SYSTEM			
#TRACHEA	(45)	(48)	(47)
INFLAMMATION, SUPPURATIVE	1 (2%)		
#LUNG	(48)	(50)	(50)
HEMORRHAGE		1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR			2 (4%)
BRONCHOPNEUMONIA, ACUTE	1 (2%)		
PNEUMONIA INTERSTITIAL CHRONIC			2 (4%)
HYPERPLASIA, FOCAL	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(49)	(50)	(50)
MYELOPOIESIS	1 (2%)		
#BONE MARROW	(38)	(43)	(40)
HEMOSIDEROSIS		1 (2%)	
LEUKEMOID REACTION	1 (3%)		
#SPLEEN	(48)	(49)	(50)
CONGESTION, NOS	1 (2%)		
ANGIECTASIS	1 (2%)		
HYPERPLASIA, LYMPHOID	7 (15%)	1 (2%)	1 (2%)
HEMATOPOIESIS	3 (6%)	4 (8%)	6 (12%)
MYELOPOIESIS	1 (2%)		
#LYMPH NODE	(37)	(42)	(40)
PIGMENTATION, NOS			1 (3%)
#MANDIBULAR L. NODE	(37)	(42)	(40)
HEMOSIDEROSIS	1 (3%)		
HYPERPLASIA, LYMPHOID		3 (7%)	1 (3%)
#HEPATIC LYMPH NODE	(37)	(42)	(40)
HYPERPLASIA, LYMPHOID	1 (3%)		
#MESENTERIC L. NODE	(37)	(42)	(40)
INFLAMMATION, GRANULOMATOUS			1 (3%)
HYPERPLASIA, LYMPHOID			1 (3%)
#RENAL LYMPH NODE	(37)	(42)	(40)
HYPERPLASIA, LYMPHOID	2 (5%)		1 (3%)
#SACRAL LYMPH NODE	(37)	(42)	(40)
HYPERPLASIA, LYMPHOID	1 (3%)		1 (3%)
#LUNG	(48)	(50)	(50)
LEUKOCYTOSIS, NOS	1 (2%)	1 (2%)	
#LIVER	(48)	(50)	(50)
LEUKOCYTOSIS, NOS	1 (2%)		
HEMATOPOIESIS	1 (2%)		1 (2%)
MYELOPOIESIS	1 (2%)		1 (2%)
#ADRENAL	(44)	(46)	(47)
MYELOPOIESIS		1 (2%)	
#THYMUS	(36)	(41)	(41)
HYPERPLASIA, LYMPHOID	5 (14%)		4 (10%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(49)	(50)	(50)
PERIARTERITIS		1 (2%)	
*ABDOMINAL CAVITY	(49)	(50)	(50)
ANEURYSM		1 (2%)	
#HEART	(49)	(49)	(49)
MINERALIZATION			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
*MESENTERY	(49)	(50)	(50)
PERIARTERITIS			1 (2%)
#OVARY	(49)	(49)	(47)
PERIARTERITIS		1 (2%)	
#ADRENAL	(44)	(46)	(47)
PERIARTERITIS			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(44)	(48)	(47)
LYMPHOCYTIC INFLAMMATORY INFILTR	5 (11%)	8 (17%)	7 (15%)
FIBROSIS	1 (2%)		
HYPERPLASIA, FOCAL		1 (2%)	
#LIVER	(48)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	6 (13%)	2 (4%)	5 (10%)
INFLAMMATION, SUPPURATIVE		2 (4%)	1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
DEGENERATION, NOS		1 (2%)	
NECROSIS, NOS	1 (2%)	1 (2%)	
NECROSIS, COAGULATIVE		1 (2%)	
HEMOSIDEROSIS	1 (2%)		
CYTOPLASMIC VACUOLIZATION	10 (21%)	16 (32%)	18 (36%)
FOCAL CELLULAR CHANGE	1 (2%)	1 (2%)	
*GALLBLADDER	(49)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		
#PANCREAS	(47)	(50)	(49)
DILATATION/DUCTS	1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (4%)	4 (8%)	3 (6%)
INFLAMMATION, CHRONIC			1 (2%)
NECROSIS, NOS			1 (2%)
ATROPHY, NOS	1 (2%)		1 (2%)
#ESOPHAGUS	(45)	(47)	(50)
PERFORATION, INFLAMMATORY	2 (4%)		
#STOMACH	(48)	(50)	(49)
MINERALIZATION	1 (2%)		
ULCER, NOS		4 (8%)	1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	4 (8%)	5 (10%)	5 (10%)
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	1 (2%)
#FORESTOMACH	(48)	(50)	(49)
HYPERPLASIA, NOS	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(49)	(50)	(50)
MINERALIZATION			1 (2%)
HYDRONEPHROSIS	1 (2%)		
GLOMERULONEPHRITIS, NOS	2 (4%)	1 (2%)	3 (6%)
LYMPHOCYTIC INFLAMMATORY INFILTR	16 (33%)	23 (46%)	22 (44%)
ATROPHY, NOS		1 (2%)	3 (6%)
METAPLASIA, OSSEOUS		2 (4%)	
#KIDNEY/TUBULE	(49)	(50)	(50)
PIGMENTATION, NOS	1 (2%)		

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM (Continued)			
#URINARY BLADDER	(46)	(47)	(46)
LYMPHOCYTIC INFLAMMATORY INFILTR	18 (39%)	17 (36%)	21 (46%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
ANGIECTASIS	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(41)	(47)	(47)
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, FOCAL	13 (32%)	14 (30%)	14 (30%)
ANGIECTASIS	2 (5%)	1 (2%)	
#ADRENAL	(44)	(46)	(47)
ATROPHY, BROWN		1 (2%)	
#ADRENAL CORTEX	(44)	(46)	(47)
HYPERTROPHY, FOCAL		1 (2%)	
#THYROID	(44)	(47)	(46)
INFLAMMATION, CHRONIC	1 (2%)		
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)	13 (28%)	12 (26%)
REPRODUCTIVE SYSTEM			
#UTERUS	(49)	(50)	(50)
HYDROMETRA			2 (4%)
CONGESTION, NOS	1 (2%)		
HEMORRHAGE		2 (4%)	
HEMORRHAGE, CHRONIC		1 (2%)	
NECROSIS, NOS		1 (2%)	
HEMOSIDEROSIS			1 (2%)
#UTERUS/ENDOMETRIUM	(49)	(50)	(50)
HYPERPLASIA, CYSTIC	39 (80%)	39 (78%)	42 (84%)
#OVARY	(49)	(49)	(47)
CYST, NOS	10 (20%)	15 (31%)	14 (30%)
HEMATOMA, NOS	1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
ANGIECTASIS			2 (4%)
NERVOUS SYSTEM			
#BRAIN	(48)	(50)	(49)
HEMORRHAGE		1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	2 (4%)
INFLAMMATION, SUPPURATIVE	1 (2%)		
SPECIAL SENSE ORGANS			
*EYE	(49)	(50)	(50)
PHTHISIS BULBI		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*MEDIASTINUM	(49)	(50)	(50)
INFLAMMATION, FIBRINOUS	1 (2%)		
*ABDOMINAL CAVITY	(49)	(50)	(50)
STEATITIS			1 (2%)
NECROSIS, FAT	4 (8%)	2 (4%)	3 (6%)
*INGUINAL REGION	(49)	(50)	(50)
NECROSIS, FAT		1 (2%)	
*PERICARDIUM	(49)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
*MESENTERY	(49)	(50)	(50)
INFLAMMATION, FIBRINOUS		1 (2%)	
NECROSIS, FAT	1 (2%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(49)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	15 (31%)	16 (32%)	20 (40%)
INFLAMMATION, CHRONIC SUPPURATIVE	1 (2%)		
ADIPOSE TISSUE			
INFLAMMATION, GRANULOMATOUS			1
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	2	1	
ACCIDENTAL DEATH	1		

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

APPENDIX E

ANALYSES OF PRIMARY TUMORS IN RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF TRIS(2-ETHYLHEXYL)PHOSPHATE

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE

	Vehicle Control	2,000 mg/kg	4,000 mg/kg
Skin: Squamous Cell Papilloma			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	2.5%	10.2%	2.6%
Terminal Rates (c)	1/40 (3%)	3/38 (8%)	1/39 (3%)
Life Table Tests (d)	P=0.593	P=0.170	P=0.756
Incidental Tumor Tests (d)	P=0.570N	P=0.208	P=0.756
Cochran-Armitage Trend Test (d)	P=0.601		
Fisher Exact Tests		P=0.181	P=0.753
Subcutaneous Tissue: Lipoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	7.2%	0.0%	0.0%
Terminal Rates (c)	2/40 (5%)	0/38 (0%)	0/39 (0%)
Life Table Tests (d)	P=0.039N	P=0.131N	P=0.123N
Incidental Tumor Tests (d)	P=0.036N	P=0.105N	P=0.126N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Tests		P=0.121N	P=0.121N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	2/50 (4%)	6/50 (12%)	6/50 (12%)
Adjusted Rates (b)	5.0%	15.3%	15.0%
Terminal Rates (c)	2/40 (5%)	5/38 (13%)	5/39 (13%)
Life Table Tests (d)	P=0.111	P=0.122	P=0.129
Incidental Tumor Tests (d)	P=0.134	P=0.147	P=0.155
Cochran-Armitage Trend Test (d)	P=0.114		
Fisher Exact Tests		P=0.134	P=0.134
Hematopoietic System: Leukemia (All Types)			
Overall Rates (a)	2/50 (4%)	7/50 (14%)	6/50 (12%)
Adjusted Rates (b)	5.0%	17.4%	15.0%
Terminal Rates (c)	2/40 (5%)	5/38 (13%)	5/39 (13%)
Life Table Tests (d)	P=0.120	P=0.075	P=0.129
Incidental Tumor Tests (d)	P=0.154	P=0.105	P=0.155
Cochran-Armitage Trend Test (d)	P=0.122		
Fisher Exact Tests		P=0.080	P=0.134
Pancreas: Acinar Cell Adenoma			
Overall Rates (a)	14/50 (28%)	5/48 (10%)	2/49 (4%)
Adjusted Rates (b)	35.0%	13.2%	5.1%
Terminal Rates (c)	14/40 (35%)	5/38 (13%)	2/39 (5%)
Life Table Tests (d)	P<0.001N	P=0.024N	P=0.001N
Incidental Tumor Tests (d)	P<0.001N	P=0.024N	P=0.001N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Tests		P=0.025N	P=0.001N
Pituitary: Chromophobe Adenoma			
Overall Rates (a)	7/49 (14%)	9/50 (18%)	7/50 (14%)
Adjusted Rates (b)	17.4%	22.2%	17.4%
Terminal Rates (c)	6/39 (15%)	7/38 (18%)	6/39 (15%)
Life Table Tests (d)	P=0.552N	P=0.377	P=0.611N
Incidental Tumor Tests (d)	P=0.489N	P=0.467	P=0.539N
Cochran-Armitage Trend Test (d)	P=0.538N		
Fisher Exact Tests		P=0.410	P=0.597N
Pituitary: Chromophobe Adenoma or Carcinoma			
Overall Rates (a)	9/49 (18%)	9/50 (18%)	8/50 (16%)
Adjusted Rates (b)	21.8%	22.2%	19.4%
Terminal Rates (c)	7/39 (18%)	7/38 (18%)	6/39 (15%)
Life Table Tests (d)	P=0.444N	P=0.581	P=0.495N
Incidental Tumor Tests (d)	P=0.363N	P=0.512N	P=0.393N
Cochran-Armitage Trend Test (d)	P=0.429N		
Fisher Exact Tests		P=0.584N	P=0.482N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	Vehicle Control	2,000 mg/kg	4,000 mg/kg
Adrenal: Pheochromocytoma			
Overall Rates (a)	2/50 (4%)	9/50 (18%)	12/50 (24%)
Adjusted Rates (b)	5.0%	22.3%	29.9%
Terminal Rates (c)	2/40 (5%)	7/38 (18%)	11/39 (28%)
Life Table Tests (d)	P=0.004	P=0.025	P=0.004
Incidental Tumor Tests (d)	P=0.005	P=0.035	P=0.005
Cochran-Armitage Trend Test (d)	P=0.004		
Fisher Exact Tests		P=0.026	P=0.004
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant			
Overall Rates (a)	2/50 (4%)	9/50 (18%)	14/50 (28%)
Adjusted Rates (b)	5.0%	22.3%	34.9%
Terminal Rates (c)	2/40 (5%)	7/38 (18%)	13/39 (33%)
Life Table Tests (d)	P<0.001	P=0.025	P=0.001
Incidental Tumor Tests (d)	P=0.001	P=0.035	P=0.001
Cochran-Armitage Trend Test (d)	P=0.001		
Fisher Exact Tests		P=0.026	P<0.001
Thyroid: Follicular Cell Adenoma or Cystadenoma			
Overall Rates (a)	0/46 (0%)	1/49 (2%)	3/49 (6%)
Adjusted Rates (b)	0.0%	2.6%	7.5%
Terminal Rates (c)	0/39 (0%)	1/38 (3%)	2/38 (5%)
Life Table Tests (d)	P=0.061	P=0.495	P=0.121
Incidental Tumor Tests (d)	P=0.072	P=0.495	P=0.159
Cochran-Armitage Trend Test (d)	P=0.066		
Fisher Exact Tests		P=0.516	P=0.133
Thyroid: Follicular Cell Carcinoma			
Overall Rates (a)	1/46 (2%)	1/49 (2%)	3/49 (6%)
Adjusted Rates (b)	2.6%	2.6%	7.9%
Terminal Rates (c)	1/39 (3%)	1/38 (3%)	3/38 (8%)
Life Table Tests (d)	P=0.195	P=0.756	P=0.296
Incidental Tumor Tests (d)	P=0.195	P=0.756	P=0.296
Cochran-Armitage Trend Test (d)	P=0.217		
Fisher Exact Tests		P=0.737N	P=0.333
Thyroid: Follicular Cell Adenoma, Cystadenoma, or Carcinoma			
Overall Rates (a)	1/46 (2%)	2/49 (4%)	6/49 (12%)
Adjusted Rates (b)	2.6%	5.3%	15.2%
Terminal Rates (c)	1/39 (3%)	2/38 (5%)	5/38 (13%)
Life Table Tests (d)	P=0.028	P=0.491	P=0.057
Incidental Tumor Tests (d)	P=0.032	P=0.491	P=0.071
Cochran-Armitage Trend Test (d)	P=0.034		
Fisher Exact Tests		P=0.524	P=0.066
Thyroid: C-Cell Adenoma			
Overall Rates (a)	4/46 (9%)	3/49 (6%)	1/49 (2%)
Adjusted Rates (b)	10.3%	7.5%	2.4%
Terminal Rates (c)	4/39 (10%)	2/38 (5%)	0/38 (0%)
Life Table Tests (d)	P=0.139N	P=0.512N	P=0.186N
Incidental Tumor Tests (d)	P=0.098N	P=0.460N	P=0.147N
Cochran-Armitage Trend Test (d)	P=0.116N		
Fisher Exact Tests		P=0.464N	P=0.162N
Thyroid: C-Cell Carcinoma			
Overall Rates (a)	2/46 (4%)	2/49 (4%)	3/49 (6%)
Adjusted Rates (b)	5.1%	5.3%	7.9%
Terminal Rates (c)	2/39 (5%)	2/38 (5%)	3/38 (8%)
Life Table Tests (d)	P=0.395	P=0.686	P=0.488
Incidental Tumor Tests (d)	P=0.395	P=0.686	P=0.488
Cochran-Armitage Trend Test (d)	P=0.433		
Fisher Exact Tests		P=0.667N	P=0.530

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	Vehicle Control	2,000 mg/kg	4,000 mg/kg
Thyroid: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	6/46 (13%)	5/49 (10%)	4/49 (8%)
Adjusted Rates (b)	15.4%	12.7%	10.1%
Terminal Rates (c)	6/39 (15%)	4/38 (11%)	3/38 (8%)
Life Table Tests (d)	P=0.321N	P=0.517N	P=0.383N
Incidental Tumor Tests (d)	P=0.273N	P=0.474N	P=0.342N
Cochran-Armitage Trend Test (d)	P=0.271N		
Fisher Exact Tests		P=0.455N	P=0.330N
Pancreatic Islets: Islet Cell Adenoma			
Overall Rates (a)	1/50 (2%)	3/48 (6%)	2/49 (4%)
Adjusted Rates (b)	2.5%	7.9%	5.1%
Terminal Rates (c)	1/40 (3%)	3/38 (8%)	2/39 (5%)
Life Table Tests (d)	P=0.390	P=0.287	P=0.491
Incidental Tumor Tests (d)	P=0.390	P=0.287	P=0.491
Cochran-Armitage Trend Test (d)	P=0.392		
Fisher Exact Tests		P=0.293	P=0.492
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (a)	1/50 (2%)	3/48 (6%)	3/49 (6%)
Adjusted Rates (b)	2.5%	7.9%	7.7%
Terminal Rates (c)	1/40 (3%)	3/38 (8%)	3/39 (8%)
Life Table Tests (d)	P=0.231	P=0.287	P=0.296
Incidental Tumor Tests (d)	P=0.231	P=0.287	P=0.296
Cochran-Armitage Trend Test (d)	P=0.233		
Fisher Exact Tests		P=0.293	P=0.301
Mammary Gland: Fibroadenoma			
Overall Rates (a)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	5.0%	2.6%	7.5%
Terminal Rates (c)	2/40 (5%)	1/38 (3%)	2/39 (5%)
Life Table Tests (d)	P=0.392	P=0.518N	P=0.491
Incidental Tumor Tests (d)	P=0.430	P=0.518N	P=0.552
Cochran-Armitage Trend Test (d)	P=0.399		
Fisher Exact Tests		P=0.500N	P=0.500
Prostate: Adenoma			
Overall Rates (a)	5/47 (11%)	7/47 (15%)	5/50 (10%)
Adjusted Rates (b)	13.5%	18.8%	12.8%
Terminal Rates (c)	5/37 (14%)	6/36 (17%)	5/39 (13%)
Life Table Tests (d)	P=0.526N	P=0.361	P=0.598N
Incidental Tumor Tests (d)	P=0.502N	P=0.400	P=0.598N
Cochran-Armitage Trend Test (d)	P=0.518N		
Fisher Exact Tests		P=0.379	P=0.590N
Testis: Interstitial Cell Tumor			
Overall Rates (a)	42/50 (84%)	41/50 (82%)	43/50 (86%)
Adjusted Rates (b)	97.7%	91.1%	97.7%
Terminal Rates (c)	39/40 (98%)	34/38 (89%)	38/39 (97%)
Life Table Tests (d)	P=0.357	P=0.520	P=0.390
Incidental Tumor Tests (d)	P=0.233	P=0.501N	P=0.440
Cochran-Armitage Trend Test (d)	P=0.446		
Fisher Exact Tests		P=0.500N	P=0.500

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill.
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher's exact test compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE

	Vehicle Control	1,000 mg/kg	2,000 mg/kg
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	5/50 (10%)	5/50 (10%)	8/50 (16%)
Adjusted Rates (b)	13.0%	13.1%	20.9%
Terminal Rates (c)	4/36 (11%)	2/34 (6%)	2/30 (7%)
Life Table Tests (d)	P=0.151	P=0.584	P=0.194
Incidental Tumor Tests (d)	P=0.326	P=0.571N	P=0.480
Cochran-Armitage Trend Test (d)	P=0.221		
Fisher Exact Tests		P=0.630N	P=0.277
Hematopoietic System: Leukemia (All Types)			
Overall Rates (a)	8/50 (16%)	5/50 (10%)	9/50 (18%)
Adjusted Rates (b)	19.0%	13.1%	23.5%
Terminal Rates (c)	4/36 (11%)	2/34 (6%)	2/30 (7%)
Life Table Tests (d)	P=0.314	P=0.343N	P=0.354
Incidental Tumor Tests (d)	P=0.452	P=0.312N	P=0.562
Cochran-Armitage Trend Test (d)	P=0.444		
Fisher Exact Tests		P=0.277N	P=0.500
Pituitary: Chromophobe Adenoma			
Overall Rates (a)	18/50 (36%)	20/49 (41%)	11/49 (22%)
Adjusted Rates (b)	46.0%	53.3%	32.6%
Terminal Rates (c)	15/36 (42%)	16/33 (48%)	8/30 (27%)
Life Table Tests (d)	P=0.224N	P=0.292	P=0.232N
Incidental Tumor Tests (d)	P=0.112N	P=0.327	P=0.206N
Cochran-Armitage Trend Test (d)	P=0.094N		
Fisher Exact Tests		P=0.387	P=0.104N
Pituitary: Chromophobe Carcinoma			
Overall Rates (a)	1/50 (2%)	1/49 (2%)	3/49 (6%)
Adjusted Rates (b)	2.8%	3.0%	8.8%
Terminal Rates (c)	1/36 (3%)	1/33 (3%)	2/30 (7%)
Life Table Tests (d)	P=0.164	P=0.742	P=0.254
Incidental Tumor Tests (d)	P=0.235	P=0.742	P=0.392
Cochran-Armitage Trend Test (d)	P=0.197		
Fisher Exact Tests		P=0.747	P=0.301
Pituitary: Chromophobe Adenoma or Carcinoma			
Overall Rates (a)	19/50 (38%)	21/49 (43%)	14/49 (29%)
Adjusted Rates (b)	48.6%	56.1%	40.2%
Terminal Rates (c)	16/36 (44%)	17/33 (52%)	10/30 (33%)
Life Table Tests (d)	P=0.392N	P=0.287	P=0.413N
Incidental Tumor Tests (d)	P=0.209N	P=0.320	P=0.321N
Cochran-Armitage Trend Test (d)	P=0.194N		
Fisher Exact Tests		P=0.387	P=0.217N
Thyroid: Follicular Cell Cystadenoma			
Overall Rates (a)	1/46 (2%)	1/50 (2%)	3/47 (6%)
Adjusted Rates (b)	3.0%	2.9%	10.1%
Terminal Rates (c)	1/33 (3%)	1/34 (3%)	2/27 (7%)
Life Table Tests (d)	P=0.153	P=0.755N	P=0.241
Incidental Tumor Tests (d)	P=0.135	P=0.755N	P=0.210
Cochran-Armitage Trend Test (d)	P=0.204		
Fisher Exact Tests		P=0.731N	P=0.317
Thyroid: Follicular Cell Carcinoma			
Overall Rates (a)	1/46 (2%)	3/50 (6%)	0/47 (0%)
Adjusted Rates (b)	3.0%	8.8%	0.0%
Terminal Rates (c)	1/33 (3%)	3/34 (9%)	0/27 (0%)
Life Table Tests (d)	P=0.438N	P=0.315	P=0.540N
Incidental Tumor Tests (d)	P=0.438N	P=0.315	P=0.540N
Cochran-Armitage Trend Test (d)	P=0.370N		
Fisher Exact Tests		P=0.341	P=0.495N

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	Vehicle Control	1,000 mg/kg	2,000 mg/kg
Thyroid: Follicular Cell Cystadenoma or Carcinoma			
Overall Rates (a)	2/46 (4%)	4/50 (8%)	3/47 (6%)
Adjusted Rates (b)	6.1%	11.8%	10.1%
Terminal Rates (c)	2/33 (6%)	4/34 (12%)	2/27 (7%)
Life Table Tests (d)	P=0.323	P=0.350	P=0.413
Incidental Tumor Tests (d)	P=0.301	P=0.350	P=0.378
Cochran-Armitage Trend Test (d)	P=0.426		
Fisher Exact Tests		P=0.379	P=0.510
Thyroid: C-Cell Adenoma			
Overall Rates (a)	5/46 (11%)	3/50 (6%)	2/47 (4%)
Adjusted Rates (b)	14.5%	8.4%	7.4%
Terminal Rates (c)	4/33 (12%)	2/34 (6%)	2/27 (7%)
Life Table Tests (d)	P=0.223N	P=0.357N	P=0.302N
Incidental Tumor Tests (d)	P=0.258N	P=0.420N	P=0.327N
Cochran-Armitage Trend Test (d)	P=0.148N		
Fisher Exact Tests		P=0.311N	P=0.209N
Thyroid: C-Cell Carcinoma			
Overall Rates (a)	1/46 (2%)	3/50 (6%)	0/47 (0%)
Adjusted Rates (b)	3.0%	8.8%	0.0%
Terminal Rates (c)	1/33 (3%)	3/34 (9%)	0/27 (0%)
Life Table Tests (d)	P=0.438N	P=0.315	P=0.540N
Incidental Tumor Tests (d)	P=0.438N	P=0.315	P=0.540N
Cochran-Armitage Trend Test (d)	P=0.370N		
Fisher Exact Tests		P=0.341	P=0.495N
Thyroid: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	6/46 (13%)	5/50 (10%)	2/47 (4%)
Adjusted Rates (b)	17.4%	14.1%	7.4%
Terminal Rates (c)	5/33 (15%)	4/34 (12%)	2/27 (7%)
Life Table Tests (d)	P=0.165N	P=0.493N	P=0.205N
Incidental Tumor Tests (d)	P=0.191N	P=0.553N	P=0.224N
Cochran-Armitage Trend Test (d)	P=0.098N		
Fisher Exact Tests		P=0.441N	P=0.127N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	11/50 (22%)	2/50 (4%)	7/50 (14%)
Adjusted Rates (b)	28.8%	5.4%	19.5%
Terminal Rates (c)	9/36 (25%)	1/34 (3%)	3/30 (10%)
Life Table Tests (d)	P=0.248N	P=0.013N	P=0.359N
Incidental Tumor Tests (d)	P=0.189N	P=0.015N	P=0.308N
Cochran-Armitage Trend Test (d)	P=0.152N		
Fisher Exact Tests		P=0.008N	P=0.218N
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	9/50 (18%)	16/50 (32%)	9/49 (18%)
Adjusted Rates (b)	25.0%	43.9%	30.0%
Terminal Rates (c)	9/36 (25%)	14/34 (41%)	9/30 (30%)
Life Table Tests (d)	P=0.352	P=0.054	P=0.430
Incidental Tumor Tests (d)	P=0.457	P=0.095	P=0.430
Cochran-Armitage Trend Test (d)	P=0.526		
Fisher Exact Tests		P=0.083	P=0.584
Uterus: Endometrial Stromal Polyp or Sarcoma			
Overall Rates (a)	9/50 (18%)	17/50 (34%)	9/49 (18%)
Adjusted Rates (b)	25.0%	45.4%	30.0%
Terminal Rates (c)	9/36 (25%)	14/34 (41%)	9/30 (30%)
Life Table Tests (d)	P=0.349	P=0.036	P=0.430
Incidental Tumor Tests (d)	P=0.433	P=0.055	P=0.430
Cochran-Armitage Trend Test (d)	P=0.525		
Fisher Exact Tests		P=0.055	P=0.584

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher's exact test compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE

	Vehicle Control	500 mg/kg	1,000 mg/kg
Subcutaneous Tissue: Sarcoma			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	0/49 (0%)
Adjusted Rates (b)	4.3%	11.0%	0.0%
Terminal Rates (c)	0/34 (0%)	0/28 (0%)	0/38 (0%)
Life Table Tests (d)	P=0.234N	P=0.273	P=0.257N
Incidental Tumor Tests (d)	P=0.598	P=0.240	P=0.604N
Cochran-Armitage Trend Test (d)	P=0.228N		
Fisher Exact Tests		P=0.339	P=0.253N
Integumentary System: Sarcoma			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	0/49 (0%)
Adjusted Rates (b)	7.2%	11.0%	0.0%
Terminal Rates (c)	1/34 (3%)	0/28 (0%)	0/38 (0%)
Life Table Tests (d)	P=0.127N	P=0.415	P=0.127N
Incidental Tumor Tests (d)	P=0.405N	P=0.398	P=0.293N
Cochran-Armitage Trend Test (d)	P=0.122N		
Fisher Exact Tests		P=0.500	P=0.125N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	5/50 (10%)	2/50 (4%)	6/49 (12%)
Adjusted Rates (b)	13.7%	7.1%	15.3%
Terminal Rates (c)	4/34 (12%)	2/28 (7%)	5/38 (13%)
Life Table Tests (d)	P=0.492	P=0.300N	P=0.564
Incidental Tumor Tests (d)	P=0.412	P=0.305N	P=0.439
Cochran-Armitage Trend Test (d)	P=0.417		
Fisher Exact Tests		P=0.218N	P=0.486
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	7/50 (14%)	3/50 (6%)	7/49 (14%)
Adjusted Rates (b)	19.5%	10.7%	17.5%
Terminal Rates (c)	6/34 (18%)	3/28 (11%)	5/38 (13%)
Life Table Tests (d)	P=0.488N	P=0.245N	P=0.537N
Incidental Tumor Tests (d)	P=0.539	P=0.249N	P=0.536
Cochran-Armitage Trend Test (d)	P=0.549		
Fisher Exact Tests		P=0.159N	P=0.597
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	7/50 (14%)	2/50 (4%)	4/49 (8%)
Adjusted Rates (b)	18.0%	7.1%	9.8%
Terminal Rates (c)	3/34 (9%)	2/28 (7%)	2/38 (5%)
Life Table Tests (d)	P=0.167N	P=0.140N	P=0.228N
Incidental Tumor Tests (d)	P=0.374N	P=0.111N	P=0.631N
Cochran-Armitage Trend Test (d)	P=0.195N		
Fisher Exact Tests		P=0.080N	P=0.274N
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	7/50 (14%)	0/50 (0%)	1/49 (2%)
Adjusted Rates (b)	17.8%	0.0%	2.6%
Terminal Rates (c)	4/34 (12%)	0/28 (0%)	1/38 (3%)
Life Table Tests (d)	P=0.008N	P=0.020N	P=0.030N
Incidental Tumor Tests (d)	P=0.008N	P=0.011N	P=0.041N
Cochran-Armitage Trend Test (d)	P=0.008N		
Fisher Exact Tests		P=0.007N	P=0.032N
Liver: Adenoma			
Overall Rates (a)	7/50 (14%)	10/50 (20%)	6/49 (12%)
Adjusted Rates (b)	19.4%	31.2%	15.3%
Terminal Rates (c)	6/34 (18%)	7/28 (25%)	5/38 (13%)
Life Table Tests (d)	P=0.373N	P=0.172	P=0.430N
Incidental Tumor Tests (d)	P=0.469N	P=0.226	P=0.543N
Cochran-Armitage Trend Test (d)	P=0.462N		
Fisher Exact Tests		P=0.298	P=0.516N

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Liver: Carcinoma			
Overall Rates (a)	9/50 (18%)	12/50 (24%)	12/49 (24%)
Adjusted Rates (b)	25.7%	32.7%	30.6%
Terminal Rates (c)	8/34 (24%)	5/28 (18%)	11/38 (29%)
Life Table Tests (d)	P=0.362	P=0.182	P=0.407
Incidental Tumor Tests (d)	P=0.273	P=0.272	P=0.406
Cochran-Armitage Trend Test (d)	P=0.255		
Fisher Exact Tests		P=0.312	P=0.294
Liver: Adenoma or Carcinoma			
Overall Rates (a)	15/50 (30%)	21/50 (42%)	18/49 (37%)
Adjusted Rates (b)	41.2%	54.4%	44.9%
Terminal Rates (c)	13/34 (38%)	11/28 (39%)	16/38 (42%)
Life Table Tests (d)	P=0.430	P=0.055	P=0.465
Incidental Tumor Tests (d)	P=0.278	P=0.100	P=0.382
Cochran-Armitage Trend Test (d)	P=0.275		
Fisher Exact Tests		P=0.149	P=0.310
Testis: Interstitial Cell Tumor			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	1/48 (2%)
Adjusted Rates (b)	2.9%	9.6%	2.6%
Terminal Rates (c)	1/34 (3%)	1/28 (4%)	1/38 (3%)
Life Table Tests (d)	P=0.571N	P=0.247	P=0.737N
Incidental Tumor Tests (d)	P=0.559	P=0.306	P=0.737N
Cochran-Armitage Trend Test (d)	P=0.596		
Fisher Exact Tests		P=0.309	P=0.742

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher's exact test compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE

	Vehicle Control	500 mg/kg	1,000 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	2/48 (4%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	6.3%	2.4%	7.5%
Terminal Rates (c)	2/32 (6%)	1/42 (2%)	3/40 (7%)
Life Table Tests (d)	P=0.483	P=0.405N	P=0.602
Incidental Tumor Tests (d)	P=0.483	P=0.405N	P=0.602
Cochran-Armitage Trend Test (d)	P=0.415		
Fisher Exact Tests		P=0.485N	P=0.519
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	2/48 (4%)	2/50 (4%)	4/50 (8%)
Adjusted Rates (b)	6.3%	4.5%	10.0%
Terminal Rates (c)	2/32 (6%)	1/42 (2%)	4/40 (10%)
Life Table Tests (d)	P=0.329	P=0.612N	P=0.444
Incidental Tumor Tests (d)	P=0.325	P=0.668N	P=0.444
Cochran-Armitage Trend Test (d)	P=0.267		
Fisher Exact Tests		P=0.676N	P=0.359
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	14/49 (29%)	10/50 (20%)	6/50 (12%)
Adjusted Rates (b)	35.5%	23.3%	13.8%
Terminal Rates (c)	7/32 (22%)	9/42 (21%)	4/40 (10%)
Life Table Tests (d)	P=0.012N	P=0.103N	P=0.020N
Incidental Tumor Tests (d)	P=0.024N	P=0.461N	P=0.021N
Cochran-Armitage Trend Test (d)	P=0.027N		
Fisher Exact Tests		P=0.224N	P=0.035N
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	3/49 (6%)	0/50 (0%)	1/50 (2%)
Adjusted Rates (b)	8.5%	0.0%	2.5%
Terminal Rates (c)	2/32 (6%)	0/42 (0%)	1/40 (3%)
Life Table Tests (d)	P=0.135N	P=0.088N	P=0.240N
Incidental Tumor Tests (d)	P=0.145N	P=0.117N	P=0.249N
Cochran-Armitage Trend Test (d)	P=0.171N		
Fisher Exact Tests		P=0.118N	P=0.301N
Liver: Adenoma			
Overall Rates (a)	2/48 (4%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	5.5%	9.5%	7.5%
Terminal Rates (c)	1/32 (3%)	4/42 (10%)	3/40 (7%)
Life Table Tests (d)	P=0.517	P=0.453	P=0.591
Incidental Tumor Tests (d)	P=0.510	P=0.404	P=0.581
Cochran-Armitage Trend Test (d)	P=0.436		
Fisher Exact Tests		P=0.359	P=0.520
Liver: Carcinoma			
Overall Rates (a)	0/48 (0%)	4/50 (8%)	7/50 (14%)
Adjusted Rates (b)	0.0%	9.5%	16.7%
Terminal Rates (c)	0/32 (0%)	4/42 (10%)	5/40 (13%)
Life Table Tests (d)	P=0.012	P=0.103	P=0.019
Incidental Tumor Tests (d)	P=0.006	P=0.103	P=0.007
Cochran-Armitage Trend Test (d)	P=0.007		
Fisher Exact Tests		P=0.064	P=0.007
Liver: Adenoma or Carcinoma			
Overall Rates (a)	2/48 (4%)	8/50 (16%)	10/50 (20%)
Adjusted Rates (b)	5.5%	19.0%	23.8%
Terminal Rates (c)	1/32 (3%)	8/42 (19%)	8/40 (20%)
Life Table Tests (d)	P=0.031	P=0.105	P=0.039
Incidental Tumor Tests (d)	P=0.020	P=0.087	P=0.020
Cochran-Armitage Trend Test (d)	P=0.016		
Fisher Exact Tests		P=0.053	P=0.017

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TRIS(2-ETHYLHEXYL)PHOSPHATE (Continued)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Pituitary: Adenoma			
Overall Rates (a)	6/41 (15%)	8/47 (17%)	2/47 (4%)
Adjusted Rates (b)	22.2%	20.0%	5.0%
Terminal Rates (c)	6/27 (22%)	8/40 (20%)	2/40 (5%)
Life Table Tests (d)	P=0.030N	P=0.534N	P=0.041N
Incidental Tumor Tests (d)	P=0.030N	P=0.534N	P=0.041N
Cochran-Armitage Trend Test (d)	P=0.082N		
Fisher Exact Tests		P=0.496	P=0.094N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher's exact test compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

APPENDIX F

HISTORICAL INCIDENCES OF TUMORS IN F344/N RATS AND B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE

TABLE F1. HISTORICAL INCIDENCE OF ADRENAL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Pheochromocytoma	Malignant Pheochromocytoma	All Pheochromocytomas
Historical Incidence at Litton Bionetics, Inc.			
Tris(2-ethylhexyl)phosphate	2/50	0/50	2/50
Diallylphthalate	13/50	0/50	13/50
2,4-Toluene diisocyanate	12/50	0/50	12/50
Total	27/150 (18.0%)	0/150 (0.0%)	27/150 (18.0%)
SD (b)	12.17%	0%	12.17%
Range (c)			
High	13/50	0/50	13/50
Low	2/50	0/50	2/50
Overall Historical Incidence			
Total	193/1,135 (17.0%)	10/1,135 (0.9%)	202/1,135 (17.8%)
SD (b)	10.20%	1.51%	10.13%
Range (c)			
High	19/49	3/48	19/49
Low	1/50	0/52	1/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F2. HISTORICAL INCIDENCE OF THYROID FOLLICULAR CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Adenoma	Carcinoma	All Benign or Malignant Tumors
Historical Incidence at Litton Bionetics, Inc.			
Tris(2-ethylhexyl)phosphate	0/46	1/46	1/46
Diallylphthalate	0/49	0/49	0/49
2,4-Toluene diisocyanate	0/46	0/46	0/46
Total	0/141 (0.0%)	1/141 (0.7%)	1/141 (0.7%)
SD (b)	0.0%	1.26%	1.26%
Range (c)			
High	0/49	1/46	1/46
Low	0/49	0/49	0/49
Overall Historical Incidence			
Total	5/1,109 (0.5%)	15/1,109 (1.4%)	21/1,109 (1.9%)
SD (b)	1.06%	2.08%	2.42%
Range (c)			
High	2/50	4/50	5/50
Low	0/52	0/52	0/52

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F3. HISTORICAL INCIDENCE OF PANCREATIC ACINAR CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Litton Bionetics, Inc.			
Tris(2-ethylhexyl)phosphate	14/50	0/50	14/50
Diallylphthalate	0/50	0/50	0/50
2,4-Toluene diisocyanate	1/47	0/47	1/47
Total	15/147 (10.2%)	0/147 (0.0%)	15/147 (10.2%)
SD (b)	15.59%	0.00%	15.59%
Range (c)			
High	14/50	0/50	14/50
Low	0/50	0/50	0/50
Overall Historical Incidence			
Total	37/1,128 (3.3%)	2/1,128 (0.2%)	38/1,128 (3.4%)
SD (b)	7.02%	0.58%	7.02%
Range (c)			
High	(d) 14/50	1/49	14/50
Low	0/50	0/52	0/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Second highest: 11/50; third highest: 2/52

TABLE F4. HISTORICAL INCIDENCE OF MAMMARY GLAND TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Fibroma	Fibroadenoma	Fibroma or Fibroadenoma
Historical Incidence at Litton Bionetics, Inc.			
Tris(2-ethylhexyl)phosphate	0/50	11/50	11/50
Diallylphthalate	0/50	12/50	12/50
2,4-Toluene diisocyanate	0/50	15/50	15/50
Total	0/150 (0.0%)	38/150 (25.3%)	38/150 (25.3%)
SD (b)	0.00%	4.16%	4.16%
Range (c)			
High	0/50	15/50	15/50
Low	0/50	11/50	11/50
Overall Historical Incidence			
Total	3/1,147 (0.3%)	269/1,147 (23.5%)	272/1,147 (23.7%)
SD (b)	0.71%	9.38%	9.08%
Range (c)			
High	1/48	18/50	18/50
Low	0/52	1/48	2/48

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F5. HISTORICAL INCIDENCE OF CIRCULATORY SYSTEM TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Hemangioma	Hemangiosarcoma	Hemangioma or Hemangiosarcoma
Historical Incidence at Litton Bionetics, Inc.			
Tris(2-ethylhexyl)phosphate	0/50	7/50	7/50
2,4-Toluene diisocyanate	0/50	1/50	1/50
Diallylphthalate	0/50	4/50	4/50
Total	0/150 (0%)	12/150 (8.0%)	12/150 (8.0%)
SD (b)	0.00%	6.00%	6.00%
Range (c)			
High	1/50	7/50	7/50
Low	0/50	0/50	0/50
Overall Historical Incidence			
Total	11/1,090 (1.0%)	44/1,090 (4.0%)	53/1,090 (4.9%)
SD (b)	1.89%	3.95%	3.64%
Range (c)			
High	3/48	7/50	7/50
Low	0/50	0/50	0/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F6. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Litton Bionetics, Inc.			
Tris(2-ethylhexyl)phthalate	2/48	0/48	2/48
2,4-Toluene diisocyanate	2/50	2/50	4/50
Diallylphthalate	0/50	1/50	1/50
Total	4/148 (2.7%)	3/148 (2%)	7/148 (4.7%)
SD (b)	2.36%	2.00%	3.04%
Range (c)			
High	2/48	2/50	4/50
Low	0/50	0/48	1/50
Overall Historical Incidence			
Total	47/1,176 (4.0%)	34/1,176 (2.9%)	80/1,176 (6.8%)
SD (b)	2.55%	2.18%	3.37%
Range (c)			
High	5/50	4/50	7/50
Low	0/50	0/50	1/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F7. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Leukemia	Lymphoma	Leukemia or Lymphoma
Historical Incidence at Litton Bionetics, Inc.			
Tris(2-ethylhexyl)phosphate	0/49	14/49	14/49
2,4-Toluene diisocyanate	3/50	10/50	13/50
Diallylphthalate	1/50	16/50	16/50
Total	4/149 (2.7%)	40/149 (26.8%)	43/149 (28.9%)
SD (b)	3.06%	6.18%	3.01%
Range (c)			
High	3/50	16/50	16/50
Low	0/49	10/50	13/50
Overall Historical Incidence			
Total	22/1,187 (1.9%)	237/1,187 (20.0%)	258/1,187 (21.7%)
SD (b)	3.13%	8.74%	9.11%
Range (c)			
High	5/48	17/50	20/49
Low	0/50	2/48	4/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F8. HISTORICAL INCIDENCE OF PITUITARY TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Adenoma, NOS	All Adenoma	Carcinoma, NOS	All Adenoma or Carcinoma
Historical Incidence at Litton Bionetics, Inc.				
Tris(2-ethylhexyl)phosphate	6/41	6/41	0/41	6/41
2,4-Toluene diisocyanate	4/46	4/46	0/46	4/46
Diallylphthalate	4/44	4/44	0/44	4/44
Total	14/131 (10.7%)	14/131 (10.7%)	0/131 (0%)	14/131 (10.7%)
SD (b)	3.32%	3.32%	0.00%	3.32%
Range (c)				
High	6/41	6/41	0/46	6/41
Low	4/46	4/46	0/46	4/46
Overall Historical Incidence				
Total	109/932 (11.7%)	116/932 (12.4%)	9/932 (1.0%)	125/932 (13.4%)
SD (b)	6.62%	6.07%	2.10%	6.92%
Range (c)				
High	11/43	11/43	3/47	14/49
Low	0/48	2/44	0/48	2/44

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

APPENDIX G

MUTAGENICITY OF TRIS(2-ETHYLHEXYL)PHOSPHATE IN SALMONELLA

TABLE G1. NATIONAL TOXICOLOGY PROGRAM DATA ON THE MUTAGENICITY OF TRIS(2-ETHYLHEXYL)-PHOSPHATE IN SALMONELLA

Strain	Dose (µg/plate)	Revertants/plate (a) -S9	+S9 (rat)	+S9 (hamster)
TA 100	0	76 ± 2.5	91 ± 4.1	101 ± 6.1
	100	69 ± 2.1	89 ± 5.5	89 ± 3.1
	333	78 ± 2.3	92 ± 8.1	87 ± 4.1
	1,000	71 ± 8.7	96 ± 11.9	106 ± 10.3
	3,333	63 ± 9.2	98 ± 5.2	102 ± 6.5
	10,000	56 ± 1.2	97 ± 6.4	101 ± 5.8
TA 1535	0	5 ± 1.9	8 ± 1.5	7 ± 2.1
	100	5 ± 0.9	4 ± 1.2	4 ± 0.6
	333	3 ± 0.9	6 ± 0.6	5 ± 1.5
	1,000	4 ± 1.5	4 ± 1.5	5 ± 0.7
	3,333	8 ± 1.2	3 ± 0.3	4 ± 0.9
	10,000	4 ± 1.2	7 ± 0.3	7 ± 1.5
TA 1537	0	3 ± 0.7	5 ± 0.6	11 ± 2.8
	100	4 ± 0.7	6 ± 0.9	9 ± 1.2
	333	5 ± 1.5	6 ± 0.6	7 ± 0.3
	1,000	3 ± 1.0	4 ± 0.3	9 ± 1.2
	3,333	4 ± 0.3	4 ± 0.7	7 ± 3.8
	10,000	3 ± 0.9	5 ± 1.3	7 ± 1.9
TA 98	0	11 ± 2.3	19 ± 2.5	18 ± 5.6
	100	8 ± 1.5	13 ± 2.8	19 ± 0.3
	333	10 ± 0.6	16 ± 0.7	18 ± 2.9
	1,000	8 ± 1.0	17 ± 2.1	19 ± 2.1
	3,333	9 ± 1.7	14 ± 2.0	18 ± 1.8
	10,000	8 ± 1.7	16 ± 1.7	17 ± 4.5

(a) The S9 fractions were prepared from the livers of Aroclor 1254-induced animals (male Sprague-Dawley rats and male Syrian hamsters). Cells and test compound or solvent (DMSO) were incubated for 20 minutes at 37° C in the presence of either S9 or buffer (Yahagi et al., 1975). After the addition of soft agar, the contents of each tube were poured onto minimal medium, and the plates were incubated at 37° C for 48 hours (Ames et al., 1975). The experiment was performed twice, each in triplicate; because the results were similar, data from only one experiment are shown.

APPENDIX H

CHEMICAL CHARACTERIZATION OF TRIS(2-ETHYLHEXYL)PHOSPHATE

APPENDIX H. CHEMICAL CHARACTERIZATION

I. Identity and Purity Determinations Performed by the Analytical Chemistry Laboratory

A. Lot No. TP 113077

1. Physical Properties

a. Appearance: Clear, colorless, viscous liquid

b. Boiling Point:	Determined	Literature Values
	294.9° C ± 0.1 (δ)° C (visual, micro boiling point), 190°-233° C (DuPont 900 DTA) There is evidence of decomposition by DTA between 190° and 233° C, which is not seen by visual boiling point. Some decomposition is evident by darkening after 295° C by visual boiling point.	216°-220° C (NPIRI Raw Materials Data Handbook, 1975)

c. Index of Refraction:	Determined	Literature Values
	n_D^{20}: 1.4426 ± 0.0003(δ)	No reference available

d. Density:	Determined	Literature Values
	d_{26}^{25}: 0.9229 ± 0.0002	d^{25}: 0.93 (NPIRI Raw Materials Data Handbook, 1975)

2. Spectral Data

a. Infrared	Determined	Literature Values
(1) Instrument:	Beckman IR-12	
(2) Cell:	Thin film between silver chloride plates	
(3) Results:	See Figure 5	No literature reference found; spectrum consistent with structure

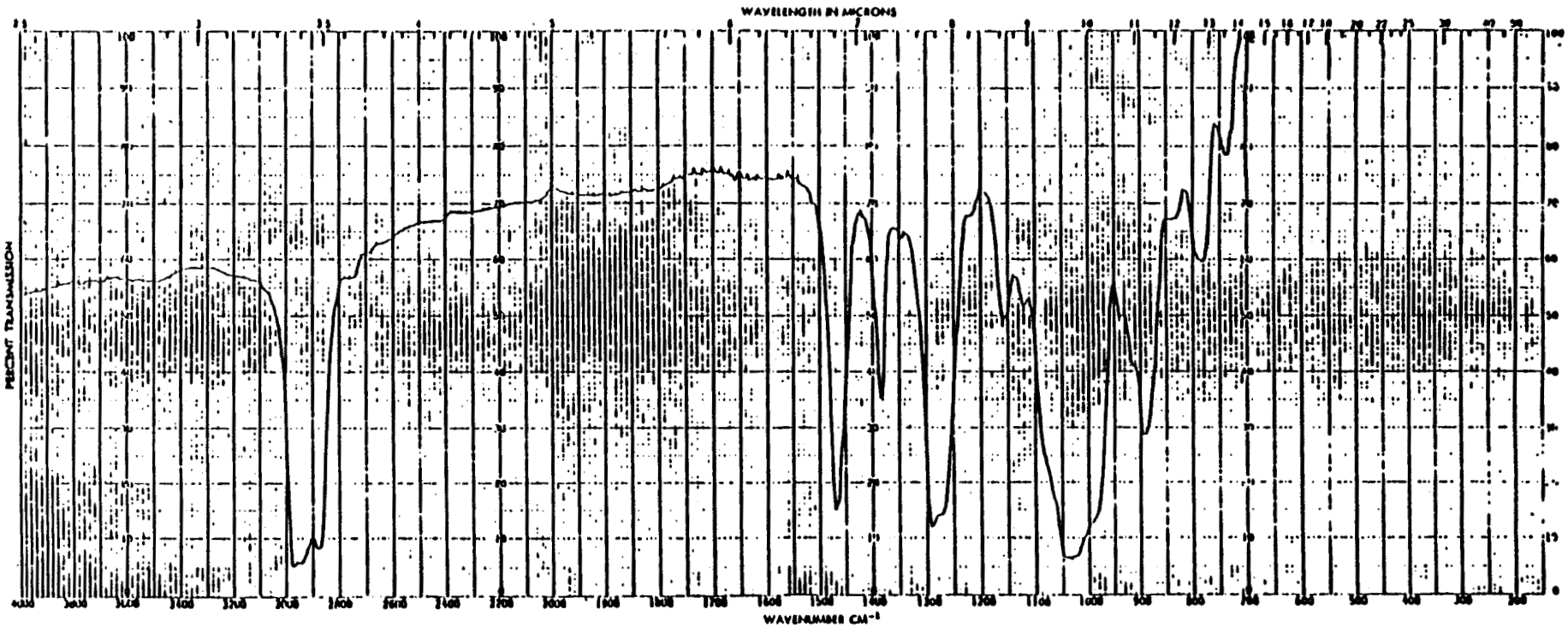

FIGURE 5. INFRARED ABSORPTION SPECTRUM OF TRIS(2-ETHYLHEXYL)PHOSPHATE (LOT NO. TP113077)

b. Ultraviolet/Visible	Determined	Literature Values
(1) Instrument:	Cary 118	
(2) Solvent:	95% ethanol	
(3) Results:	No absorbance between 350 and 800 nm (visible range). No maximum between 216 and 350 nm (ultraviolet range), but a small absorbance, less than 0.5 absorbance units, toward the short wavelength end of spectrum	No literature reference found; spectrum consistent with structure

c. Nuclear Magnetic Resonance

	Determined	Literature Values
(1) Instrument:	Varian EM-360-A	
(2) Solvent:	30% in deuterated chloroform; tetramethyl-silane internal standard	
(3) Assignments:	See Figure 6	No literature reference found. Spectrum consistent with structure.

(4) Chemical Shift (δ):

a 0.68-1.13 ppm
b 1.13-1.73 ppm
c 3.84-4.03 ppm

(5) Coupling Constant:

$J_{b\text{-}c} = 5$ Hz
$J_{P\text{-}c} = 5$ Hz

(6) Integration Ratios:

a 16.15
b 28.57
c 6.21

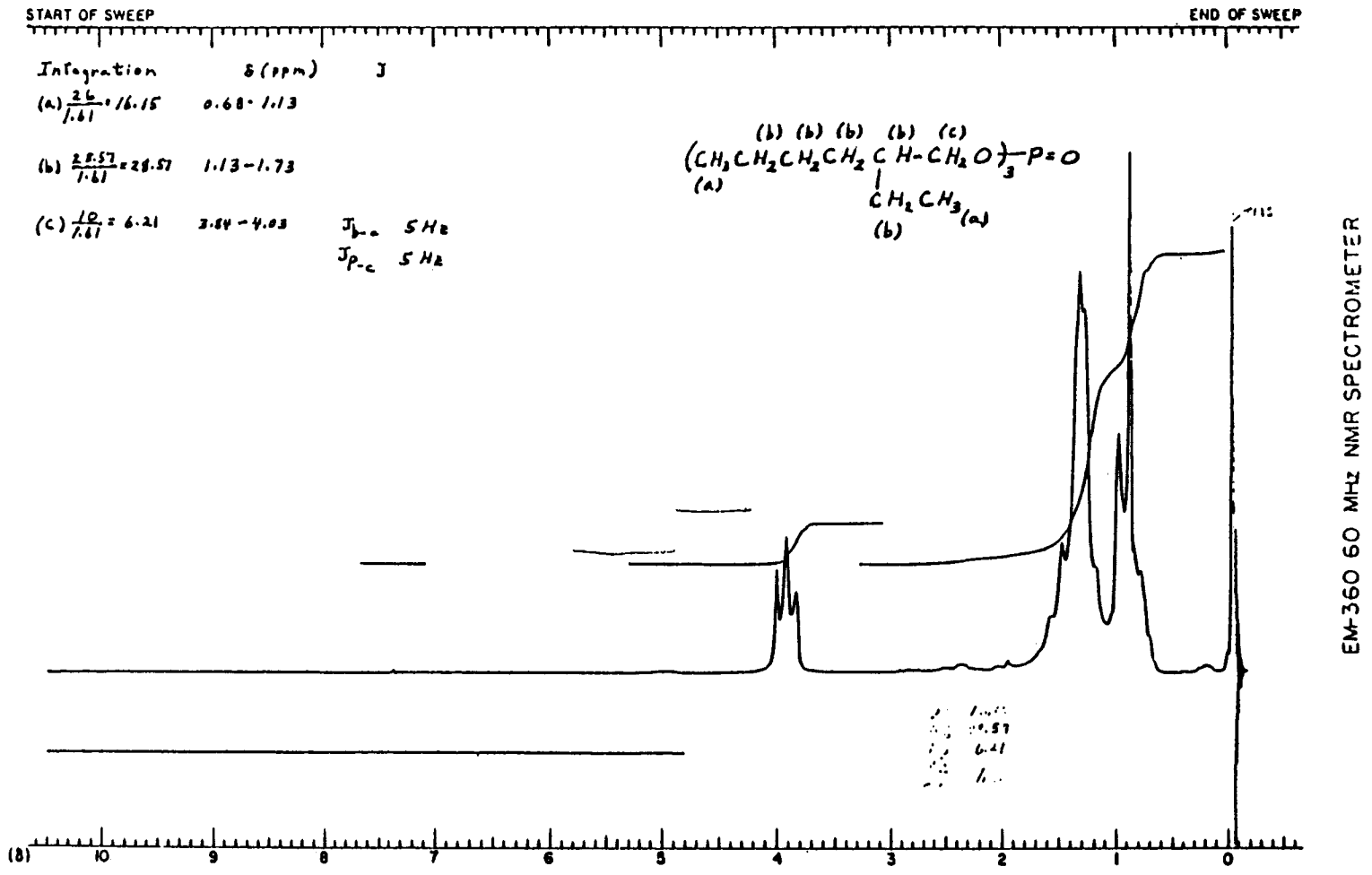

FIGURE 6. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF TRIS(2-ETHYLHEXYL)PHOSPHATE (LOT NO. TP113077)

3. Water Analysis (Karl Fischer):

0.087% ± 0.004(δ)%

4. Elemental Analysis:

Element	C	H	P
Theory (T)	66.32	11.83	7.13
Determined (D)	68.28 68.20	11.84 11.85	7.17 7.10
Percent D/T	102.9	100.1	100.1

5. Chromatographic Analyses

a. Thin-Layer Chromatography

(1) Plates: Silica gel 60, F-254
(2) Reference Standard: Tri-n-butyl phosphate
(3) Amount Spotted: 100 µg and 300 µg (10 µg/µl in acetone)
(4) Visualization: Plates sprayed with 4N H_2SO_4 and heated until spots appear, then sprayed with 0.5% $KMnO_4$ in 1N NaOH and heated until spots darken.

System 1: Chloroform, 100%

(a) R_f: Origin (slight trace), 0.35 (major), 0.57 (trace), 0.76 (trace)

(b) R_{st}: Origin, 2.69, 4.38, 5.85

System 2: Methylethylketone, 100%

(a) R_f: Origin (trace), 0.73 (major)

(b) R_{st}: Origin, 1.20

b. Gas Chromatography:

(1) Instrument: Varian 3740
(2) Detector: Flame ionization
(3) Carrier gas: Nitrogen
(4) Flow Rate: 70 ml/min
(5) Inlet temperature: 200° C
(6) Detector temperature: 350° C

System 1:

(a) Column: 3% OV-17 on 80/100 Supelcoport, 1.8 m × 4 mm ID, glass

(b) Oven temperature program: 50° C, 5 min; 50°-250° C at 10° C/min

(c) Sample injected: A 20% solution (4 µl) of tris(2-ethylhexyl)phosphate in toluene was injected. Solutions of 1.0% and 0.5% in toluene were injected to quantitate the major peak and check for overloading.

(b) Results: Major peak and six impurities. One impurity had an area of 1.7% of the area of the major peak. The other five impurities had a total area of 0.45% of the major peak area. All impurities eluted before the major peak.

Peak	Retention Time (min.)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	9.68	0.37	0.19
2	14.84	0.57	0.11
3	20.86	0.81	0.05
4	23.28	0.90	0.09
5	24.24	0.94	0.01
6	25.03	0.97	1.7
7	25.85	1.0	100

System 2:

(a) Column: 3% Dexsil 400 on 80/100 Chromasorb W(AW), 1.8 m × 4 mm ID, glass

(b) Oven temperature program: 50° C, 5 min; 50°-250° C at 10° C/min

(c) Sample injected: A 20% solution (4 µl) of tris(2-ethylhexyl)phosphate in toluene was injected. Solutions of 1.0% and 0.5% in toluene were injected to quantitate the major peak and check for overloading.

(b) Results: Major peak and six impurities. One impurity had an area of 2.2% of the area of the major peak. The other five impurities had a total area of 0.4% of the major peak area. All impurities eluted before the major peak.

Peak	Retention Time (min.)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	11.89	0.46	0.19
2	15.33	0.59	0.10
3	21.21	0.82	0.05
4	23.25	0.90	0.01
5	23.70	0.92	0.08
6	25.14	0.97	2.2
7	25.90	1.0	100

B. Lot No. TP 121580

1. Physical Properties

a. Appearance:	Clear, colorless, viscous liquid

2. Spectral Data

a. Infrared	**Determined**	**Literature Values**
(1) Instrument:	Perkin-Elmer 283	
(2) Cell:	Thin film between silver chloride plates	
(3) Results:	See Figure 7	No literature reference found; spectrum consistent with structure.

b. Ultraviolet/Visible	**Determined**	**Literature Values**
(1) Instrument:	Cary 219	
(2) Solvent:	95% ethanol	
(3) Results:	No absorbance between 350 and 800 nm (visible range). No maximum between 215 and 350 nm (ultraviolet range), but a slight gradual increase in absorbance toward 215 nm at concentrations of 1.0% (v/v)	No literature reference found; spectrum consistent with structure

c. Nuclear Magnetic Resonance

	Determined	**Literature Values**
(1) Instrument:	Varian EM-360-A	
(2) Solvent:	Deuterated chloroform; tetramethylsilane internal standard	
(3) Assignments:	See Figure 8	No literature reference found. Spectrum consistent with structure.

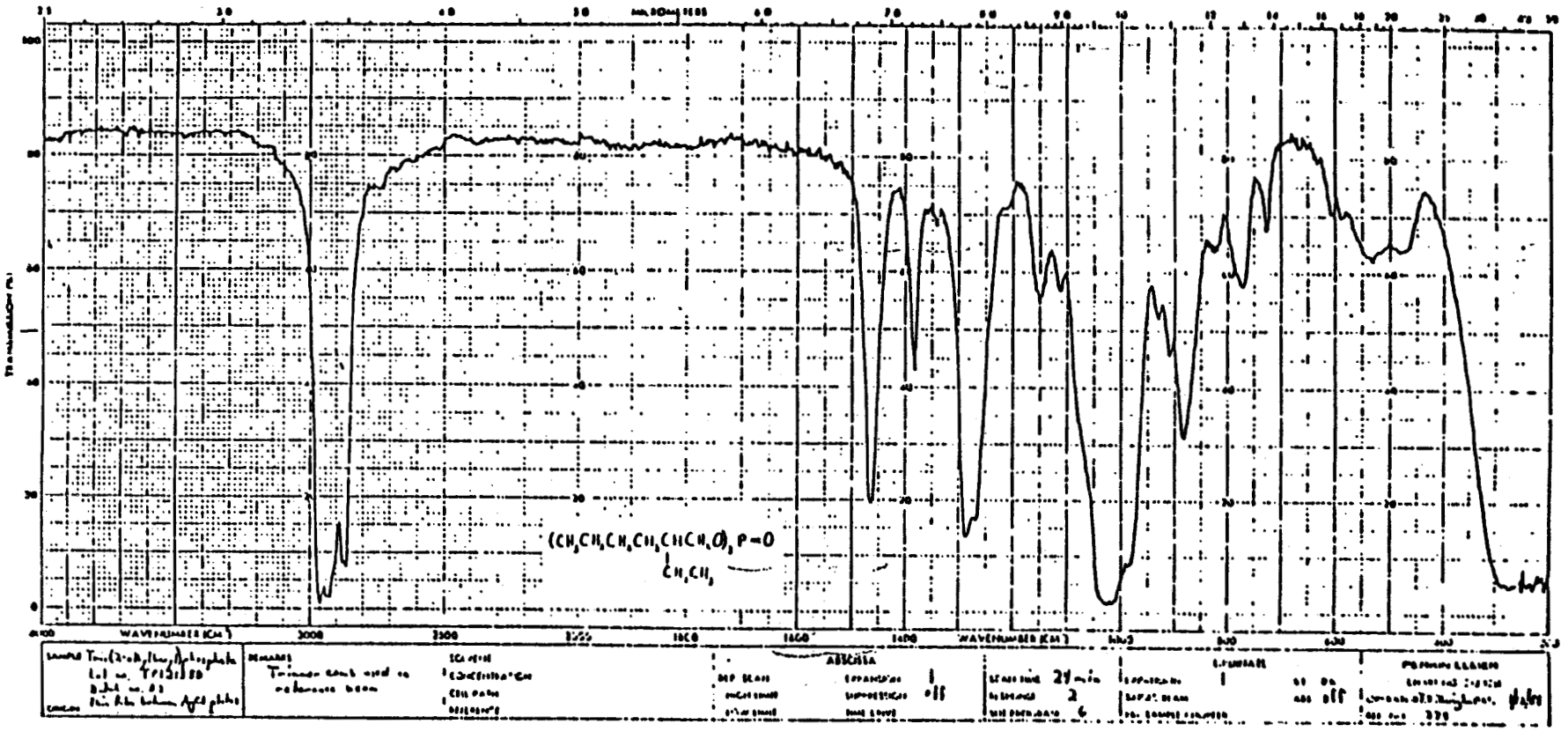

FIGURE 7. INFRARED ABSORPTION SPECTRUM OF TRIS(2-ETHYLHEXYL)PHOSPHATE (LOT NO. TP121580)

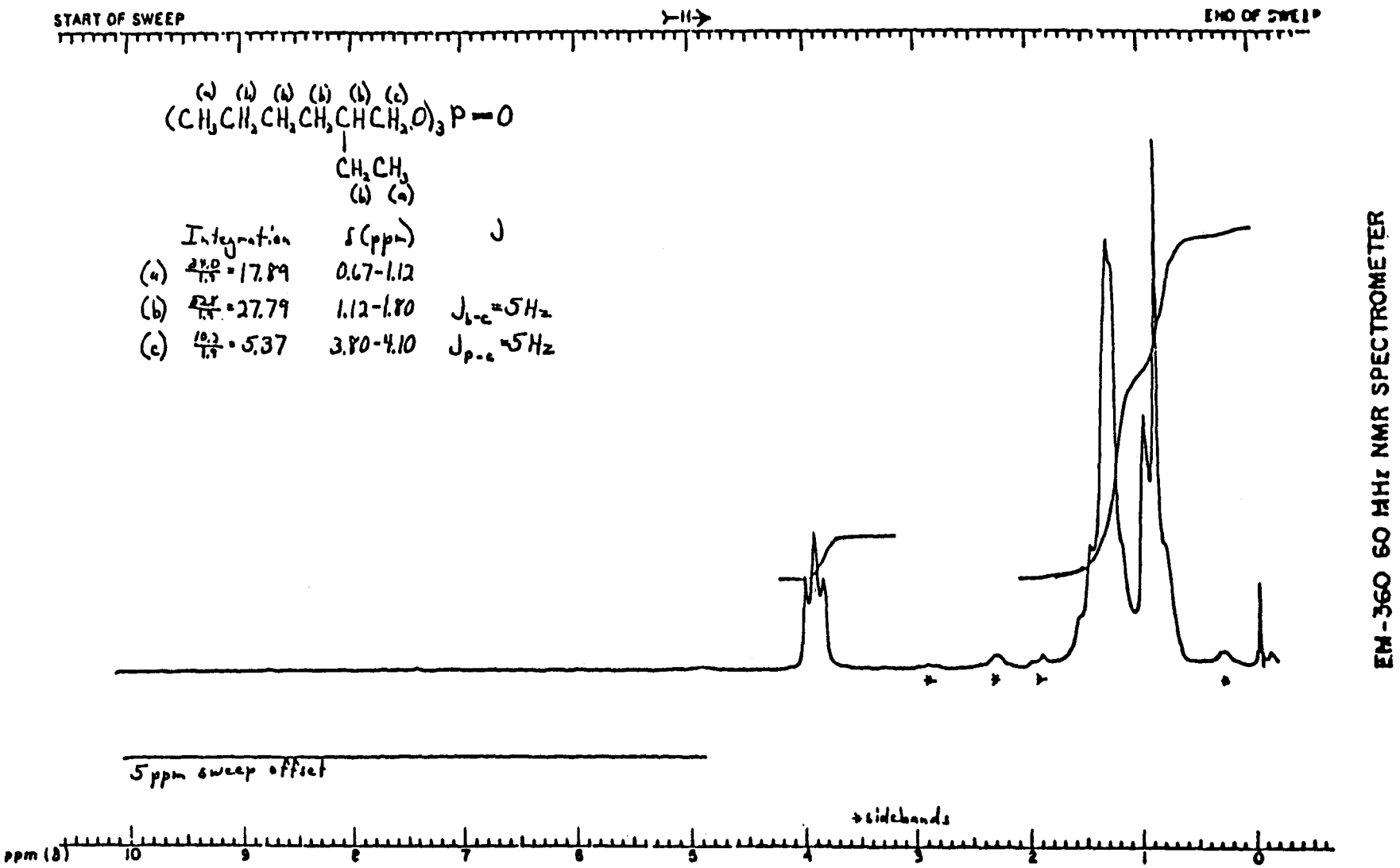

FIGURE 8. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF TRIS(2-ETHYLHEXYL)PHOSPHATE (LOT NO. TP121580)

(4) Chemical Shift (δ):

a 0.67-1.12 ppm
b 1.12-1.80 ppm
c 3.80-4.10 ppm

(5) Coupling Constant:

J_{b-c} = 5 Hz
J_{P-c} = 5 Hz

(6) Integration Ratios:

a 17.89
b 27.79
c 5.37

3. Water Analysis (Karl Fischer):

0.064% ± 0.002(δ)%

4. Elemental Analysis:

Element	C	H	P
Theory (T)	66.32	11.83	7.13
Determined (D)	66.53 66.56	12.15 12.28	7.32 7.16
Percent D/T	100.3	103.3	101.5

5. Chromatographic Analyses

a. Thin-Layer Chromatography

(1) Plates: Silica gel 60, F-254, 0.25 mm layer thickness
(2) Reference Standard: Tri-n-butyl phosphate,100 µg (10 µl of a 10 µg/µl solution in acetone)
(3) Amount Spotted: 10, 100, and 300 µg (1, 10, and 30 µg/µl of a 1µg/µl solution in acetone)
(4) Visualization: Plates sprayed with 4N H_2SO_4 and heated until spots appear, then sprayed with 0.5% $KMnO_4$ in 1N NaOH, and heated until spots darken.

System 1: Chloroform, 100%

(a) R_f: 0.30 (major)

(b) R_{st}: 2.00

System 2: Methylethylketone, 100%

(a) R_f: 0.69

(b) R_{st}: 1.25

b. Gas Chromatography:

(1) Instrument: Varian 3700
(2) Detector: Flame ionization
(3) Carrier gas: Nitrogen
(4)Carrier flow Rate: 70 ml/min
(5) Inlet temperature: 200° C
(6) Detector temperature: 250° C

System 1:

(a) Column: 3% SP-2250 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass.
[Note: This column is a methyl phenyl silicone column (50% phenyl) like OV-17 and is a recommended substitute for OV-17.]

(b) Oven temperature program: 50° C, 5 min; 50°-250° C at 10° C/min

(c) Samples injected: Neat liquid (4 µl) and solutions of 1% and 0.5% (v/v) in toluene to detect impurities, quantitate the major peak, and check for overloading.

(b) Results: Major peak and five impurities with a combined area of 0.45% of the major peak area. All impurities eluted before the major peak.

Peak	Retention Time (min.)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	11.5-13.6	0.45-0.53	0.03
2	14.8	0.58	0.05
3	20.7	0.81	0.08
4	24.1-25.0	0.95-0.98	0.02
5 (a)	25.1	0.99	0.27
6	25.4	1.00	100

(a) Shoulder on major peak

System 2:

(a) Column: 3% Dexsil 400 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass

(b) Oven temperature program: 50° C, 5 min; 50°-250° C at 10° C/min

(c) Samples injected: Neat liquid (3 µl) and solutions of 1.0% and 0.5% (v/v) in toluene to detect impurities, quantitate the major peak and check for detector overloading.

(d) Results: Major peak and five impurities with a combined area of 1.1% of the major peak area. All impurities eluted before the major peak. The largest impurity had an area 0.78% that of the major peak.

Peak	Retention Time (min.)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	11.2-11.8	0.41-0.43	0.09
2	16.6	0.61	0.06
3	22.5	0.83	0.06
(a) 4	24.3-26.4	0.89-0.97	0.14
(b) 5	26.7	0.98	0.78
6	27.2	1.00	100

(a) Group of unresolved peaks
(b) Shoulder on major peak

II. Test Chemical Stability Study Performed by the Analytical Chemistry Laboratory

A. Sample Preparation and Storage: Samples of tris(2-ethylhexyl)phosphate were stored at −20°, 5°, 25°, and 60° C for 2 weeks in glass screw-capped tubes with Teflon®-lined lids.

B. Analytical Method: Aliquots (approximately 100 mg) of each of the above samples were taken, and analyzed by gas chromatography using the following system:

1. **Instrument:** Varian 3740
2. **Column:** 3% Dexsil 400 on 80/100 Chromasorb W(AW), 1.8 m × 4 mm ID, glass
3. **Detector:** Flame ionization
4. **Carrier gas:** Nitrogen
5. **Carrier flow rate:** 70 ml/min
6. **Inlet temperature:** 200° C
7. **Detector temperature:** 350° C
8. **Oven temperature program:** 235° C isothermal
9. **Retention time of major component:** 5.3 min
10. **Retention time of internal standard** (dibutyl cyclohexanephosphonate)**:** 1.0 min
11. **Samples injected:** For each storage temperature, a solution was injected (4 µl) of 0.9% tris(2-ethylhexyl)phosphate and 0.5% dibutyl cyclohexanephosphonate in toluene. Sample peaks were compared with internal standard peaks.

C. Results

Storage Temperature	Percent Recovery
−20° C	100.0 ± 1.7
+ 5° C	100.0 ± 1.7
+25° C	100.6 ± 1.7
+60° C	99.5 ± 1.7

D. Conclusion : Tris(2-ethylhexyl)phosphate is stable as the bulk chemical when stored for 2 weeks at temperatures of up to 60° C.

III. Test Chemical Stability at the Testing Laboratory

A. Storage Conditions: The chemical was stored at 4° C.

B. Analytical Method:

1. Purity Determination: Aliquots of standard, reference, and test samples were diluted in toluene and the purity of each were determined using the following gas chromatographic system:

a. **Instrument:** Hewlett Packard® 5880 with 7672A liquid sampler
b. **Column:** 3% OV-17 on 80/100 Supelcoport, 1.8 m × 2 mm ID, silanized glass
c. **Detector:** Flame ionization
d. **Carrier gas:** Nitrogen
e. **Carrier flow rate:** 40 ml/min
f. **Inlet temperature:** 225° C
g. **Detector temperature:** 275° C
h. **Oven temperature program:** 50° C for 5 min; 50°-250° C at 10° C/min; 250° C for 10 min

2. Identity Determination: The infrared absorption spectra of the sample were obtained as a neat liquid between KBr plates using a Perkin Elmer® Model 398 spectrophotometer.

C. Results:

1. Purity:

Date of Analysis	Lot No.	Area (percent of total) Bulk	Reference
12/20/78	TP113077	95.5	--
7/12/79	TP113077	96.0	97.0
11/15/79	TP113077	98.9	98.9
4/01/80	TP113077	98.2	98.2
7/17/80	TP113077	97.5	97.5
12/11/80	TP113077	97.6	97.6
2/17/81	TP113077	97.8	97.9
2/16/81	TP121580	98.9	--
6/22/81	TP121580	99.0	98.9
9/05/81	TP121580	99.1	99.2
1/15/82	TP121580	99.1	99.2

2. Identity: All spectra were consistent with the original spectra supplied by the analytical chemistry laboratory.

D. Conclusion: No notable degradation occurred throughout the studies.

APPENDIX I

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

APPENDIX I. PREPARATION AND CHARACTERIZATION

I. Studies Conducted at the Analytical Chemistry Laboratory

A. Preparation Procedure

1. Stock Solution: A stock solution of the chemical was prepared by weighing 10.007 g of tris(2-ethylhexyl)phosphate into a 50-ml volumetric flask and diluting to the mark with corn oil, with occasional swirling. The solution was then manually shaken for 30 sec and placed in an ultrasonic vibratory bath for 5 min. As soon as the solution had been prepared, eight accurately weighed 1.6-g aliquots were removed and sealed in separate 60-ml septum vials (Microsep F-138 gas chromatography septa with Teflon® film facing, from Canton Biomedical Products, Inc.; aluminum crimp seals from Wheaton Scientific Co., Inc.). Duplicate aliquots were used as initial, or zero-time samples, and for storage at room temperature (25° C) for 1, 5, and 7 days, respectively.

2. Sample Extraction and Analysis: Extracting solvent containing an internal reference standard was prepared by weighing 8.0726 ± 0.0002 g of dibutyl cyclohexanephosphonate in a 25-ml beaker and quantitatively transferring it to a volumetric flask (1 liter) with absolute methanol. The flask was then filled to the volume mark with additional methanol. Concentration of reference standard: 8.0726 mg/ml.

To extract each sample aliquot, the septum vial was opened, 50 ml of the extracting solvent was added by volumetric pipette, and the vial was immediately resealed. The corn oil/methanol mixture was manually shaken for 15 sec, agitated on a vortex mixer for 1 min, and placed in an ultrasonic bath for 2 min. The vial was then centrifuged for 5 min and a 5-ml aliquot of the methanol solution was analyzed by the gas chromatographic system outlined below:

a. Instrument: Bendix 2500 with Hewlett-Packard® 3380A Automatic Integrator

b. Column: 3% OV-1 on 80/100 mesh Supelcoport, 1.8 m × 4 mm ID, glass

c. Detection: Flame ionization

d. Temperatures:

(1) Inlet, 250° C
(2) Oven, 200° C, isothermal
(3) Detector, 290° C

e. Carrier gas: Nitrogen

f. Flow rate: 50 ml/min

g. Retention times:

(1) Test chemical, 10.5 min
(2) Reference standard, 1.3 min

3. Quality Control Protocols: Analyses were performed in duplicate with dibutyl cyclohexanephosphonate as an internal reference standard. Recovery studies (zero-time samples) were performed in duplicate at the same concentration level as the test samples, both at the start and at the end of the 7-day period. Gas chromatographic linearity was determined with standard solutions in methanol at 9.53, 7.23, and 4.85 mg/ml concentrations for the tris(2-ethylhexyl)phosphate, and 9.74, 7.33, and 4.86 mg/ml for the internal reference. The least squares plot correlation coefficients were 0.995 for the test chemical and 0.999 for the internal reference (effectively 1.0, linear).

4. Results:

Storage Time (days)	Average Percent Chemical Found in Chemical/Vehicle Mixture (a)
1	(b) 20.3 ± 0.7
5	20.1 ± 0.7
7	20.5 ± 0.7

(a) Zero-time recovery yield, 100% ± 3%. Theoretical concentration of chemical in corn oil, 20.07% ± 0.01%.
(b) The error values in this table are standard deviations.

APPENDIX J

ANALYSIS OF DOSE MIXTURES: METHODS

APPENDIX J. ANALYSIS: METHODS

I. Testing Laboratory

A. Procedure: Tris(2-ethylhexyl)phosphate was extracted from corn oil into methanol containing a fixed amount of triphenyl methane per milliliter of extractant. Triphenyl methane served as the internal standard for gas-chromatographic quantitation of tris(2-ethylhexyl)phosphate with the ISTD method of the Hewlett-Packard® microprocessor.

1. **Instrument:** HP5880 or HP5840 with 7672 auto-sampler
2. **Column:** 3% OV-1 on 80/100 or 100/120 mesh Supelcoport, 1.8 m × 2 mm ID, glass
3. **Detector:** Flame ionization
4. **Carrier gas:** Nitrogen
5. **Flow rate:** 50 ml/min

6. Isothermal Analysis:	7. Programmed Analysis:
Detector temperature: 290° C	290° C
Injector temperature: 250° C	275° C
OvenTemperature: 200° C	175°-235° C at 25° C/min;
Retention times:	held at 235° C for 7 min
a. tris(2-ethylhexyl)phosphate, 7.8-9.9 min	5 min
b. triphenyl methane, 1.7-2.3 min	3 min

II. Analytical Chemistry Laboratory

A. Procedure

1. Preparation of Standard Spiked Corn Oil: Two working standard solutions of tris(2-ethylhexyl)phosphate in methanol were prepared independently. These solutions were further diluted with methanol to make a total of six solutions ranging from approximately 5 to 50 mg/ml, depending on the concentration of the referee sample. Aliquots (20 ml) of the six standard solutions were pipetted into individual 35-ml septum vials containing 2 g of undosed corn oil to make spiked corn oil standards bracketing the specified dose range of the referee sample. One 35-ml septum vial containing 2 g of undosed corn oil was treated with 20 ml of methanol for use as a blank. The spiked corn oils and the corn oil blank were extracted immediately and were analyzed using the procedure below.

2. Preparation of the Referee Sample: Three portions (approximately 2 g each) of the dosed referee corn oil sample were transferred to individually tared 35-ml septum vials and were weighed to the nearest 0.001 g. Methanol (20 ml) was pipetted into each vial, then the referee samples were extracted immediately and analyzed using the procedure below.

3. Analysis: The vials were sealed, vigorously agitated for 10 sec on a vortex mixer, and shaken at maximum stroke for 15 min on a Burrell, Model 75, Wrist-Action® shaker. After extraction mixtures were centrifuged for 3 min, a 5-ml aliquot of the upper methanol layer from each vial was combined with 5 ml of internal standard solution (docosane in chloroform, 7 mg/ml) and diluted to 100 ml with methanol. The solutions were thoroughly mixed, and the tris(2-ethylhexyl)phosphate content of each solution was determined using the gas chromatography system below.

a. Instrument: Varian 3700 Gas Chromatograph with Autosampler and Varian CDS 111-C integrator
b. Column: 3% OV-1 on 80/100 mesh Supelcoport, 1.8 m × 4 mm ID, glass
c. Detection: Flame ionization
d. Temperatures:
(1) Inlet, 250° C
(2) Oven, 200° C, isothermal
(3) Detector, 290° C
g. Carrier gas: Nitogen
h. Flow rate: 30 ml/min
i. Volume of solution injected: 3 µl
j. Retention times:
(1) Tris(2-ethylhexyl)phosphate, 10.8-13.2 min
(2) Docosane internal standard, 4.7-5.7 min

The total milligrams of tris(2-ethylhexyl)phosphate in the referee corn oil samples were computed from the linear regression equation obtained by plotting the ratio of the peak area of each spiked corn oil sample to the peak area of the internal standard versus the milligrams of chemical in the respective spiked corn oil sample.

4. Quality Assurance Measures: The dosed referee corn oil sample was analyzed in triplicate and the corn oil blank sample was analyzed once. Individually spiked portions of undosed corn oil (six levels) prepared from two independently weighed standards were used for obtaining standard curve data. Triplicate injections of each standard and sample were made into the gas chromatograph in a randomized order.

APPENDIX K

ANALYSES OF DOSE MIXTURES: DATA

APPENDIX K. ANALYSES: DATA

I. Two-Year Studies: To estimate the accuracy of the dose preparation during the study, samples of the preparations were analyzed periodically. The results of the initial mixes ranged from 95.3% to 111% of the theoretical concentration (Table K1).

Split sample referee analyses were performed by the testing and analytical laboratories to verify analytical procedures (Table K2). The analyses by both laboratories were within ± 10% of the target concentrations. In addition, the interlaboratory values were within 10% of each other except for the initial referee analysis. Occasionally, the testing laboratory's periodic analysis indicated a sample was not within 10% of the theoretical concentration. Extrapolating the data from the analyzed samples indicated the dose mixtures were within 10% of the target values more than 92% of the time.

TABLE K1. ANALYSIS OF DOSE MIXTURES OF TRIS(2-ETHYLHEXYL)PHOSPHATE IN THE TWO-YEAR GAVAGE STUDIES

Date Mixed	Concentration of Tris(2-ethylhexyl)phosphate in Corn Oil for Target Concentration (mg/ml) (a)				
	100	200	400	150.3	300.6
12/28/79	102	204	408		
2/25/80	96.2	200	392	152	302
4/21/80	106	212	423	149	311
6/16/80	103	204	417	152	314
8/11/80	97.2	208	418	148	327
10/6/80	101	200	417	143	306
12/1/80	107	208	404	156	302
1/26/81	104	215	438	157	304
3/23/81	130	231	491	176	368
3/26/81	(b) 97.3	(b) 202	(b) 394	(b) 153	(b) 300
5/18/81	97.3	198	381	147	294
7/13/81	95.3	197	384	144	291
9/8/81	110	207	436	167	330
11/2/81	98.2	195	387	146	287
12/28/81				152	299
Mean (mg/ml)	104	206	415	153	310
Standard Deviation	9.1	9.6	29.5	9.4	21.4
Coefficient of Variation (%)	8.7	4.7	7.1	6.1	6.9
Range (mg/ml)	95.3-130	195-231	381-491	143-176	287-368
Number of Samples	13	13	13	13	13

(a) The data presented are the results of duplicate analyses.
(b) Remix. Not included in mean.

TABLE K2. RESULTS OF REFEREE ANALYSIS OF TRIS(2-ETHYLHEXYL)PHOSPHATE IN DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (a)	
		Analytical Lab	Testing Lab
4/21/80	100	90	106
10/06/80	200	193	200
5/18/81	150.3	145	147
12/28/81	150.3	152	152

(a) Milligrams per milliliter

APPENDIX L

INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS OF NIH 07 DIET

Pelleted Diet: December 1979 to March 1982

TABLE L1. INGREDIENTS OF NIH 07 RAT AND MOUSE DIET (a)

Ingredients (b)	Percent by Weight
Dried skim milk	5.00
Fish meal (60% protein)	10.00
Soybean meal (49% protein)	12.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Ground #2 yellow shelled corn	24.00
Ground hard winter wheat	23.00
Wheat middlings	10.00
Brewer's dried yeast	2.00
Dry molasses	1.50
Soy oil	2.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Pre-mixes (vitamin and mineral)	0.25
Salt	0.50

(a) NIH, 1978; NCI, 1976
(b) Ingredients should be ground to pass through a U.S. Standard Screen #16 before mixing.

TABLE L2. VITAMINS AND MINERALS IN THE NIH 07 DIET (a)

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D activated animal sterol
K_3	2.8 g	Menadione activity
d-A-tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	d-Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B_{12}	4,000 µg	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	d-biotin
Minerals		
Cobalt	0.4	Cobalt carbonate
Copper	4.0	Copper sulfate
Iron	120.0	Iron sulfate
Manganese	60.0	Manganous oxide
Zinc	16.0	Zinc oxide
Iodine	1.4	Calcium iodate

(a) Per ton (2,000 lb) of finished product

TABLE L3. NUTRIENT COMPOSITION OF NIH 07 DIET: PELLETS

	Mean	Range	Number of Samples
Nutrient (percent by weight)			
Crude protein	24.29 ± 0.81	22.7-26.1	24
Crude fat	4.81 ± 0.38	4.1-5.5	24
Crude fiber	3.31 ± 0.50	1.4-4.3	24
Ash	6.76 ± 0.44	5.83-7.43	24
Vitamins (a)			
Vitamin A (IU/kg)	10,192 ± 2,534	6,700-17,000	24
Vitamin D (IU/kg)	6,300		1
A-tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm)	16.2 ± 4.5	7.4-27	24
Riboflavin (ppm)	6.9	6.1-7.4	2
Niacin (ppm)	75	65-85	2
Pantothenic acid (ppm)	30.2	29.8-30.5	2
Pyridoxine (ppm)	7.2	5.6-8.8	2
Folic acid (ppm)	2.1	1.8-2.4	2
Biotin (ppm)	0.24	0.21-0.27	2
Vitamin B_{12} (ppb)	12.8	10.6-15.0	2
Choline (ppm)	3,315	3,200-3,430	2
Essential Amino Acids (a) (percent of total diet)			
Arginine	1.260	1.21-1.31	2
Cystine	0.395	0.39-0.40	2
Glycine	1.175	1.15-1.20	2
Histadine	0.553	0.530-0.576	2
Isoleucine	0.908	0.881-0.934	2
Leucine	1.905	1.85-1.96	2
Lysine	1.250	1.20-1.30	2
Methionine	0.310	0.306-0.314	2
Phenylalanine	0.967	0.960-0.974	2
Threonine	0.834	0.840-0.827	2
Tryptophan	0.175	0.171-0.178	2
Tyrosine	0.587	0.566-0.607	2
Valine	1.805	1.05-1.12	2
Essential Fatty Acids (a) (percent of total diet)			
Linoleic	2.37		1
Linolenic	0.308		1
Arachidonic	0.008		1

(a) One or two batches of feed analyzed for nutrients reported in this table were manufactured in January and/or April 1983.

TABLE L4. CONTAMINANT LEVELS OF NIH 07 DIET: PELLETS

Contaminant	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.39 ± 0.23	<0.05-1.06	24
Cadmium (ppm)	0.11 ± 0.07	<0.05-0.40	24
Lead (ppm)	0.91 ± 0.51	0.50-2.65	24
Mercury (ppm)	(a) 0.05		
Selenium (ppm)	0.29 ± 0.09	0.10-0.52	24
Aflatoxins (ppb)	(a,b) <10		
Nitrate nitrogen (ppm)	7.00 ± 3.70	<0.1-13.0	24
Nitrite nitogen (ppm)	1.45 ± 1.02	<0.1-4.00	24
BHA (ppm)	3.83 ± 3.88	<0.2-13.0	24
BHT	2.97 ± 1.74	0.8-7.60	24
Aerobic plate count (CFU/g)	48,786 ± 32,701	(c) 5,500-120,000	22
Coliform (MPN/g) (d)	39 ± 57	(e) <3-240	20
E. Coli (MPN/g)	(f) <3		24
Total nitrosamines (ppb)	7.63 ± 6.67	(g) 2.2-24.5	22
N-Nitrosodimethylamine (ppb)	5.81 ± 6.30	(g) 1.1-20.0	22
N-Nitrosopyrrolidine (ppb)	1.30 ± 0.78	(g) 0.5-3.5	22
Pesticides (ppm)			
Alpha BHC	(a) <0.01		24
Beta BHC	(a) <0.02		24
Gamma BHC-Lindane	(a) <0.01		24
Delta BHC	(a) <0.01		24
Heptachlor	(a) <0.01		24
Aldrin	(a) <0.01		24
Heptachlor epoxide	(a) <0.01		24
DDE	(a) <0.01		24
DDD	(a) <0.01		24
HCB	(a) <0.01		24
Mirex	(a) <0.01		24
Methoxychlor	(a) <0.05	(h) 0.09 (8/26/81)	24
Dieldrin	(a) <0.01		24
Endrin	(a) <0.01		24
Telodrin	(a) <0.01		24
Chlordane	(a) <0.05		24
Toxaphene	(a) <0.1		24
Estimated PCB's	(a) <0.2		24
Ronnel	(a) <0.01		24
Ethion	(a) <0.02		24
Trithion	(a) <0.05		24
Diazinon	(a) <0.01	(h) 0.2 (4/27/81)	24
Methyl parathion	(a) <0.02		24
Ethyl parathion	(a) <0.02		24
Malathion	<0.100 ± 0.07	<0.05-0.27	24
Endosulfan I	(a) <0.01		24
Endosulfan II	(a) <0.01		24
Endosulfan Sulfate	(a) <0.03		24

(a) All values less than detection limit given in the table as the mean
(b) Detection limit reduced from 10 ppb to 5 ppb after 7/81
(c) Excludes two extreme values 300,000 and 320,000 obtained during 12/79 and 2/80
(d) MPN = most probable number
(e) Excludes four values in the range 1,100-2,400 obtained during 2/80, 5/80, 11/80, and 12/80
(f) All values were <3 MPN/g
(g) All values are corrected for percent recovery; excludes three values in the range of 115-280 ppb obtained during the period 1/80-4/80.
(h) One value above the detection limit (noted in the range column) was obtained on this date.

APPENDIX M

ADRENAL MEDULLARY TISSUE IN CONTROL MALE RATS

APPENDIX M. ADRENAL MEDULLARY TISSUE

The low incidence of pheochromocytomas observed in control male rats was unusual. Therefore, the amount of adrenal tissue sampled was evaluated. Results are presented in Table M1.

The findings were as follows:

1. Ninety-nine adrenals were present in 50 animals.
2. Ninety-three adrenal medullae were present, 6 adrenals had no medulla.
3. Of the 93 medullae:
    a. Good medulla tissue was present in 86
    b. Mild medulla tissue was present in 3
    c. Trace medulla tissue was present in 4

4. Good bilateral medullary tissue was present in 80% of the control rats.

5. Good unilateral medullary tissue was present in an additional 12%.

6. Trace unilateral medullary tissue was present in an additional 4%.

7. Only 4% (2/50) of control rats had no medullary tissue present, but each rat had two adrenals included in this section.

Conclusions: The medullary tissue appeared very well represented, and the quality of the section did not appear to account for the low incidence of pheochromocytomas in this group. The adrenal was included in the slides for all control male rats, and in 49/50 rats, both adrenals were present. Further, in 90% of the animals, both adrenal medullae were present in the histologic sections. This suggests that the low incidence of pheochromocytomas cannot be a result of the sampling techniques.

TABLE M1. CLASSIFICATION OF MEDULLARY TISSUE IN CONTROL MALE RATS

Number of Animals	Adrenals per Rat	Total Adrenals	Medullae per Rat	Total Medullae	Tissue (Medulla) Present
40	2	80	2	80	Both good (a)
3	2	6	2	6	1 good and 1 mild (b)
2	2	4	2	4	1 good and 1 trace (c)
2	2	4	1	2	Trace
2	2	4	0	0	--
1	1	1	1	1	Good
Total					
50	11	99	8	93	

(a) Good = A good sample of medullary tissue was present.
(b) Mild = A small portion of medullary tissue (greater than 50 cells) was present.
(c) Trace = Few medullary cells were present.

APPENDIX N

SENTINEL ANIMAL PROGRAM

APPENDIX N. SENTINEL ANIMAL PROGRAM

A. METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect test results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via viral serology on sera from extra (sentinel) animals in the test rooms. These animals are untreated, and these animals and the test animals are both subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Fifteen B6C3F$_1$ mice and 15 F344/N rats of each sex are selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group are killed at 6, 12, and 18 months on study. Data from animals surviving 24 months are collected from 5/50 randomly selected control animals of each sex and species. The blood from each animal is collected and clotted, and the serum is separated. The serum is cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests are performed:

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	PVM (pneumonia virus of mice) Reo 3 (reovirus type 3) GDVII (Theiler's encephalomyelitis virus) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia) Sendai	M.Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus	MHV (mouse hepatitis virus)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai	RCV (rat coronavirus)	

B. RESULTS

Results are presented in Table N1.

TABLE N1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES (a)

Interval (months)	No. of Animals	Positive Serologic Reaction for
RATS		
6	9/10	RCV (b)
12	8/8	RCV
	6/10	Sendai
18	9/10	RCV
	3/10	Sendai
24	3/10	RCV
	1/10	Sendai
MICE		
6	--	--
12	--	--
18	--	--
24	--	--

(a) Blood samples were taken from sentinel animals at 6, 12, and 18 months after the start of dosing and from the vehicle control animals just before they were killed; samples were sent to Microbiological Associates, Inc. (Bethesda, MD) for the Animal Disease Screening Program.
(b) Rat coronavirus

APPENDIX O

DATA AUDIT SUMMARY

APPENDIX O. AUDIT

The experimental data and tables of the draft Technical Report on the toxicology and carcinogenesis studies of tris(2-ethylhexyl)phsphate were examined for Good Laboratory Practices compliance and scientific procedures by the following persons on August 8-12, 1983: National Toxicology Program--C. Davies, Dr. M. Powers, Dr. B.A. Schwetz, Dr. C. Whitmire, and Dr. M. Wolfe; Experimental Pathology Laboratories, Inc.--Dr. W. Busey and H. Cook; Food and Drug Administration--Dr. E. Butler and Dr. G. James; Tracor Jitco, Inc.--P. Errico; Litton Bionetics, Inc.--R. Cypher and M. Rodwin.

The report of the audit of the tris(2-ethylhexyl)phosphate studies is on file in the National Toxicology Program. The main discrepancies or problems and their resolution were as follows:

1. Pathology data: In the mouse studies, some of the histopathology information described on the individual animal data record by the pathologist was not coded into the computer data system. This information would not have changed the conclusions of the studies even if it had been coded into the data base. The noncoded findings did not consist of tumor data and were primarily background observations of nontumor toxicity.

2. Cause of death: Some of the animal deaths that were identified as "natural deaths" probably resulted from gavage errors. The deaths of the nine rats and five mice which were coded as natural deaths but showed evidence of gavage trauma were evenly distributed between vehicle control animals and dosed animals. The NTP Technical Report was thus corrected with no impact on the final conclusions of the studies.

These findings and comments are based on the NTP audit and information obtained from laboratory personnel of Litton Bionetics, Inc. There were no discrepancies that were considered of sufficient magnitude to influence significantly the final interpretations of these studies. Minor problems not mentioned here which were not considered to affect the outcome of the studies were not necessarily pursued to final resolution but are identified in the NTP audit report. In conclusion, no data discrepancies were found which significantly influenced the final interpretation of these experiments.

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