NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 296

TOXICOLOGY AND CARCINOGENESIS STUDIES OF TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM SULFATE (THPS)

(CAS NO. 55566-30-8)

AND

TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM CHLORIDE (THPC)

(CAS NO. 124-64-1)

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 (NCTR), 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 TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM SULFATE (THPS)

(CAS NO. 55566-30-8)

AND

TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM CHLORIDE (THPC)

(CAS NO. 124-64-1)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

February 1987

NTP TR 296

NIH Publication No. 87-2552

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

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 for use in June 1983 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.

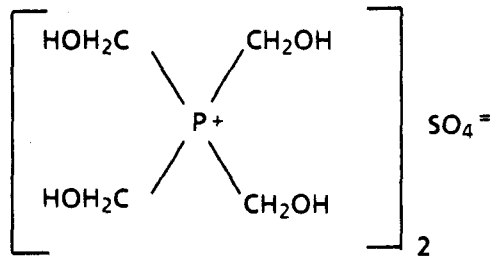
Additionally, the following concepts (as patterned from the International Agency for Research on Cancer Monographs) have been adopted by the NTP to give further clarification of these issues:

> 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 Bioassay Program, now part of the National Institute of Environmental Health Sciences, National Toxicology Program. The studies described in this Technical Report have been conducted in compliance with NTP chemical health and safety requirements and must meet or exceed all applicable Federal, state, and local health and safety regulations. Animal care and use were in accordance with the U.S. Public Health Service Policy on Humane Care and Use of Animals. All NTP toxicology and carcinogenesis studies are subjected to a data audit before being presented for peer review.

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).

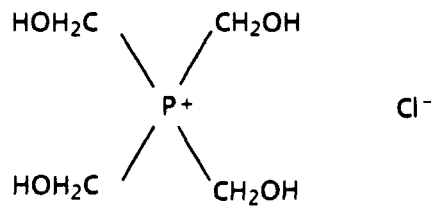
These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge (and while supplies last) from the NTP Public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



TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM SULFATE

CAS No. 55566-30-8

$C_8H_{24}O_{12}P_2S$ Molecular weight 406.28



TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM CHLORIDE

CAS No. 124-64-1

$C_4H_{12}O_4PCl$ Molecular weight 190.56

ABSTRACT

Toxicology and carcinogenesis studies of tetrakis(hydroxymethyl)phosphonium sulfate (THPS) and tetrakis(hydroxymethyl)phosphonium chloride (THPC) were conducted because of the widespread use of these chemicals as flame retardants in cotton fabrics. THPS was available as a 72% aqueous solution and THPC as a 75% aqueous solution. Short-term gavage studies with a range of doses were conducted first to identify toxic effects and affected sites and to determine doses for the 2-year studies. The doses selected for the 14-day studies ranged from 12.5 to 200 mg/kg THPS for rats and mice, 9.4 to 150 mg/kg THPC for rats, and 18.8 to 300 mg/kg THPC for mice. Mortality and reduction in body weight gain occurred at the two highest doses in the 14-day studies. There was hind limb paralysis in some rats and mice dosed at the highest concentrations of THPS and THPC.

In the 13-week studies, doses of THPS ranged from 5 to 60 mg/kg in rats and from 2 to 180 mg/kg in mice; doses of THPC ranged from 3.75 to 60 mg/kg in rats and from 1.5 to 135 mg/kg in mice. Mortality and reduction in body weight gain occurred at the two higher doses for both sexes and species. Vacuolar degeneration of hepatocytes or hepatocellular necrosis was a common histopathologic finding. Hind limb paralysis was noted in rats and mice receiving the highest dose of THPC, and axonal degeneration, characterized by swollen axon sheaths, missing or fragmented axons, and some proliferation of neurolemma cells, was observed in rats. These lesions were found in the sciatic nerve, dorsal roots of the caudal spinal nerves, and tracts of the spinal cord, particularly in the dorsal column of the lumbar cord.

Two-year studies were conducted in F344/N rats by administering 0, 5, or 10 mg/kg THPS or 0, 3.75, or 7.5 mg/kg THPC in deionized water by gavage to groups of 49 or 50 animals of each sex, 5 days per week for 103 or 104 weeks. Groups of 49 or 50 $B6C3F_1$ mice were administered 0, 5, or 10 mg/kg THPS (each sex), 0, 7.5, or 15 mg/kg THPC (males), or 0, 15, or 30 mg/kg THPC (females).

Survival of male rats was reduced for the low dose (after week 102) and the high dose (after week 67) groups given THPS compared with that of the vehicle controls; survival at terminal kill was as follows: vehicle control, 28/50; low dose, 13/50; high dose, 16/50. Survival of the high dose group of female rats given THPC was lower after week 70 than that of the vehicle controls (survival at terminal kill: 37/50; 34/50; 21/50). Mean body weights of rats dosed with THPS or THPC were comparable to those of the vehicle controls. There was no difference in survival or mean body weights between the vehicle controls and mice dosed with either THPS or THPC. No neurotoxicity or any other signs of clinical toxicity were observed.

A nonneoplastic effect common to 13-week and 2-year exposure to THPS or THPC was an increase in the incidence of hepatocellular lesions, primarily cytoplasmic vacuolization. The incidences of this lesion in the 2-year studies were dose related for all studies except for the mice receiving THPS. Other lesions observed included focal hyperplasia of the adrenal medulla in high dose male mice given THPS and follicular cell hyperplasia of the thyroid gland in high dose female mice given THPC. The increased incidences of hematopoietic system lesions observed in these studies were not considered biologically related to chemical exposure because the increases were marginal, no dose-response relationship was observed, and the incidences of these lesions are highly variable in untreated rats and mice.

The incidences of mononuclear cell leukemia in low dose male rats administered THPS or THPC were somewhat greater than those in the vehicle controls (THPS: 30/50; 36/50; 20/50; THPC: 19/50; 25/50; 16/50). Low dose male mice administered THPS had an increased incidence of malignant lymphomas when compared with vehicle controls (2/50; 9/50; 0/50). These marginal increases in the incidences of hematopoietic system tumors were not considered related to chemical exposure, since they were significant only by the life table tests and were not dose related.

THPC demonstrated no mutagenic activity in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 with or without metabolic activation. Both THPS and THPC induced forward mutations in mouse lymphoma L5178Y cells without metabolic activation; neither was tested in the presence of S9. THPC increased the frequency of sister-chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells in the presence and absence of exogenous metabolic activation.

An audit of the experimental data was conducted for the 2-year studies of THPS and THPC. No discrepancies were found that influenced the final interpretations.

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenicity** of THPS in either sex of F344/N rats or $B6C3F_1$ mice given 5 or 10 mg/kg. There was *no evidence of carcinogenicity* of THPC in either sex of F344/N rats given 3.75 or 7.5 mg/kg, in male $B6C3F_1$ mice given 7.5 or 15 mg/kg, or in female $B6C3F_1$ mice given 15 or 30 mg/kg.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 9.

CONTENTS

CONTENTS (Continued)

APPENDIXES

APPENDIXES (Continued)

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on THPS and THPC on March 26, 1986, 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: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) 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

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

Frederica Perera, Dr. P.H.
Division of Environmental Sciences
School of Public Health, Columbia University
New York, New York

James Swenberg, D.V.M., Ph.D.
Head, Department of Biochemical Toxicology and Pathobiology
Chemical Industry Institute of Toxicology
Research Triangle Park, North Carolina

Ad Hoc Subcommittee Panel of Experts

Charles C. Capen, D.V.M., Ph.D.
Department of Veterinary Pathobiology
Ohio State University
Columbus, Ohio

Vernon M. Chinchilli, Ph.D.
Department of Biostatistics
Medical College of Virginia
Virginia Commonwealth University
Richmond, Virginia

John J. Crowley, Ph.D. (Principal Reviewer)
Division of Public Health Science
The Fred Hutchinson Cancer Research Center
Seattle, Washington

Kim Hooper, Ph.D.
Hazard Evaluation System and Information Services
Department of Health Services
State of California
Berkeley, California

Donald H. Hughes, Ph.D. (Principal Reviewer)
Scientific Coordinator, Regulatory Services Division, The Procter and Gamble Company
Cincinnati, Ohio

Franklin E. Mirer, Ph.D.
Director, Health and Safety Department
International Union, United Auto Workers, Detroit, Michigan

James A. Popp, D.V.M., Ph.D.
Head, Department of Experimental Pathology and Toxicology
Chemical Industry Institute of Toxicology
Research Triangle Park, North Carolina

I.F.H. Purchase, B.V.Sc., Ph.D., F.R.C. Path.*
Director, Central Toxicology Laboratory
Imperial Chemical Industries, PLC
Alderley Park, England

Robert A. Scala, Ph.D. (Principal Reviewer)
Senior Scientific Advisor, Medicine and Environmental Health Department
Research and Environmental Health Division, Exxon Corporation
East Millstone, New Jersey

Andrew Sivak, Ph.D.
Vice President, Biomedical Science
Arthur D. Little, Inc.
Cambridge, Massachusetts

*Unable to attend

SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF THPS AND THPC

On March 26, 1986, the draft Technical Report on the toxicology and carcinogenesis studies of tetrakis(hydroxymethyl)phosphonium sulfate (THPS) and tetrakis(hydroxymethyl)phosphonium chloride (THPC) received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. C.W. Jameson, NTP, introduced the toxicology and carcinogenesis studies of THPS and THPC by reviewing the experimental design, results, and proposed conclusions (no evidence of carcinogenicity of THPS for rats or mice of each sex and no evidence of carcinogenicity of THPC for rats or mice of each sex).

Dr. Scala, a principal reviewer, agreed with the conclusions as written. He was pleased that the Chemical Manager emphasized the dosing errors in mice for 3 days but expressed concern about the effect these dosing mixups in some animal groups may have had on the validity of the studies and asked for more explanation. He noted that since THPS and THPC differ in their chemical structure only by the sulfate or chloride anion, yet show differences in toxic effects, some speculative discussion would have been interesting.

As a second principal reviewer, Dr. Crowley agreed with the conclusions but questioned the possible effects of the dosing mixups. In view of the elevated rates of mononuclear cell leukemia in male rats at the end of the study, he wondered if the life table test was the appropriate statistical test for interpreting the data. Dr. S. Eustis, NIEHS, emphasized that mononuclear cell leukemia takes several months to develop and is considered a fatal disease. Dr. J. Haseman, NIEHS, said that this was a good illustration of the difficulty of choosing the most appropriate statistical test, and this uncertainty was considered in the overall evaluation of the studies. Dr. J. Huff, NTP, added that leukemia is often a late-developing neoplasm and is usually fatal within 6-8 weeks after occurrence.

As a third principal reviewer, Dr. Hughes also agreed with the conclusions. He concurred with the other reviewers in calling for more explanation on the dosing mixups. He thought the rationale for choosing the gavage route of exposure was not particularly convincing, especially since information on absorption, distribution, metabolism, and excretion was not available. Dr. Hughes commented that the section in the Introduction on the reported initiation/promotion studies with THPC was potentially misleading because he viewed THPC as a "suspected" promoter rather than a promoter per se.

In response to the reviewers' concerns about the dosing mixups, Dr. Jameson said that the laboratory technicians inadvertently switched vials of THPS and THPC for dosing mice on only 3 days at about the midpoint of the study. This represents less than 0.6% (3/520) of the gavage days. No adverse effects were observed, and the NTP considered the incident to have no impact on the outcome of the studies. Documentation from the laboratory indicated this was an isolated incident. More information is given in the text of the Technical Report. [See pages 25-26.]

Dr. Scala moved that the Technical Report on THPS and THPC with the conclusions as written for rats and mice of each sex, no evidence of carcinogenicity, be accepted subject to inclusion of the more detailed explanation of the dosing mixups as presented by Dr. Jameson. Dr. Popp seconded the motion, which was approved unanimously with 11 affirmative votes.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Tetrakis(hydroxymethyl)phosphonium Sulfate (THPS) and Tetrakis(hydroxymethyl)phosphonium Chloride (THPC) is based on the 13-week studies of THPS that began in April 1979 and ended in July 1979, the 2-year studies of THPS that began in March 1980 and ended in April 1982, the 13-week studies of THPC that began in October 1979 and ended in January 1980, and the 2-year studies of THPC that began in September 1980 and ended in September 1982 at Battelle Columbus Laboratories.

National Toxicology Program
(Evaluated Experiment, Interpreted Results, and Reported Findings)

C.W. Jameson, Ph.D., Chemical Manager

Jack Bishop, Ph.D.
Michael P. Dieter, Ph.D.
Scot L. Eustis, D.V.M., Ph.D.
Joseph K. Haseman, Ph.D.
James Huff, Ph.D.
E.E. McConnell, D.V.M.
John Mennear, Ph.D.
G.N. Rao, D.V.M., Ph.D.
B.A. Schwetz, D.V.M., Ph.D.
James K. Selkirk, Ph.D.

NTP Pathology Working Group for THPS
(Evaluated Slides and Prepared Pathology Report for Rats on 6/2/83)

Robert Sauer, V.M.D. (Chair) (Clement Associates)
Richard Bruner, D.V.M. (USAF)
Scot L. Eustis, D.V.M., Ph.D. (NTP)
Fletcher Hahn, D.V.M., Ph.D.
Lovelace Inhalation Research Institute
Bob Jones, M.D.
Lovelace Inhalation Research Institute
James MacLachlan, B.V.Sc., Ph.D.
North Carolina State University
Henk Solleveld, D.V.M., Ph.D. (NTP)

NTP Pathology Working Group for THPS
(Evaluated Slides and Prepared Pathology Report for Mice on 6/3/83)

Robert Sauer, V.M.D. (Chair) (Clement Associates)
Gary A. Boorman, D.V.M., Ph.D. (NTP)
Scot L. Eustis, D.V.M., Ph.D. (NTP)
Henk Solleveld, D.V.M., Ph.D. (NTP)

Principal Contributors at Battelle Columbus Laboratories
(Conducted Studies and Evaluated Tissues for THPS)

A. Peters, D.V.M., Principal Investigator
E. Leighty, Ph.D., Chemist
R. Persing, D.V.M., Pathologist (for rats)
D. Donofrio, D.V.M., Pathologist (for mice)

Principal Contributors at Experimental Pathology Laboratories, Inc.
(Conducted Pathology Quality Assurance for THPS)

Deborah Banas, D.V.M.
J. Gauchat, Pathology Coordinator

NTP Pathology Working Group for THPC
(Evaluated Slides and Prepared Pathology Report for Rats on 6/3/85)

Leroy Hall, D.V.M., Ph.D. (Chair) (NTP)
Gary A. Boorman, D.V.M., Ph.D. (NTP)
Melvin Hamlin, D.V.M. (Experimental Pathology Laboratories, Inc.) (Observer)
Kunitoshi Mitsumori, D.V.M., Ph.D. (NTP)
Ronald Persing, D.V.M. (Battelle Columbus Laboratories) (Observer)
Henk Solleveld, D.V.M., Ph.D.
IVEG, TNO, The Netherlands
Jeffrey Wilson, M.Sc. (Sandoz)

CONTRIBUTORS (Continued)

NTP Pathology Working Group for THPC
(Evaluated Slides and Prepared Pathology Report for Mice on 6/20/85)

Robert Kovatch, D.V.M. (Chair)
Pathology Associates
Gary A. Boorman, D.V.M., Ph.D. (NTP)
Sondra Grumbein, D.V.M., Ph.D.
Battelle Columbus Laboratories
Kunitoshi Mitsumori, D.V.M. (NTP)
Kenneth Pierce, D.V.M., Ph.D.
NTP Guestworker
Linda Uraih, D.V.M. (NTP)
Jeffrey Wilson, M.Sc. (Sandoz)

Principal Contributors at Battelle Columbus Laboratories
(Conducted Studies and Evaluated Tissues for THPC)

A. Peters, D.V.M., Principal Investigator
R. Persing, D.V.M., Pathologist (for rats)
E. Leighty, Ph.D., Chemist
S. Grumbein, D.V.M., Ph.D., Pathologist (for mice)

Principal Contributors at Experimental Pathology Laboratories, Inc.
(Conducted Pathology Quality Assurance for THPC)

Melvin Hamlin, D.V.M. (for rats)
J. Gauchat, Pathology Coordinator
Jerry Hardisty, D.V.M. (for mice)

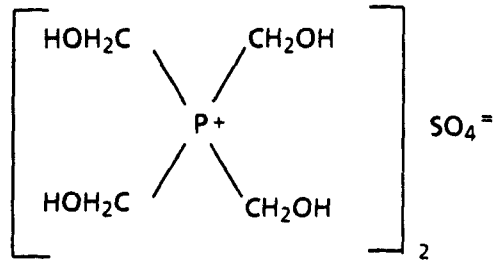
Principal Contributors at Carltech Associates, Inc.
(Contractor for Technical Report Preparation)

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

I. INTRODUCTION

Production
Acute Toxicity
Genetic Toxicology
Carcinogenicity
Study Rationale

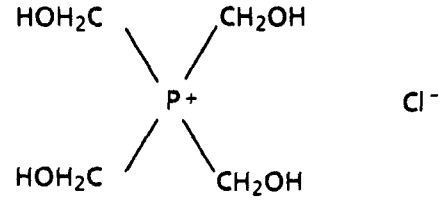
I. INTRODUCTION



TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM SULFATE

CAS No. 55566-30-8

$C_8H_{24}O_{12}P_2S$ Molecular weight 406.28



TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM CHLORIDE

CAS No. 124-64-1

$C_4H_{12}O_4PCl$ Molecular weight 190.56

Tetrakis(hydroxymethyl)phosphonium (THP) salts represent the major class of chemicals used as flame retardants for cotton fabrics. Before 1976, all THP flame retardants were the chloride salt tetrakis(hydroxymethyl)phosphonium chloride (THPC) (Kirk-Othmer, 1980). The textile industry favored this compound because of the relatively low cost of the reactants. THPC is a crystalline compound that is readily soluble in water and is produced in high yield through the reversible reaction of formaldehyde with phosphine and hydrogen chloride. THPC is added to cotton fabric by treatment with ammonia or other amine-containing compounds, reacts with the amine groups, and hydrolyzes and loses chlorine to yield a highly cross-linked aminated phosphine oxide. The final flame retardant permeating the fibers of the fabric is durable and not readily removed by laundering.

Heat and moisture can degrade THPC finishes to release formaldehyde and hydrogen chloride. The carcinogen bis(chloromethyl)ether has been reported to spontaneously form in the presence of moisture and excess formaldehyde and hydrogen chloride (Kallos and Solomon, 1973). Afansa'eva and Evseenko (1971) reported detectable levels of formaldehyde, hydrochloric acid, and phosphine for as long as 1 year after fabric treatment. Bis(chloromethyl)ether was not detectable at the 0.1-ppm level in commercial THPC or in extracts of fabric treated with THPC (Loewengart and Van Duuren, 1977) and was also reported undetectable at levels of 0.1 ppb in manufacturing, use, and storage processes by chemical manufacturers. However, societal pressures dictated that industry develop a replacement for THPC. This was accomplished by replacing hydrogen chloride in the THPC with the sulfate anion to form tetrakis(hydroxymethyl)phosphonium sulfate, or THPS.

Production

The TSCA inventory for THPS and THPC indicated two U.S. suppliers. The combined

annual use of each compound is between 1,000 and 5,000 tons in the United States.

Acute Toxicity

No LD_{50} values for THPS were reported in the literature. The oral LD_{50} value of THPC was reported as 282 mg/kg in male rats (Ulsamer et al., 1980). The dermal LD_{50} value in albino rabbits was greater than 4,084 mg/kg after a 24-hour exposure; erythema and edema of the integumentary system were observed, but mortality was not increased. Both THPC and THPS were toxic when applied dermally for longer exposures. Rabbits and rats were dosed daily for 20 days with 15%, 20%, or 30% aqueous solutions of THPC (Aoyama, 1975). Severe skin lesions occurred, and all rats in the highest dose group died after 9 days' administration. Dermal application of THPS to mice at doses of 125, 350, 700, and 1,000 mg/kg resulted in superficial necrosis at the application site and body weight loss (Connor et al., 1980). The two higher concentrations also resulted in the paralysis of back muscles in survivors. Similar effects in mice for THPC were reported by Afansa'eva and Evseenko (1971). Hepatocellular toxicity (shown by increased serum transaminase enzyme activity in rats) and increased liver mucopolysaccharide levels in mice were observed after administration of THPC in drinking water at 20-200 ppm (Ishizu, 1975).

Genetic Toxicology

Reports on the mutagenicity of THPS and THPC in the literature are generally negative. The few exceptions lack sufficient experimental data to allow a critical evaluation of the results. Salmonella/microsomal assays in the presence or absence of metabolic activation have shown uniformly negative results for both THPC and THPS (Connor et al., 1980; Ulsamer et al., 1980), as well as for six other phosphorus-containing flame retardants (MacGregor et al., 1980). A review of the extensive mutagenicity data generated by Japanese investigators from 1973 to 1978 confirmed the negative results for THPC activity in Salmonella (Kawachi et al., 1980a,b) but indicated positive results in the *Bacillus subtilis rec* assay with and without metabolic activation and equivocal results in chromosomal aberration tests with rat bone marrow and hamster lung fibroblast cells. The authors provided no experimental details or reference to original publications but concluded that THPC is neither a carcinogen nor a mutagen.

Dimethyl sulfoxide extracts of THPS- and THPC-treated cotton fabrics were reported to mutate V79 hamster lung cells in the presence and absence of rat liver S9 (Ehrlich et al., 1980). These extracts also induced cell transformation in baby hamster kidney cells and 3T3 mouse embryo cells. The mutagenic components of these fabric extracts were not identified or quantitated. Coutino (1979) investigated the effects of several chemicals on the mitotic process of cultured Chinese hamster ovary cells and reported a significant increase in the occurrence of sticky chromosomes, anaphase bridges, chromosomal lag, and multipolar spindles after exposure of cells to 2.4×10^{-4} M THPS. The author proposed that interaction with chromosomal structural proteins and/or the spindle fiber apparatus, rather than direct alteration of DNA, be considered responsible for these observed mitotic abnormalities.

NTP short-term test data reveal no mutagenic effect of THPC in bacteria. The chemical was not mutagenic in the Salmonella/microsome assay with the preincubation protocol in strains TA98, TA100, TA1535, or TA1537 with or without metabolic activation from S9 of Aroclor 1254-induced male Sprague-Dawley rat and male Syrian hamster liver (Appendix J, Table J1). However, both THPC and THPS demonstrated genotoxic activity in mammalian cells. Both compounds were positive in the mouse lymphoma L5178Y/TK$^{+/-}$ forward mutation assay without metabolic activation (Table J2; Appendix I, Table I1); neither was tested with metabolic activation. THPC induced a dose-related increase in the level of sister-chromatid exchanges (SCEs) in Chinese hamster ovary (CHO) cells both with and without activation by Aroclor 1254-induced male Sprague-Dawley rat liver S9 (Table J3). The positive SCE response was more pronounced without activation. THPC was also found to be an inducer of chromosomal aberrations in CHO cells both with and without activation (Table J4). Once again, the positive response was stronger in the absence of S9.

Results of in vivo tests for mutagenic effects of THPS in rodents were presented by Connor et al. (1980). THPS was administered to mice by gavage or dermal application or by mixing treated cloth with the animals' feed. The urine of these dosed mice was analyzed for mutagenicity in the Salmonella/microsome assay, and frequencies of micronuclei and chromosomal aberrations were evaluated in bone marrow cells. None of these investigations demonstrated mutagenic activity for THPS. THPS was tested in the dominant lethal assay with ICR mice (Legator, 1977). At the highest dose of 1,000 mg/kg, there was a significant decrease in the number of pregnant females per male as well as some slight increase in the number of fetal deaths per pregnant female. However, these effects were attributed to the extreme toxicity of THPS at this high dose rather than to any specific mutagenic activity of the compound.

Carcinogenicity

In a preliminary dermal experiment with mice, Loewengart and Van Duuren (1977) applied 2 mg THPC in 0.1 ml dimethyl sulfoxide to 20 female IRC/Ha Swiss mice three times per week for 400 days. A squamous cell carcinoma occurred in one dosed mouse; none occurred in vehicle controls. Further initiation/promotion studies were conducted with THPC. All study chemicals were applied to the shaved backs of ICR/Ha Swiss mice for 400 days. There were 20 mice per dose group for each experiment. Using phorbol myristate acetate (2.5 µg in 0.1 ml acetone) as a promoter, the investigators concluded that THPC was inactive as an initiator of carcinogenesis. With 7,12-dimethylbenz(a)anthracene (DMBA, 20 µg in 0.1 ml acetone) used as the initiator, THPC (2 mg in 0.1 ml dimethyl sulfoxide) was applied three times per week. Papillomas that progressed to squamous cell carcinomas occurred in 3/20 dosed mice. No tumors were observed in the DMBA control groups. The authors concluded that THPC had moderate tumor-promoting activity, but the interpretation of the results was complicated by the unusually low number of tumors observed in the positive controls, which the authors attributed to the use of dimethyl sulfoxide as the application solvent. A larger study was conducted in 60 female ICR/Ha Swiss mice with acetone:water (9:1) used as the vehicle for administration of THPC and following the dosing regimen used in the previous study. No tumors were attributed to THPC administration. The difference in tumor response was ascribed to the difference in solvents and the unusual effects of dimethyl sulfoxide in mouse skin carcinogenesis (Van Duuren et al., 1978).

Study Rationale

These two tetrakis(hydroxymethyl)phosphonium salts were nominated for toxicity and carcinogenicity study by the National Cancer Institute because of potential human exposure. They constitute the predominant chemicals used as flame retardants for cotton apparel, especially children's sleepwear. The possibility that a known carcinogen, bis(chloromethyl)ether, might spontaneously form from excess chemical, heat, and moisture in THPC-treated cotton clothing was the major impetus for initiating studies of THPC; industry's substitution of THPS for use as a cotton flame retardant prompted the decision to compare the toxicity and carcinogenicity of both tetrakis(hydroxymethyl)phosphonium salts in rodents. The gavage route of administration was chosen to obtain maximum systemic exposure and to mimic ingestion of the flame retardants by babies and young children.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF THPS AND THPC

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

SINGLE-ADMINISTRATION STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

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

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF THPS AND THPC

THPS

Tetrakis(hydroxymethyl)phosphonium sulfate (THPS) was obtained from Hooker Chemicals and Plastics Corporation (Niagara Falls, New York) as a 75% (nominal) aqueous solution in one 5-gallon lot (lot no. 7340). The identity and purity analyses of THPS were conducted at Midwest Research Institute (Kansas City, Missouri) (Appendix K).

The identity of the THPS study material was confirmed by infrared, ultraviolet/visible, and nuclear magnetic resonance analyses (Appendix K). All spectroscopic data were in general agreement with limited literature values or consistent with those expected for the substance. The purity of the THPS study material was determined to be approximately 72% THPS and 28% water by iodate/thiosulfate titration, elemental analysis, and thin-layer chromatographic analyses.

The bulk chemical was stable when stored for 2 weeks at temperatures up to 60° C (Appendix K). The study laboratory stored several 2-g portions of the bulk chemical as reference samples at −20° C and the remainder of the lot at room temperature. Results of periodic reanalysis of the bulk and reference samples at the study laboratory by infrared spectroscopy and titration procedures indicated that no detectable deterioration occurred over the course of the studies.

THPC

Tetrakis(hydroxymethyl)phosphonium chloride (THPC) was obtained from Aceto Chemical Company (Flushing, New York) as an 80% (nominal) aqueous solution in two 5-gallon cans (lot no. ON2). The identity and purity analyses of THPC were conducted at Midwest Research Institute (Kansas City, Missouri) (Appendix L).

The identity of the THPC study material was confirmed by infrared, ultraviolet/visible, and nuclear magnetic resonance analyses (Appendix L). All spectroscopic data were in agreement with literature values or were consistent with those expected for the substance. The purity of the THPC study material was determined to be approximately 75% THPC and 25% water by iodate-thiosulfate titration, elemental analysis, and thin-layer chromatographic analyses.

The bulk chemical was stable when stored for 2 weeks at temperatures as high as 60° C (Appendix L). The study laboratory stored several 2-g portions of the bulk chemical as reference samples at −20° C and the remainder of the lot at room temperature. Results of periodic reanalysis of the bulk and reference samples at the study laboratory by infrared and titration procedures indicated that no detectable deterioration occurred over the course of the studies.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

Since both study chemicals (72% THPS or 75% THPC in aqueous solution) were stable when stored for 2 weeks at temperatures ranging from −20° to 60° C and dose mixtures were to be prepared by dilution of the study chemical with water, stability studies of dose mixtures were not conducted (Appendixes M and N). Aqueous solutions containing from 74% to 25% (w/v) of the study chemicals were readily prepared and were homogeneous.

The study material was diluted with deionized water to give a stock solution containing THPS or THPC at the desired concentration for the high dose (Table 1). Other concentrations were prepared by dilution of an appropriate portion of the stock solution with deionized water.

Formulations of THPS and THPC in water were periodically selected at random and analyzed in duplicate by the study laboratory to determine the accuracy with which formulations were prepared over the course of the studies (Appendixes O and P). In addition to the analyses of the dose mixtures performed by the study laboratory, referee analyses of a split sample were performed by the analytical chemistry laboratory twice each year during the 2-year studies.

The first set of dose mixtures prepared for the 13-week studies was analyzed and found to be within ±10% of the target concentrations. Sets of samples were analyzed at approximately 8-week intervals during the 2-year studies. All mixes of THPS were within the specified ±10% of the target concentrations. (Table 2; Appendix Q). For the THPC study, the mixes were formulated within ±10% of the target concentrations approximately 91% (49/54) of the time (Table 2; Appendix R). Of the five dose formulations determined to be out of specifications, three were within ±12% and the remaining two were within ±20%.

TABLE 1. PREPARATION OF DOSE MIXTURES OF THPS AND THPC

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation			
THPS or THPC weighed into a graduated cylinder and water added to vol; vigorously shaken for 10 sec	Stock solution prepared by placing THPS or THPC in graduated cylinder and adding distilled water to vol; mechanically stirred for 5-10 min	Mixed on a w/v basis with distilled water and stirred mechanically for 5-10 min	THPS or THPC added to appropriate volume of deionized water and mixed by inverting 20 times
Maximum Storage Time			
14 d	14 d	14 d	14 d
THPS Storage Conditions			
23° C	23° C	1 week at 4° C, followed by 1 wk at room temperature	Same as 13-wk studies
THPC Storage Conditions			
23° C	23° C	23° C	23° C

TABLE 2. SUMMARY OF RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF THPS AND THPC

	Target Concentration (mg/ml)	
THPS	**1.0**	**2.0**
Mean (mg/ml)	1.0	2.0
Standard deviation	0.039	0.083
Coefficient of variation (percent)	3.9	4.3
Range (mg/ml)	0.94-1.1	1.9-2.1
Number of samples	12	12

	Target Concentration (mg/ml) (a)			
THPC	**1.0**	**2.0**	**4.0**	**8.0**
Mean (mg/ml)	0.98	2.09	4.17	7.85
Standard deviation	0.090	0.096	0.232	0.300
Coefficient of variation (percent)	9.2	4.6	5.6	3.8
Range (mg/ml)	0.83-1.20	1.93-2.22	3.70-4.45	7.20-8.53
Number of samples	14	14	13	13

(a) Milligrams of bulk chemical/milliliters of water

II. MATERIALS AND METHODS

SINGLE-ADMINISTRATION STUDIES

THPS

Four-week-old F344/N rats and B6C3F$_1$ mice of each sex were obtained from Charles River Breeding Laboratories and held for 16 days before being placed on study. Groups of five rats and five mice of each sex were administered a single dose of 100, 200, 400, 800, or 1,600 mg/kg THPS in water by gavage. Animals were housed five per cage. Feed and water were available ad libitum. Further details of animal maintenance are given in Table 3.

THPC

Four- to five-week-old F344/N rats and B6C3F$_1$ mice of each sex were obtained from Charles River Breeding Laboratories. Rats were held for 17 days and mice for 18 days before being placed on study. Groups of five rats and five mice of each sex were administered a single dose of 75, 150, 300, 600, or 1,200 mg/kg THPC in deionized water by gavage. Animals were housed five per cage. Feed and water were available ad libitum. Further details of animal maintenance are given in Table 4.

FOURTEEN-DAY STUDIES

THPS

Four-week-old F344/N rats and 5-week-old B6C3F$_1$ mice of each sex were obtained from Charles River Breeding Laboratories and observed for 20 days (rats) or 14 days (mice) before being placed on study. Groups of five rats and five mice of each sex were administered 12.5, 25, 50, 100, or 200 mg/kg THPS in water by gavage for 14 consecutive days. Controls were untreated. Animals were housed five per cage. Feed and water were available ad libitum. Further details of animal maintenance are given in Table 3.

THPC

Six-week-old F344/N rats and B6C3F$_1$ mice of each sex were obtained from Harlan Industries and observed for 16 days before being placed on study. Groups of five rats of each sex were administered 9.4, 18.8, 37.5, 75, or 150 mg/kg THPC in deionized water by gavage for 14 consecutive days. Groups of five mice of each sex were administered 18.8, 37.5, 75, 150, or 300 mg/kg THPC. Controls were untreated. Animals were housed five per cage. Feed and water were available ad libitum. Further details on animal maintenance are given in Table 4.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of THPS and of THPC to determine the doses to be used in the 2-year studies.

THPS

Five- to six-week-old F344/N rats and B6C3F$_1$ mice of each sex were obtained from Harlan Industries and were observed for 14 days before being placed on study. Groups of 10 rats and 10 mice of each sex were administered 0, 5, 10, 20, 40, or 60 mg/kg THPS in distilled water by gavage 5 days per week for 13 weeks.

THPC

Four-week-old F344/N rats and B6C3F$_1$ mice of each sex were obtained from Charles River Breeding Laboratories and were observed for 18 days before being placed on study. Groups of 10 rats of each sex were administered 0, 3.75, 7.5, 15, 30, or 60 mg/kg THPC in distilled water by gavage, 5 days per week for 13 weeks. Groups of 10 mice of each sex were administered 0, 1.5, 4.5, 15, 45, or 135 mg/kg THPC on the same schedule.

THPS and THPC

Further experimental details are summarized in Tables 3 and 4. Rats and mice were weighed weekly and checked twice daily; moribund animals were killed. At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Tables 3 and 4.

TABLE 3. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF THPS

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN			
Size of Study Groups			
5 males and 5 females of each species	Same as single-administration studies	10 males and 10 females of each species	50 males and 49 or 50 females of each species
Doses			
100, 200, 400, 800, or 1,600 mg/kg THPS in water by gavage; dose vol--5 ml/kg	12.5, 25, 50, 100, or 200 mg/kg THPS in distilled water by gavage; dose vol--5 ml/kg; controls untreated	0, 5, 10, 20, 40, or 60 mg/kg THPS in distilled water by gavage; dose vol--5 ml/kg	0, 5, or 10 mg/kg THPS in distilled water by gavage; dose vol--5 ml/kg
Date of First Dose			
11/6/78	Rats--12/28/78; mice--1/4/79	4/17/79	3/27/80
Date of Last Dose			
NA	Rats--1/10/79; mice--1/17/79	7/16/79	3/29/82
Duration of Dosing			
Once only	14 consecutive d	5 d/wk for 13 wk	5 d/wk for 104 wk
Type and Frequency of Observation			
Observed 2 × d; animals weighed initially	Clinical signs recorded 1 × d; weighed initially and at termination	Observed 2 × d; weighed initially and 1 × wk thereafter	Observed 2 × d; clinical signs recorded daily between 6/25/80 and 11/30/81; monthly during other periods. Body weights recorded 1 × wk for 13 wk, then 1 × mo
Necropsy and Histologic Examination			
None	Necropsy performed on all animals; histologic exam not performed	Necropsy performed on all animals; the following tissues from high dose and vehicle control animals and animals dying early examined microscopically: mandibular lymph node, salivary gland, femur, thyroid gland, parathyroids, small intestine, colon, liver, prostate/testis or ovaries/uterus, lungs and mainstem bronchi, mammary gland, heart, esophagus, stomach, brain, thymus, trachea, pancreas, spleen, kidney, adrenal glands, urinary bladder, pituitary gland, and gallbladder (mice)	Necropsy performed on all animals; the following tissues examined histologically: gross lesions and tissue masses, blood smear, mandibular or mesenteric lymph node, salivary gland, femur or vertebrae including marrow, thyroid gland, parathyroids, small intestine, colon, liver, gallbladder (mice), prostate/testis or ovaries/uterus, lungs and mainstem bronchi, skin, heart, esophagus, stomach, brain, pancreas, adrenal glands, thymus, trachea, urinary bladder, kidneys, spinal cord, eyes, spleen, mammary gland, and pituitary gland
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	F344/N rats; $B6C3F_1$ mice
Animal Source			
Charles River Breeding Laboratories (Portage, MI)	Same as single-administration studies	Harlan Industries (Indianapolis, IN)	Charles River Laboratories (Kingston, NY)
Study Laboratory			
Battelle Columbus Laboratories	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies

TABLE 3. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF THPS (Continued)

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)			
Time Held Before Study			
16 d	Rats--20 d; mice--14 d	14 d	15 d
Age When Placed on Study			
45 d	7 wk	53 d	Rats--6 wk; mice--7 wk
Age When Killed			
60 d	9-10 wk	21 wk	112 wk
Necropsy Dates			
11/21/78	Rats--1/12/79; mice--1/19/79	7/17-7/20/79	Rats--4/5-4/17/82; mice--3/30-4/1/82
Method of Animal Distribution			
Two-step randomization to cages and then to groups according to tables of random numbers	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Feed			
Purina Lab Chow®	Purina Lab Chow®	NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners, PA)	NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners, PA) and Purina rodent diet (Ralston Purina, St. Louis, MO) (7 d--rats)
Bedding			
Absorb-Dri® (Lab Products, Inc., Garfield, NJ)	Same as single-administration studies	Same as single-administration studies	Absorb-Dri® (Absorb-Dri, Inc., Rochelle, NJ)
Water			
Freely available; automatic watering system (Edstrom Industries, Waterford, WI)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Cages			
Polycarbonate (Lab Products, Inc., Garfield, NJ)	Same as single-administration studies	Same as single-administration studies	Polycarbonate (Lab Products, Inc., Rochelle, NJ)
Cage Filters			
Spun-bonded polyester filter sheets (Snow Filtration, Cincinnati, OH)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Animals per Cage			
5	5	5	5
Animal Room Environment			
Temp--21°-23° C; hum--40%-60%; fluorescent light 12 h/d; 15 room air changes/h	Same as single-administration studies	Same as single-administration studies	Temp--23° ± 3° C; hum--40%-60%; fluorescent light 12 h/d; 15 room air changes/h

TABLE 4. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF THPC

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN			
Size of Study Groups			
5 males and 5 females of each species	5 males and 5 females of each species	10 males and 10 females of each species	49 or 50 males and 50 females of each species
Doses			
75, 150, 300, 600, or 1,200 mg/kg THPC in deionized water by gavage; dose vol--5 ml/kg	Rats--9.4, 18.8, 37.5, 75, or 150 mg/kg THPC in deionized water by gavage; dose vol--5 ml/kg; mice--18.8, 37.5, 75, 150, or 300 mg/kg THPC in deionized water by gavage; controls untreated	Rats--0, 3.75, 7.5, 15, 30, or 60 mg/kg THPC in deionized water by gavage; mice--0, 1.5, 4.5, 15, 45, or 135 mg/kg THPC in deionized water by gavage; dose vol--5 ml/kg	Rats--0, 3.75, or 7.5 mg/kg THPC in deionized water by gavage; male mice--0, 7.5, or 15 mg/kg; female mice--0, 15, or 30 mg/kg; dose vol--5 ml/kg
Date of First Dose			
10/30/78	5/31/79	10/16/79	9/15/80
Date of Last Dose			
N/A	6/13/79	1/14/80	9/3/82
Duration of Dosing			
Single dose only	14 consecutive d	5 d/wk for 13 wk	5 d/wk for 103 wk
Type and Frequency of Observation			
Observed 2 × d	Observed 2 × d; weighed initially and at necropsy	Observed 2 × d; weighed 1 × wk	Observed 2 × d; weighed 1 × wk for 12 wk and then monthly
Necropsy and Histologic Examination			
None	Necropsy performed on all animals; histologic examinations not performed	Necropsy performed on all animals; histologic examinations performed on the following tissues from all rats that died before end of studies in the vehicle control, 30 mg/kg, and 60 mg/kg groups, and from 2 rats/sex in 15 mg/kg group; from all mice that died before end of studies, from vehicle control, 45 mg/kg, and 135 mg/kg groups, and from 2 mice/sex in 15 mg/kg group: skin, mandibular lymph node, mammary gland, salivary gland, skeletal muscle, sciatic nerve, bone marrow, thymus, trachea, lungs and bronchi, heart, thyroid gland, parathyroids, esophagus, stomach, small intestine, large intestine, mesenteric lymph node, liver, pancreas, spleen, kidneys, adrenal glands, urinary bladder, prostate/testis or ovaries/uterus, brain, pituitary gland, spinal cord, and gallbladder (mice).	Necropsy and histologic examination performed on all animals; the following tissues examined: gross lesions and tissue masses, regional lymph nodes, mandibular or mesenteric lymph node, salivary gland, sternum or femur or vertebrae including marrow, thyroid gland, parathyroids, small intestine, colon, liver, prostate/testis or ovaries/uterus, heart, esophagus, stomach, brain, thymus, trachea, pancreas, spleen, skin, lungs and mainstem bronchi, kidneys, adrenal glands, urinary bladder, pituitary gland, eyes, mammary gland, and gallbladder (mice)

TABLE 4. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF THPC (Continued)

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Necropsy and Histologic Examination (Continued)			
		Liver, stomach, and skeletal muscle examined from all rats in 3.75, 7.5, and 15 mg/kg groups and kidneys from female rats in 3.75, 7.5, and 15 mg/kg groups. Foreleg sections examined in 15 and 45 mg/kg mouse groups; liver examined in 1.5 and 4.5 mg/kg mouse groups; spinal cord examined from 2 mice/sex/dose.	
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	F344/N rats; B6C3F$_1$ mice
Animal Source			
Charles River Breeding Laboratories (Portage, MI)	Harlan Industries (Indianapolis, IN)	Same as single-administration studies	Same as single-administration studies
Study Laboratory			
Battelle Columbus Laboratories	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Method of Animal Identification			
None	Toe mark	Toe mark	Toe and ear marks
Time Held Before Study			
Rats--17 d; mice--18 d	16 d	18 d	Rats--17 d; mice--24 d
Age When Placed on Study			
7 wk	8 wk	7 wk	Rats--7 wk; mice--8 wk
Age When Killed			
9 wk	11 wk	20 wk	Rats--111 wk; mice--112-113 wk
Necropsy Dates			
11/13/78	6/19/79	Rats--1/16/80-1/17/80; mice--1/17/80-1/18/80	9/13/82-9/15/82
Method of Animal Distribution			
Animals assigned from weight classes to cages according to a table of random numbers; cages assigned to groups according to another table of random numbers	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Feed			
Purina 5001 Lab Chow,[•] pelleted (Ralston Purina, St. Louis, MO); available ad libitum	Same as single-administration studies	NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners, PA); available ad libitum	Same as 13-wk studies
Bedding			
Absorb-Dri[•] (Lab Products, Inc., Garfield, NJ)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies

TABLE 4. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF THPC (Continued)

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)			
Water Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Cages Polycarbonate (Lab Products, Inc., Rochelle Park, NJ)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Cage Filters Spun-bonded polyester filter sheets (Snow Filtration, Cincinnati, OH)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Animals per Cage 5	5	5	5
Animal Room Environment Temp--21°-23° C; hum--40%-60%; fluorescent light 12 h/d; 15 room air changes/h	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies

TWO-YEAR STUDIES

Study Design

THPS

Groups of 49 or 50 rats and 50 mice of each sex were administered 0, 5, or 10 mg/kg THPS in deionized water by gavage, 5 days per week for 104 weeks (rats) or 103 weeks (mice). On March 2, 3, and 4, 1981 (12th month of studies), high dose male and low dose female mice accidentally received 15 mg/kg THPC, low dose male mice received 7.5 mg/kg THPC, and high dose female mice received 30 mg/kg THPC.

THPC

Groups of 50 rats of each sex were administered 0, 3.75, or 7.5 mg/kg THPC in deionized water by gavage, 5 days per week, for 103 weeks. Groups of 49 or 50 male mice were administered 0, 7.5, or 15 mg/kg THPC, and groups of 50 female mice were administered 0, 15 or 30 mg/kg THPC for 103 weeks. On March 2, 3, and 4, 1981 (the 6th month of the studies), low dose mice of each sex received 5 mg/kg THPS and high dose mice of each sex accidentally received 10 mg/kg THPS. On October 14, 1981 (the 13th month of the study), five female vehicle control mice (numbers 1-5) received 30 mg/kg THPC. On October 29, 1981, all low dose female rats (3.75 mg/kg) received 7.5 mg/kg THPC.

The above-described misdosing with the wrong chemical was the result of a technician error that occurred when the THPS and THPC dosing vials for mice were switched before delivery to the animal rooms for 3 days in March 1981. As soon as the error was discovered, dosing was stopped; new dose mixtures were prepared and verified to insure that the proper compound was being administered to the animals. In addition, new, more rigorous procedures were instituted; dosing technicians had to go to the dose preparation area, sign for the dose mixtures, and verify that they were getting the right compound.

After the misdosing incident, there were no deaths and no effect on body weights of any of the animals involved. Because the dosing error occurred during a short period of time relatively early in the studies and the chemicals involved are different salt forms of the same tetrahydroxymethyl phosphonium moiety, the misdosing incident is considered to have no impact on the final outcome of these studies. In addition, documentation from the study laboratory, detailing steps taken to insure misdosing of this kind would not happen again, would indicate that this was an isolated incident that did not recur during these studies.

Source and Specifications of Animals

The male and female F344/N rats and $B6C3F_1$ (C57BL/6N, female, × C3H/HeN, MTV^-, male) mice used in these studies were produced under strict barrier conditions at Charles River Laboratories under a contract to the Carcinogenesis Program. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Animals were shipped to the study laboratory at 4-5 weeks of age and were quarantined at the study laboratory for 15 days (THPS), 17 days (THPC rats), or 24 days (THPC mice). Thereafter, a complete necropsy was performed on five animals of each sex and species in each study to assess their health status. The rats and mice were placed on study at 6-7 weeks of age (THPS), 7 weeks (THPC rats), or 8 weeks (THPC mice). The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix S).

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 $B6C3F_1$ study 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 electrophoresis profiles that demonstrate phenotype expressions of known genetic loci.

The C57BL/6N 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/6N 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 the results of the studies are not affected because concurrent controls were included in each study.

Animal Maintenance

Rats and mice were housed five per cage. Feed and water were available ad libitum. Further details of animal maintenance are given in Tables 3 and 4.

Clinical Examinations and Pathology

All animals were observed twice daily, and clinical signs were recorded daily from month 4 to month 21 and monthly at other times. Body weights by cage were recorded once per week for the first 13 weeks (THPS) or 12 weeks (THPC) of the studies and once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals including those found dead, unless they were excessively autolyzed or cannibalized, missexed, or found missing. 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.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined microscopically are listed in Tables 3 and 4.

When the pathology evaluation was completed, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent quality assessment laboratory. The 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 a quality assessment pathologist. The quality assessment report and slides were submitted to the Pathology Working Group (PWG) Chairperson, who reviewed all target tissues and those about which there was a disagreement between the laboratory and quality assessment pathologists.

Representative slides selected by the Chairperson were reviewed by the PWG, which includes the laboratory pathologist, without knowledge of previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the laboratory pathologist was asked to reconsider the original diagnosis. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Slides/tissues are generally not evaluated in a blind fashion (i.e., without knowledge of dose group) unless the lesions in question are subtle or unless there is an inconsistent diagnosis of lesions by the laboratory pathologist. Nonneoplastic lesions are not examined routinely by the quality assessment pathologist or PWG unless they are considered part of the toxic effect of the chemical.

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) life table test for a dose-related trend. When significant survival differences were detected, additional analyses using these procedures were carried out to determine the time point at which significant differences in the survival curves were first detected. All reported P values for the survival analysis are two-sided.

Calculation of Incidence: The incidence of neoplastic or nonneoplastic lesions is 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 include 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 a necropsy was 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. Continuity-corrected tests are used in the analysis of tumor incidence, and reported P values 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 studies 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 vehicle 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 at risk in each group. These results, including the data from animals killed at the end of the studies, 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). The underlying variable considered by this analysis is time to death due to tumor. If the tumor is rapidly lethal, then time to death due to tumor closely approximates time to tumor onset. In this case, the life table test also provides a comparison of the time-specific tumor incidences.

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 vehicle control groups were compared in each of five time intervals: weeks 0-52, weeks 53-78, weeks 79-92, 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 a necropsy was 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 Haseman, 1984, for the computational details of both methods.)

Unadjusted Analyses--Primarily, survival-adjusted methods are used to evaluate tumor incidence. In addition, the results of the Fisher exact test for pairwise comparisons and the Cochran-Armitage linear trend test (Armitage, 1971; Gart et al., 1979) are given in the appendixes 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.

Historical Control Data: Although the concurrent control group is always the first and most appropriate control group used for evaluation, there are certain instances in which historical control data can be helpful in the overall assessment of tumor incidence. Consequently, control tumor incidences from the NTP historical control data base (Haseman et al., 1984, 1985) are included for those tumors appearing to show compound-related effects.

III. RESULTS

RATS

SINGLE-ADMINISTRATION STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

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

MICE

SINGLE-ADMINISTRATION STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

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

III. RESULTS: RATS

SINGLE-ADMINISTRATION STUDIES

THPS

All rats that received 1,600 mg/kg, 4/5 males and 5/5 females that received 800 mg/kg, and 4/5 males and 4/5 females that received 400 mg/kg THPS died within 24 hours of dosing (Table 5). Mean body weights were not recorded, and necropsies were not performed.

THPC

All male and female rats that received 600 or 1,200 mg/kg THPC and all males that received 300 mg/kg THPC were dead by day 2 (Table 6). Surviving rats of each sex that received 150 mg/kg had reddish fluid around the nostrils by day 3 and labored breathing. Final weights were not recorded. Necropsies were not performed.

TABLE 5. SURVIVAL OF RATS IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF THPS

Dose (mg/kg)	Survival	
	Male (a)	Female (b)
100	5/5	5/5
200	(c) 4/5	(d) 3/5
400	(c) 1/5	(c) 1/5
800	(c) 1/5	(e) 0/5
1,600	(e) 0/5	(e) 0/5

(a) LD_{50} value by probit analysis: 333 mg/kg (95% confidence interval, 185-585 mg/kg)
(b) LD_{50} value by probit analysis: 248 mg/kg (95% confidence interval, 144-426 mg/kg)
(c) Day of death: all 2
(d) Day of death: 2, 4
(e) Day of death: all 1

TABLE 6. SURVIVAL OF RATS IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF THPC

Dose (mg/kg)	Survival	
	Male (a)	Female (b)
75	5/5	5/5
150	(c) 4/5	(d) 3/5
300	(e) 0/5	(f) 0/5
600	(e) 0/5	(e) 0/5
1,200	(e) 0/5	(e) 0/5

(a) LD_{50} value by Spearman-Karber method: 185 mg/kg (95% confidence limits, 141-242 mg/kg)
(b) LD_{50} value by Spearman-Karber method: 161 mg/kg (95% confidence limits, 115-224 mg/kg)
(c) Day of death: 3
(d) Day of death: 1, 4
(e) Day of death: all 2
(f) Day of death: 3, 4, 6, 6, 13

FOURTEEN-DAY STUDIES

THPS

All rats that received 100 or 200 mg/kg died before the end of the studies (Table 7). Rats that received 25 or 50 mg/kg gained notably less weight than did the controls. Males that received 50 mg/kg lost weight. Males that received 100 or 200 mg/kg had tremors after the second day of dosing. One male that received 200 mg/kg had partial loss of movement of the hindlegs 5 days after dosing. No compound-related lesions were observed at necropsy.

THPC

All rats that received 150 mg/kg THPC died within 8 days of dosing (Table 8). Two male rats that received 75 mg/kg died by day 15. The final mean body weight of male rats that received 18.8 or 37.5 mg/kg was 6% or 11% lower than that of the controls. The final mean body weight of female rats that received 18.8 or 37.5 mg/kg was comparable to that of the controls. The 75 mg/kg groups of males and females had rough coats by day 3; swollen abdomens and arched backs were evident by day 13. At necropsy, rats that received 150 mg/kg had yellow to tan or mottled red livers.

TABLE 7. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FOURTEEN-DAY GAVAGE STUDIES OF THPS

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams)			Final Weight Relative to Controls (percent)
		Initial (b)	Final	Change (c)	
MALE					
(d) 0	5/5	218	257	+39	--
12.5	4/5	217	255	+38	99.2
25	4/5	216	229	+13	89.1
50	5/5	223	203	−20	79.0
100	(e) 0/5	221	(f)	(f)	(f)
200	(g) 0/5	211	(f)	(f)	(f)
FEMALE					
(d) 0	5/5	134	151	+17	--
12.5	4/5	136	152	+16	100.7
25	5/5	138	149	+11	98.7
50	5/5	138	141	+3	93.4
100	(h) 0/5	137	(f)	(f)	(f)
200	(i) 0/5	140	(f)	(f)	(f)

(a) Number surviving/number in group
(b) Initial mean group body weight
(c) Mean body weight change
(d) Controls were untreated.
(e) Day of death: 9, 9, 10, 11, 12
(f) No data are reported because of the 100% mortality in this group.
(g) Day of death: 2, 2, 3, 4, 6
(h) Day of death: 9, 10, 11, 12, 12
(i) Day of death: 2, 2, 2, 2, 5

TABLE 8. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FOURTEEN-DAY GAVAGE STUDIES OF THPC

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
(d) 0	5/5	114	175	+61	--
9.4	5/5	117	179	+62	102.2
18.8	5/5	108	164	+56	93.7
37.5	5/5	116	156	+40	89.1
75	(e) 3/5	102	107	+5	61.1
150	(f) 0/5	106	(g)	(g)	(g)
FEMALE					
(d) 0	5/5	94	123	+29	--
9.4	5/5	95	125	+30	101.6
18.8	5/5	92	118	+26	95.9
37.5	5/5	96	122	+26	99.2
75	5/5	92	90	-2	73.2
150	(h) 0/5	94	(g)	(g)	(g)

(a) Number surviving/number initially in group
(b) Initial mean group body weight
(c) Mean body weight change
(d) Controls were untreated.
(e) Day of death: 12, 15
(f) Day of death: 3, 5, 7, 7, 8
(g) No data are reported due to the 100% mortality in this group.
(h) Day of death: 3, 3, 5, 5, 8

THIRTEEN-WEEK STUDIES

THPS

Three of 10 male rats that received 60 mg/kg died before the end of the studies (Table 9). All other rats survived to the end of the studies. Final mean body weights were 5%, 15%, and 22% lower than those of the vehicle controls for males that received 20, 40, or 60 mg/kg and from 7% to 19% lower for all groups of dosed female rats. Diarrhea occurred in all groups of dosed rats during weeks 3 and 4.

Vacuolar degeneration of the hepatocytes occurred in all males receiving 10 mg/kg or more, in all females receiving 40 or 60 mg/kg, and in 5/10 females receiving 20 mg/kg. The severity of this lesion was greatest in the 60 mg/kg group. In other groups, the severity was generally minimal to mild. Lymphoid depletion in the spleen or thymus was observed in the three males in the 60 mg/kg group which died before the end of the studies. Bone marrow hypoplasia was diagnosed in 3/10 male and 4/10 female rats in the 60 mg/kg groups.

Dose Selection Rationale: Because of the vacuolar degeneration of the hepatocytes and reduced body weight gain, THPS doses selected for rats for the 2-year studies were 5 and 10 mg/kg administered by gavage in water 5 days per week.

TABLE 9. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF THPS

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams)			Final Weight Relative to Vehicle Controls (percent)
		Initial (b)	Final	Change (c)	
MALE					
0	10/10	105	291	+186	--
5	10/10	105	291	+186	0.0
10	10/10	110	285	+175	97.9
20	10/10	103	275	+172	94.5
40	10/10	105	248	+143	85.2
60	(d) 7/10	108	228	+120	78.4
FEMALE					
0	10/10	91	182	+91	--
5	10/10	90	169	+79	92.9
10	10/10	87	163	+76	89.6
20	10/10	90	165	+75	90.7
40	10/10	87	160	+73	87.9
60	10/10	86	148	+62	81.3

(a) Number surviving/number in group
(b) Initial mean group body weight
(c) Mean body weight change
(d) Week of death: 11, 11, 12

THPC

All males and 5/10 females that received 60 mg/kg THPC and 2/10 males and 1/10 females that received 15 mg/kg died before the end of the studies (Table 10). Deaths in the 15 mg/kg groups may have been due to gavage error. The final mean body weight of males that received 30 mg/kg was 89% that of the vehicle controls. The final mean body weight of females that received 60 mg/kg was 80% that of the vehicle controls. Rough coats, hunched backs, diarrhea, lethargy, and paresis and hyperextension of the rear limbs were observed for rats that received 60 mg/kg.

Periportal hepatocellular necrosis was observed in 9/10 males and 7/10 females that received 15 mg/kg, 10/10 males and 10/10 females that received 30 mg/kg, and 7/10 males and 8/10 females that received 60 mg/kg. (The severity at 15 mg/kg was minimal.) Periportal cytoplasmic vacuolization was observed in 8/10 males that received 7.5 mg/kg, 9/10 males and 8/10 females that received 15 mg/kg, and all rats that received 30 or 60 mg/kg. Degeneration of the axons was found in 2/10 females that received 60 mg/kg but not in any of the rats that received 30 mg/kg.

Dose Selection Rationale: Because of the hepatocellular necrosis observed at 15 mg/kg, THPC doses selected for rats for the 2-year studies were 3.75 and 7.5 mg/kg administered by gavage in water 5 days per week.

TABLE 10. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF THPC

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	150 ± 6	350 ± 7	+200 ± 2	--
3.75	10/10	150 ± 4	343 ± 10	+193 ± 9	98
7.5	10/10	151 ± 5	326 ± 8	+175 ± 5	93
15	(d) 8/10	149 ± 4	335 ± 6	+188 ± 4	96
30	10/10	153 ± 5	312 ± 9	+159 ± 7	89
60	(e) 0/10	151 ± 4	(f)	(f)	(f)
FEMALE					
0	10/10	116 ± 2	191 ± 2	+75 ± 2	--
3.75	10/10	115 ± 2	196 ± 3	+81 ± 2	103
7.5	10/10	113 ± 3	197 ± 4	+84 ± 3	103
15	(g) 9/10	114 ± 2	197 ± 2	+82 ± 2	103
30	10/10	114 ± 2	197 ± 4	+83 ± 4	103
60	(h) 5/10	114 ± 2	152 ± 9	+39 ± 11	80

(a) Number surviving/number initially in the group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors of the group ± standard error of the mean
(d) Week of death: 5, 8
(e) Week of death: 4, 5, 7, 8, 8, 8, 9, 9, 9, 10
(f) No data are reported due to the 100% mortality in this group.
(g) Week of death: 5
(h) Week of death: 4, 6, 8, 10, 11

TWO-YEAR STUDIES

Body Weights and Clinical Signs

THPS

Mean body weights of dosed and vehicle control rats of each sex were comparable throughout most of the studies (Table 11 and Figure 1). Compound-related clinical signs consisted primarily of rough hair coats and diarrhea.

THPC

Mean body weights of dosed and vehicle control male and female rats were comparable throughout most of the studies (Table 12 and Figure 2). Compound-related clinical signs consisted primarily of rough hair coats and diarrhea.

TABLE 11. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF THPS

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	5 mg/kg Av. Wt. (grams)	5 mg/kg Wt. (percent of veh. controls)	5 mg/kg No. of Survivors	10 mg/kg Av. Wt. (grams)	10 mg/kg Wt. (percent of veh. controls)	10 mg/kg No. of Survivors
MALE								
0	119	50	118	99	50	114	96	50
1	143	50	139	97	50	141	99	50
2	166	50	164	99	50	167	101	50
3	191	50	187	98	50	191	100	49
4	214	50	208	97	50	213	100	48
5	232	50	227	98	50	232	100	46
6	248	50	244	98	50	247	100	45
7	266	50	257	97	50	252	95	45
8	277	50	271	98	50	268	97	45
9	292	50	281	96	50	288	99	45
10	306	50	296	97	50	297	97	45
11	316	50	310	98	50	313	99	45
12	326	50	319	98	50	324	99	45
13	332	50	329	99	50	335	101	45
16	355	50	355	100	50	357	101	45
21	384	50	381	99	50	385	100	45
25	405	50	401	99	50	399	99	45
29	425	50	420	99	50	417	98	45
33	436	50	431	99	50	426	98	45
37	447	48	442	99	50	433	97	45
42	456	48	455	100	50	447	98	45
46	453	48	459	101	49	448	99	45
50	469	48	468	100	49	456	97	45
54	481	48	473	98	49	464	96	45
58	473	48	465	98	49	454	96	43
63	467	48	464	99	49	449	96	41
68	484	48	475	98	48	471	97	40
72	468	48	468	100	48	464	99	37
77	473	47	468	99	47	465	98	37
81	481	46	477	99	45	475	99	35
86	482	42	479	99	43	472	98	32
90	465	41	471	101	37	458	98	28
94	469	37	469	100	34	472	101	23
99	453	33	434	96	29	446	98	22
103	435	31	443	102	18	436	100	18
105	433	29	440	102	13	433	100	16
FEMALE								
0	103	(a) 50	105	102	50	103	100	50
1	116	50	118	102	50	113	97	50
2	128	50	127	99	50	125	98	50
3	139	50	139	100	50	135	97	50
4	148	50	149	101	50	145	98	50
5	157	50	156	99	50	153	97	50
6	162	50	162	100	50	157	97	50
7	165	50	168	102	50	163	99	50
8	170	50	172	101	50	167	98	50
9	176	50	178	101	50	173	98	50
10	182	50	183	101	50	179	98	50
11	186	50	186	100	50	182	98	50
12	188	50	188	100	50	185	98	50
13	191	50	192	101	50	189	99	50
16	198	50	201	102	50	194	98	50
21	209	50	211	101	50	207	99	50
25	215	50	217	101	50	212	99	49
29	224	50	224	100	50	217	97	48
33	228	50	226	99	50	225	99	48
37	231	50	232	100	50	227	98	48
42	239	50	241	101	50	239	100	47
46	246	50	248	101	50	243	99	47
50	250	50	257	103	50	254	102	47
54	262	50	262	100	50	259	99	47
58	271	50	272	100	50	270	100	46
63	288	50	287	100	50	283	98	45
68	299	50	300	100	50	295	99	45
72	300	50	302	101	50	298	99	45
77	309	49	305	99	49	302	98	44
81	317	49	316	100	48	314	99	43
86	318	47	317	100	46	318	100	42
90	319	45	322	101	43	316	99	40
94	322	42	328	102	41	324	101	38
99	320	39	325	102	40	307	96	38
103	319	38	326	102	39	326	102	31
105	317	37	321	101	38	321	101	30

(a) One vehicle control female, removed after 73 weeks on study, was inadvertently treated as part of the low dose group for an unknown period of time.

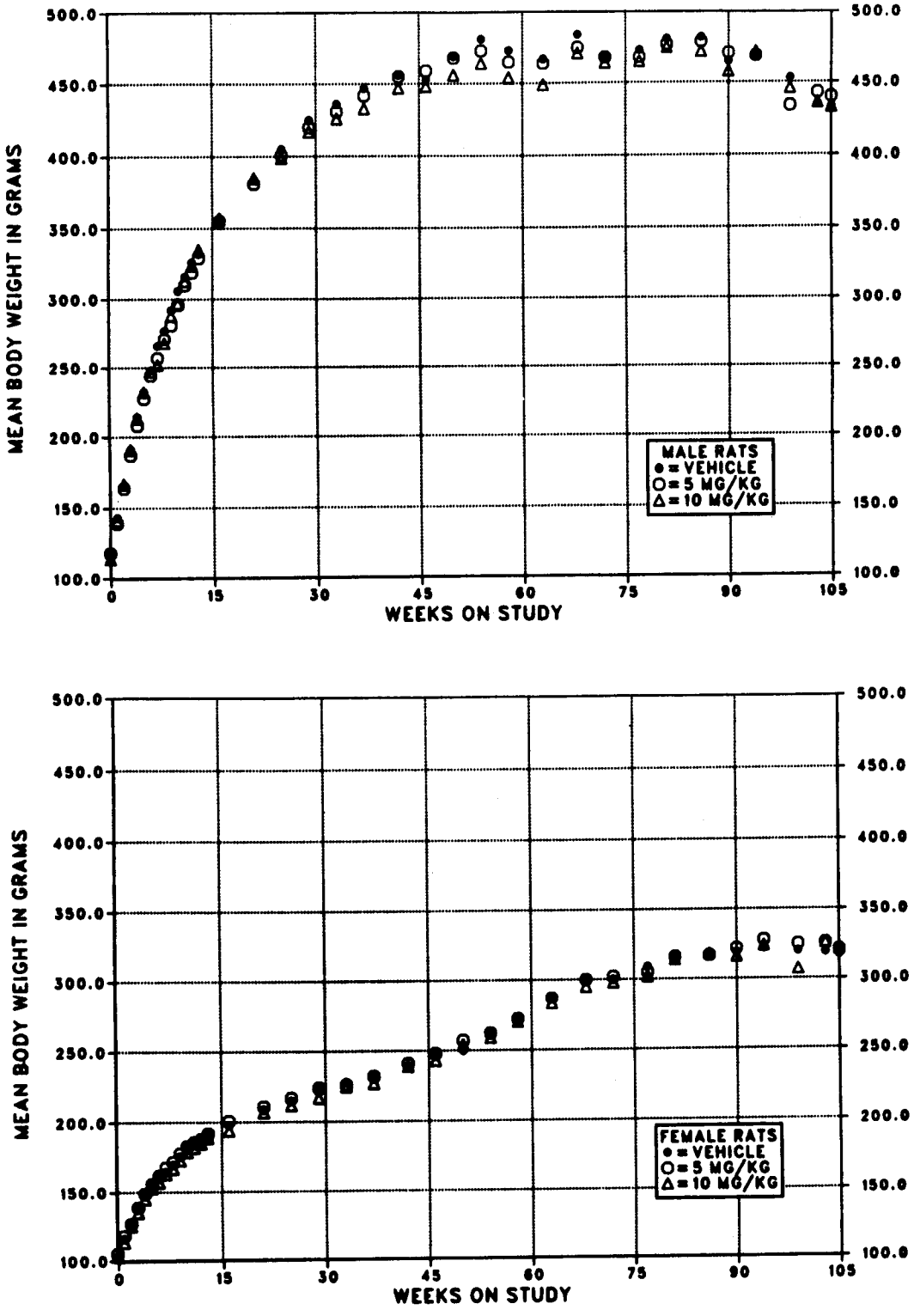


FIGURE 1. GROWTH CURVES FOR RATS ADMINISTERED THPS IN WATER BY GAVAGE FOR TWO YEARS

TABLE 12. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF THPC

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	3.75 mg/kg Av. Wt. (grams)	3.75 mg/kg Wt. (percent of veh. controls)	3.75 mg/kg No. of Survivors	7.5 mg/kg Av. Wt. (grams)	7.5 mg/kg Wt. (percent of veh. controls)	7.5 mg/kg No. of Survivors
MALE								
0	112	50	117	104	50	115	103	50
1	159	50	166	104	50	164	103	50
2	190	50	203	107	50	201	106	50
3	225	50	230	102	50	232	103	49
4	253	50	252	100	50	256	101	48
5	268	50	270	101	50	271	101	47
6	282	50	285	101	50	287	102	47
7	297	50	300	101	50	302	102	47
8	312	50	315	101	50	318	102	47
9	323	50	325	101	50	328	102	47
10	332	50	329	99	50	338	102	47
11	335	50	336	100	50	345	103	47
12	349	50	349	100	50	354	101	47
16	374	50	378	101	50	382	102	47
20	400	50	406	102	49	404	101	47
24	414	50	418	101	48	417	101	47
29	430	50	434	101	48	432	100	46
33	439	50	442	101	47	444	101	46
37	446	50	445	100	47	449	101	46
43	458	50	452	99	46	456	100	46
47	462	50	460	100	46	461	100	45
52	467	49	464	99	46	468	100	45
56	473	49	469	99	46	471	100	45
61	475	49	470	99	45	472	99	45
64	488	48	478	98	45	479	98	44
69	487	46	486	100	44	483	99	43
74	486	44	476	98	44	477	98	43
77	488	43	480	98	43	485	99	43
81	485	42	476	98	41	480	99	41
85	482	41	474	98	40	475	99	39
89	472	38	462	98	39	466	99	36
94	467	37	448	96	35	453	97	32
98	455	35	438	96	27	444	98	27
103	460	27	433	94	18	427	93	20
FEMALE								
0	103	50	102	99	50	105	102	50
1	127	50	126	99	50	129	102	50
2	144	50	143	99	50	146	101	50
3	156	50	155	99	50	157	101	50
4	143	50	142	99	50	144	101	50
5	165	50	164	99	50	164	99	50
6	178	50	175	98	50	175	98	50
7	184	50	184	100	50	184	100	49
8	193	50	189	98	50	191	99	49
9	196	50	191	97	50	194	99	49
10	199	50	195	98	50	197	99	49
11	200	50	197	99	50	198	99	49
12	205	50	202	99	50	204	100	49
16	210	50	211	100	50	212	101	49
20	220	50	218	99	50	221	100	49
24	229	50	226	99	50	228	100	49
29	234	50	232	99	50	236	101	49
33	245	50	242	99	50	244	100	49
37	247	50	244	99	50	247	100	49
43	258	50	259	100	49	262	102	49
47	263	50	263	100	49	265	101	49
52	271	50	271	100	49	274	101	49
56	274	50	275	100	49	277	101	47
61	286	50	281	98	49	283	99	47
64	292	50	289	99	48	292	100	47
69	300	50	296	99	48	301	100	44
74	309	49	305	99	48	306	99	34
77	313	47	311	99	47	308	98	35
81	316	46	313	99	45	310	98	33
85	321	45	316	98	43	312	97	32
89	323	44	317	98	43	314	97	30
94	325	43	320	98	41	322	99	28
98	327	40	317	97	37	315	96	24
103	319	37	312	98	34	301	94	22

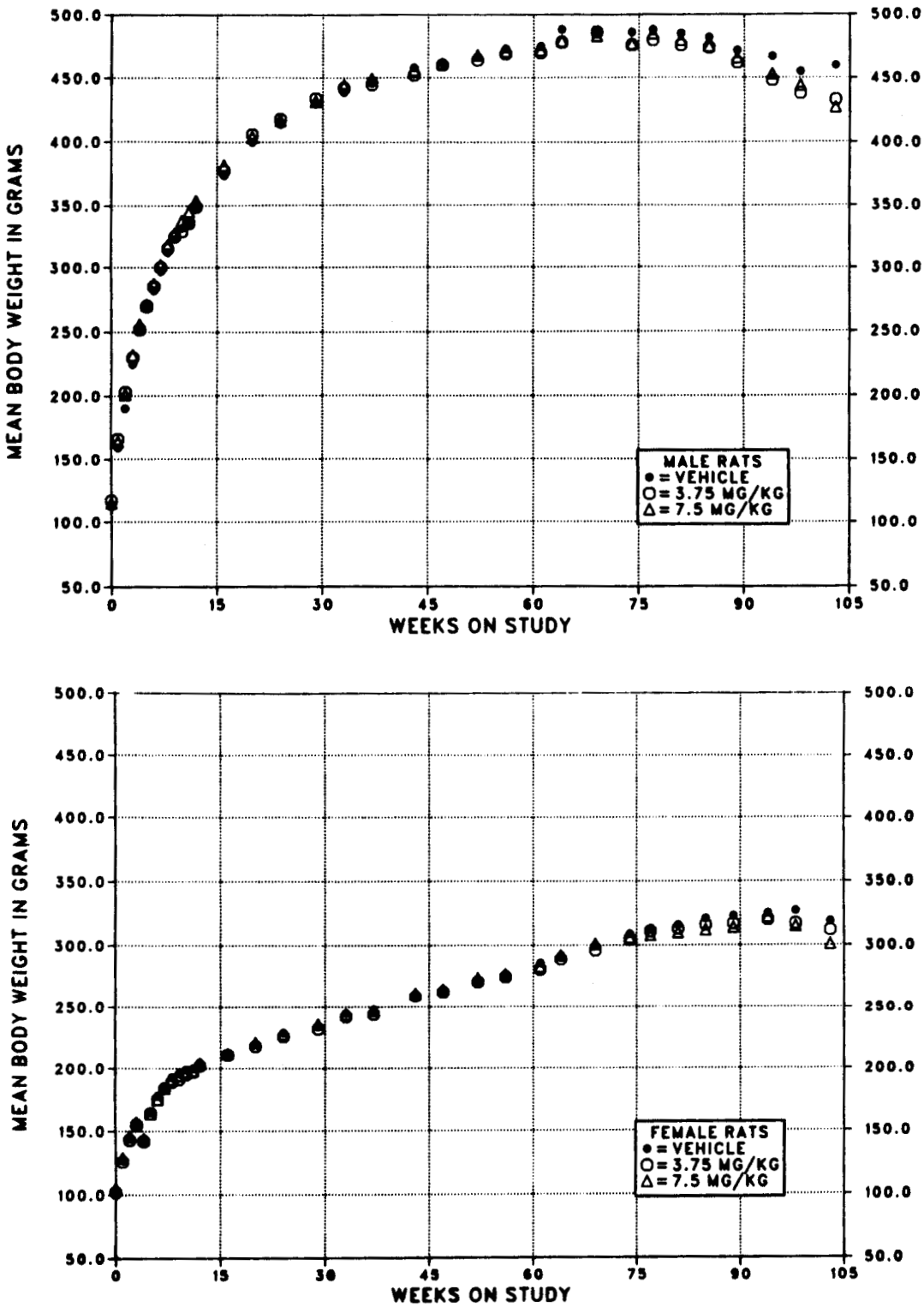


FIGURE 2. GROWTH CURVES FOR RATS ADMINISTERED THPC IN WATER BY GAVAGE FOR TWO YEARS

Survival

THPS

Estimates of the probabilities of survival for male and female rats administered THPS at the doses used in these studies and for vehicle controls are shown in the Kaplan and Meier curves in Figure 3. The survival of both the male low dose (after week 102) and high dose (after week 67) groups was significantly lower than that of the vehicle controls (Table 13).

THPC

Estimates of the probabilities of survival for male and female rats administered THPC at the doses used in these studies and for vehicle controls are shown in the Kaplan and Meier curves in Figure 4. The survival of the high dose group of female rats was significantly lower than that of the vehicle controls (after week 70) and that of the low dose group (P = 0.013) (Table 14).

TABLE 13. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF THPS

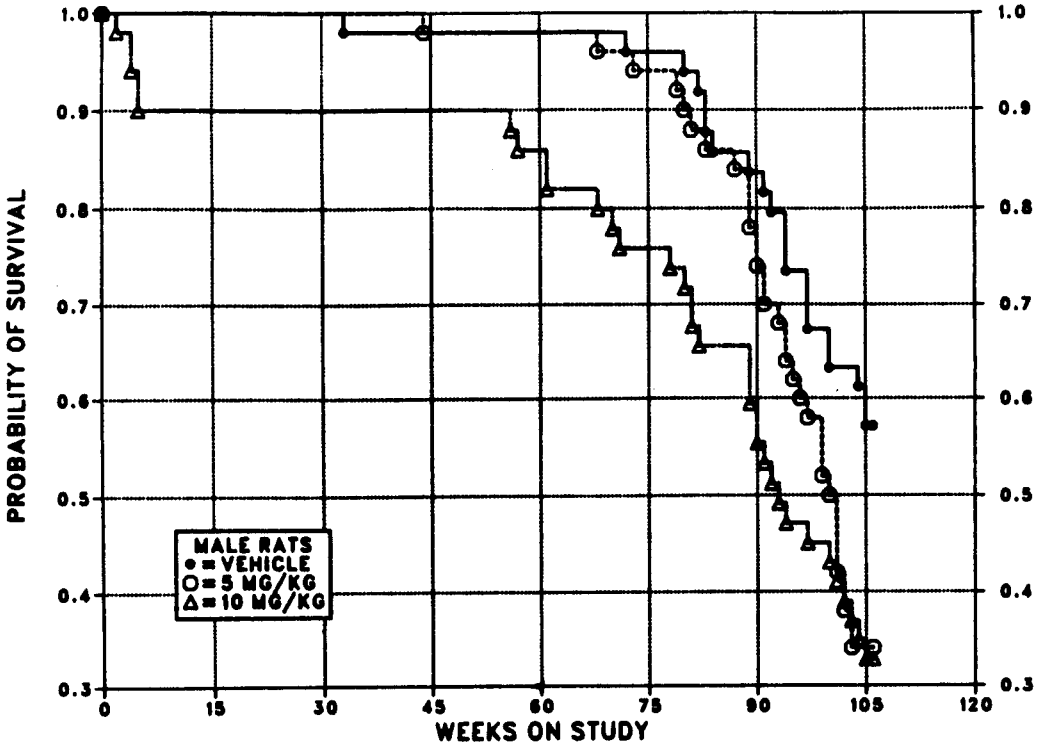
	Vehicle Control	5 mg/kg	10 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	21	33	33
Accidentally killed	1	(c) 4	1
Killed at termination	28	13	16
Survival P values (d)	0.004	0.036	0.006
FEMALE (a)			
Animals initially in study	(e) 49	50	50
Nonaccidental deaths before termination (b)	12	12	20
Accidentally killed	0	0	1
Killed at termination	37	38	29
Survival P values (d)	0.095	0.976	0.132

(a) Terminal-kill period: week 106
(b) Includes animals killed in a moribund condition
(c) Individual animal records indicate that four low dose male rats may have drowned during week 104 of the study.
(d) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.
(e) One vehicle control female was discarded because it was dosed as a low dose female for an unknown length of time.

TABLE 14. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF THPC

	Vehicle Control	3.75 mg/kg	7.5 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	23	32	32
Accidentally killed	1	1	0
Killed at termination	26	17	18
Survival P values (c)	0.088	0.097	0.104
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	12	16	27
Accidentally killed	1	0	2
Killed at termination	36	33	21
Died during termination period	1	1	0
Survival P values (c)	<0.001	0.477	0.001

(a) Terminal-kill period: week 104
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.



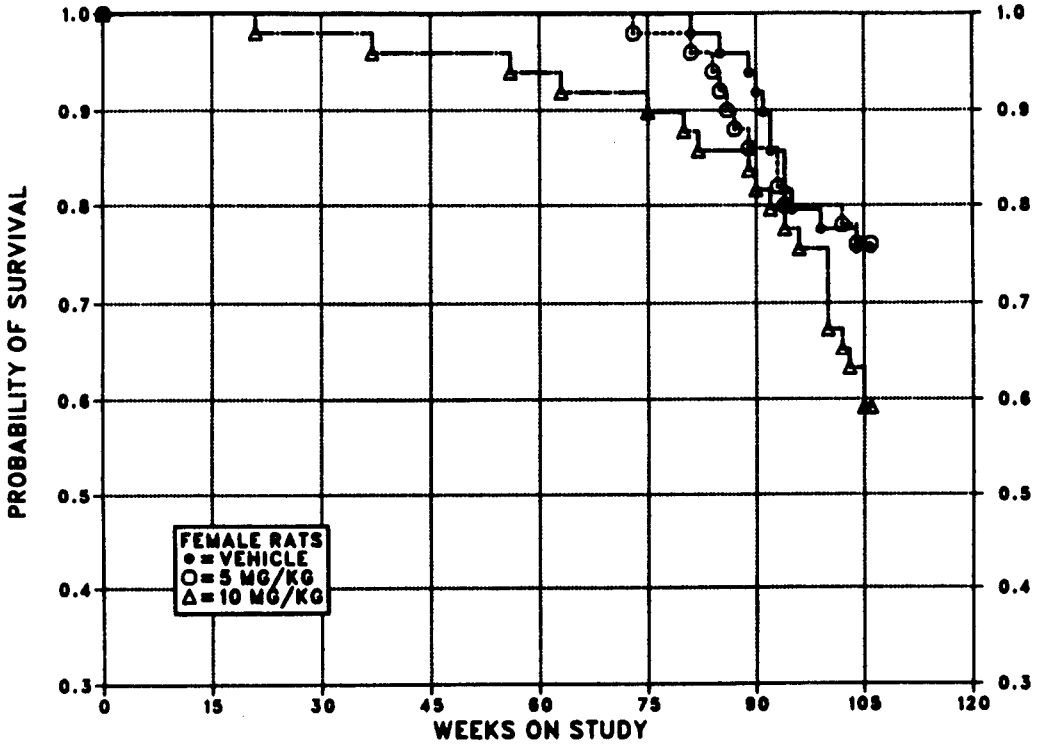


FIGURE 3. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED THPS IN WATER BY GAVAGE FOR TWO YEARS

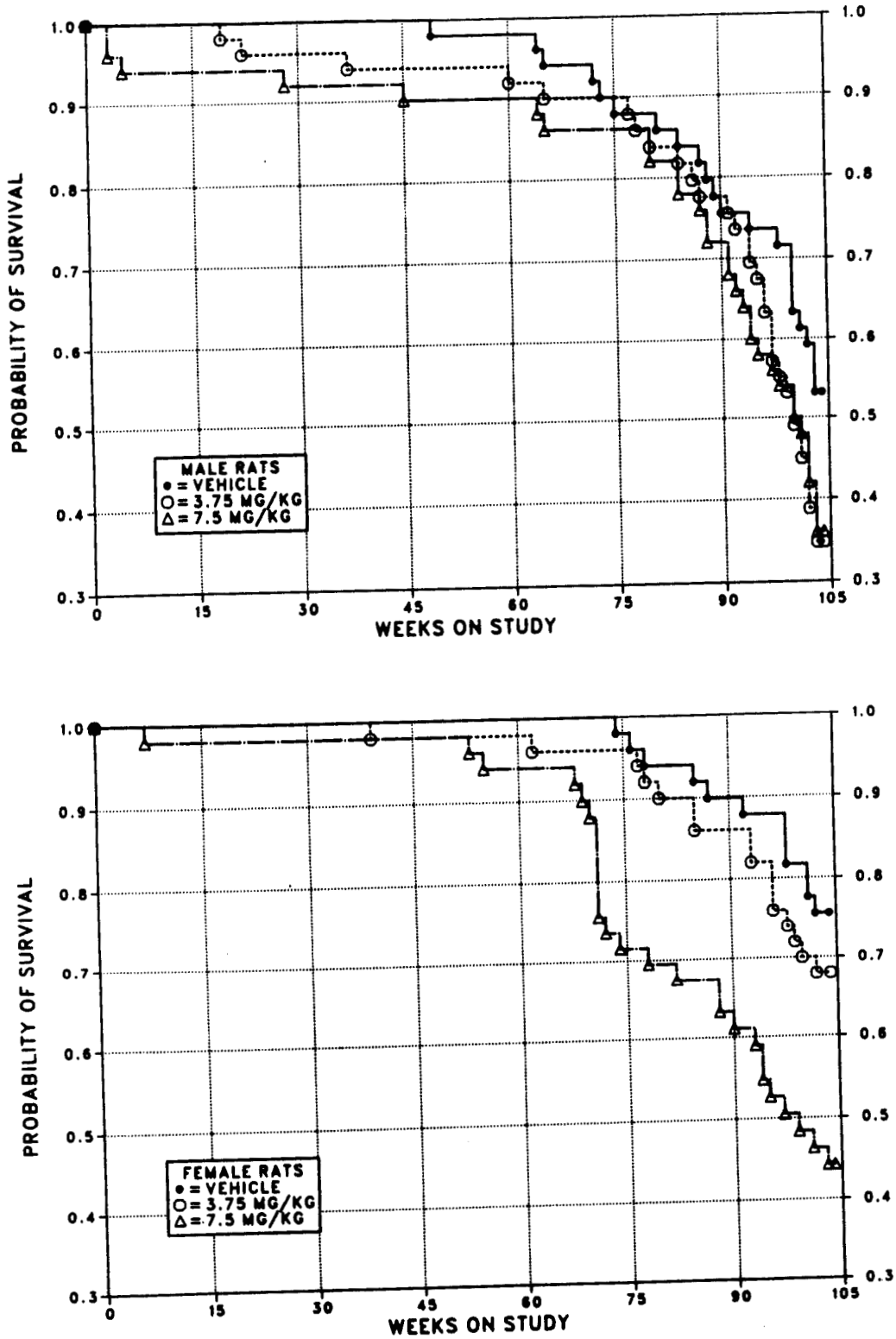


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED THPC IN WATER BY GAVAGE FOR TWO YEARS

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy increases in the incidences of rats with neoplastic or nonneoplastic lesions in the hematopoietic system, pituitary gland, liver, lung, spleen, and uterus.

Histopathologic findings in the THPS studies on neoplasms in rats are summarized in Tables A1 and B1; Tables A2 and B2 give the survival and tumor status for individual male and female rats. Tables A3 and B3 contain the statistical analyses of those primary tumors in the THPS studies 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 Tables A3 and B3 (footnotes). The historical incidence of tumors in control male and female F344/N rats is given in Tables A4 and B4. Findings on nonneoplastic lesions in the THPS studies are summarized in Tables A5 and B5.

Histopathologic findings in the THPC studies on neoplasms in rats are summarized in Tables E1 and F1; Tables E2 and F2 give the survival and tumor status for individual male and female rats. Tables E3 and F3 contain the statistical analyses of those primary tumors in the THPC studies 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 Tables E3 and F3 (footnotes). The historical incidence of tumors in control male F344/N rats is given in Table E4. Findings on nonneoplastic lesions in the THPC studies are summarized in Tables E5 and F4.

Hematopoietic System (THPS): The incidence of mononuclear cell leukemia in low dose (but not high dose) male rats was significantly greater than that in the vehicle controls by the life table test (Table 15). The incidences of mononuclear cell leukemia in dosed and vehicle control female rats were not significantly different (vehicle control, 23/49; low dose, 19/50; high dose, 22/50).

Hematopoietic System (THPC): The incidence of mononuclear cell leukemia in low dose male rats was significantly greater than that in the vehicle controls by the life table test (Table 15).

TABLE 15. ANALYSIS OF HEMATOPOIETIC SYSTEM TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDIES OF THPS AND THPC (a)

	Vehicle Control	Low Dose	High Dose
THPS		**5 mg/kg**	**10 mg/kg**
Mononuclear Cell Leukemia (b)			
Overall Rates	30/50 (60%)	36/50 (72%)	20/50 (40%)
Adjusted Rates	66.3%	97.0%	78.9%
Terminal Rates	13/28 (46%)	12/13 (92%)	11/16 (69%)
Week of First Observation	72	80	82
Life Table Tests	P=0.267	P=0.003	P=0.437
Incidental Tumor Tests	P=0.265N	P=0.304	P=0.225N
THPC		**3.75 mg/kg**	**7.5 mg/kg**
Mononuclear Cell Leukemia (b)			
Overall Rates	19/50 (38%)	25/50 (50%)	16/50 (32%)
Adjusted Rates	47.0%	69.8%	55.6%
Terminal Rates	6/26 (23%)	8/17 (47%)	7/18 (39%)
Week of First Observation	73	80	80
Life Table Tests	P=0.398	P=0.049	P=0.484
Incidental Tumor Tests	P=0.201N	P=0.282	P=0.250N

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix A, Table A3 (footnotes).
(b) Historical incidence of leukemia in water gavage vehicle controls (mean ± SD): 74/150 (49% ± 11%); historical incidence in untreated controls: 458/1,727 (27% ± 9%)

Anterior Pituitary Gland (THPS): The incidence of adenomas in low dose male rats was significantly greater than that in the vehicle controls by the life table test (Table 16). A carcinoma was observed in one low dose male rat. The incidences of adenomas in female rats were as follows: vehicle control, 23/46; low dose, 19/50; high dose, 16/46.

Liver (THPS): Cytoplasmic vacuolization was observed at increased incidences in dosed male and female rats; the incidence of cystic degeneration was increased in dosed male rats (Table 17).

Liver (THPC): Cytoplasmic vacuolization was observed at increased incidences in dosed male and female rats (Table 17). This lesion was characterized by large, generally homogeneous, eosinophilic droplets in the cytoplasm of hepatocytes near triads. The nuclei of those cells were either not apparent or were displaced to one side. Cystic degeneration was observed at increased incidences in dosed male rats.

TABLE 16. ANALYSIS OF ANTERIOR PITUITARY GLAND LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS

	Vehicle Control	5 mg/kg	10 mg/kg
Hyperplasia			
Overall Rates	8/50 (16%)	3/49 (6%)	5/48 (10%)
Adenoma			
Overall Rates	21/50 (42%)	26/49 (53%)	14/48 (29%)
Adjusted Rates	54.9%	75.9%	65.1%
Terminal Rates	12/28 (43%)	6/13 (46%)	9/16 (56%)
Week of First Observation	72	68	89
Life Table Tests	P=0.309	P=0.012	P=0.455
Incidental Tumor Tests	P=0.278N	P=0.334	P=0.385N
Carcinoma			
Overall Rates	0/50 (0%)	1/49 (2%)	0/48 (0%)
Adenoma or Carcinoma (a)			
Overall Rates	21/50 (42%)	27/49 (55%)	14/48 (29%)
Adjusted Rates	54.9%	77.1%	65.1%
Terminal Rates	12/28 (43%)	6/13 (46%)	9/16 (56%)
Week of First Observation	72	68	89
Life Table Tests	P=0.301	P=0.008	P=0.455
Incidental Tumor Tests	P=0.281N	P=0.282	P=0.385N

(a) Historical incidence in water gavage vehicle controls (mean ± SD): 51/150 (34% ± 9%); historical incidence in untreated controls: 363/1,614 (22% ± 11%)

TABLE 17. INCIDENCES OF CYTOPLASMIC VACUOLIZATION AND CYSTIC DEGENERATION OF THE LIVER IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF THPS AND THPC

	THPS				THPC		
	Vehicle Control	5 mg/kg	10 mg/kg		Vehicle Control	3.75 mg/kg	7.5 mg/kg
Cytoplasmic Vacuolization							
Male	2/50	4/50	9/49	Male	0/50	9/50	23/49
Female	1/49	3/50	8/49	Female	3/50	11/50	25/50
Cystic Degeneration							
Male	7/50	15/50	14/49	Male	12/50	26/50	23/49
Female	None observed			Female	None observed		

Lung (THPC): Acute congestion and edema were observed at increased incidences in dosed rats that died during the studies (acute congestion--male: vehicle control, 0/50; low dose, 1/50; high dose, 9/50; female: 3/50; 2/50; 12/50; edema--male: 1/50; 1/50; 6/50; female: 0/50; 2/50; 11/50).

Spleen (THPC): Hematopoiesis of the red pulp was observed at increased incidences in dosed female rats (male: vehicle control, 1/50; low dose, 5/50; high dose, 3/49; female: 3/50; 9/50; 15/50).

Uterus (THPS): Endometrial stromal polyps in female rats occurred with a significant positive trend, and the incidence in the high dose group was significantly greater than that in the vehicle controls (Table 18).

TABLE 18. ANALYSIS OF UTERINE TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS

	Vehicle Control	5 mg/kg	10 mg/kg
Endometrial Stromal Polyp (a)			
Overall Rates	6/49 (12%)	9/50 (18%)	12/49 (24%)
Adjusted Rates	16.2%	23.0%	36.2%
Terminal Rates	6/37 (16%)	8/38 (21%)	9/29 (31%)
Week of First Observation	106	102	82
Life Table Tests	P=0.024	P=0.307	P=0.035
Incidental Tumor Tests	P=0.035	P=0.304	P=0.045

(a) Historical incidence in water gavage vehicle controls (mean ± SD): 27/148 (18% ± 5%); historical incidence in untreated controls: 381/1,750 (22% ± 8%)

SINGLE-ADMINISTRATION STUDIES

THPS

All mice that received 400, 800, or 1,600 mg/kg THPS were dead by day 2 (Table 19). Mean body weights were not recorded; necropsies were not performed.

THPC

All males and females that received 600 or 1,200 mg/kg THPC were dead by day 4 (Table 20). Three of five female mice that received 300 mg/kg died before the end of the studies. All mice were lethargic and had rough coats within several hours of dosing. All surviving mice appeared normal within 24 hours of dosing. Final body weights were not recorded; necropsies were not performed.

TABLE 19. SURVIVAL OF MICE IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF THPS (a)

Dose (mg/kg)	Survival	
	Male	Female
100	5/5	5/5
200	5/5	5/5
400	(b) 0/5	(b) 0/5
800	(b) 0/5	(c) 0/5
1,600	(c) 0/5	(d) 0/5

(a) The survival patterns preclude meaningful LD_{50} value determinations.
(b) Day of death: all 2
(c) Day of death: 1, 1, 2, 2, 2
(d) Day of death: all 1

TABLE 20. SURVIVAL OF MICE IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF THPC

Dose (mg/kg)	Survival	
	Male	Female (a)
75	5/5	5/5
150	5/5	5/5
300	5/5	(b) 2/5
600	(b) 0/5	(c) 0/5
1,200	(d) 0/5	(b) 0/5

(a) LD_{50} value by Spearman-Karber method: 280 mg/kg (95% confidence limits, 201-390 mg/kg)
(b) Day of death: all 3
(c) Day of death: 3, 3, 3, 3, 4
(d) Day of death: 1, 3, 3, 3, 3

FOURTEEN-DAY STUDIES

THPS

Four of five male and 5/5 female mice that received 200 mg/kg and 1/5 male and 2/5 female mice that received 100 mg/kg died before the end of the studies (Table 21). Male mice that received 100 or 200 mg/kg and female mice that received 100 mg/kg lost weight. The final mean body weights of mice that received 25 or 50 mg/kg were 91% and 88% that of the controls for males and 97% and 93% that of the controls for females. Labored breathing and rough coats were observed in male and female mice at 100 and 200 mg/kg; female mice in these groups had loss of movement in their hindlegs.

THPC

All males and females that received 300 mg/kg THPC died by day 12 of the studies (Table 22). Mice that received 150 mg/kg lost weight. Final mean body weights of mice that received 18.8, 37.5, or 75 mg/kg were 91%-97% of the control values. No clinical signs of toxicity were observed in animals surviving to the end of the studies. No compound-related effects were observed at necropsy.

TABLE 21. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOURTEEN-DAY GAVAGE STUDIES OF THPS

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
(d) 0	5/5	25.2	29.2	+4.0	--
12.5	(e) 4/5	24.6	28.3	+3.7	96.9
25	5/5	25.6	26.6	+1.0	91.1
50	5/5	24.4	25.6	+1.2	87.7
100	(f) 4/5	24.0	21.8	-2.2	74.7
200	(g) 1/5	25.2	16.0	-9.2	54.8
FEMALE					
(d) 0	5/5	18.4	21.0	+2.6	--
12.5	5/5	18.6	20.8	+2.2	99.0
25	(h) 4/5	18.4	20.3	+1.9	96.7
50	5/5	17.6	19.6	+2.0	93.3
100	(i) 3/5	18.2	18.0	-0.2	85.7
200	(j) 0/5	18.8	(k)	(k)	(k)

(a) Number surviving/number in group
(b) Initial mean group body weight
(c) Mean body weight change
(d) Controls were untreated.
(e) Day of death: 2
(f) Day of death: 10
(g) Day of death: 8, 10, 10, 12
(h) Day of death: 6
(i) Day of death: 3, 14
(j) Day of death: 8, 9, 9, 9, 12
(k) No data are reported because of the 100% mortality in this group.

TABLE 22. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOURTEEN-DAY GAVAGE STUDIES OF THPC

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
(d) 0	5/5	24.6	28.2	+3.6	--
18.8	5/5	24.6	27.4	+2.8	97.2
37.5	5/5	25.4	26.6	+1.2	94.3
75	5/5	24.6	26.4	+1.8	93.6
150	5/5	24.0	23.2	−0.8	82.3
300	(e) 0/5	22.8	(f)	(f)	(f)
FEMALE					
(d) 0	5/5	20.0	23.0	+3.0	--
18.8	5/5	19.2	21.4	+2.2	93.0
37.5	5/5	20.0	21.4	+1.4	93.0
75	5/5	19.2	21.0	+1.8	91.3
150	5/5	19.6	18.4	−1.2	80.0
300	(g) 0/5	19.2	(f)	(f)	(f)

(a) Number surviving/number initially in group
(b) Initial mean group body weight
(c) Mean body weight change
(d) Controls were untreated.
(e) Day of death: 7, 8, 9, 9, 10
(f) No data are reported due to the 100% mortality in this group.
(g) Day of death: 6, 10, 11, 12, 12

THIRTEEN-WEEK STUDIES

THPS

Two vehicle control female mice were killed during the second week of the studies because they had inner ear infections. One of 10 females that received 60 mg/kg and 2/10 males and 1/10 females that received 40 mg/kg died before the end of the studies (Table 23). Final mean body weights of mice that received 20, 40, or 60 mg/kg were 4%, 7%, and 11% lower than those of the vehicle controls for males and 3%, 5%, and 11% lower for females. At various times during the first 11 weeks of the studies, mice from vehicle control groups, as well as from some dose groups, lost weight.

Periportal vacuolar degeneration occurred in 10/10 male and 10/10 female mice that received 60 mg/kg (minimal to moderate severity), 10/10 male and 9/10 female mice that received 40 mg/kg, and 8/10 male mice that received 20 mg/kg (minimal to mild severity). The dosed mice that died before the end of the studies had severe pulmonary lesions that were characterized by degeneration and/or necrosis with hyperplasia and/or squamous metaplasia of bronchiolar epithelium. Subacute multifocal or diffuse pneumonia was usually present in these animals, together with bronchiolar/alveolar hyperplasia that was sometimes severe. In one animal, diffuse bronchiolar/alveolar squamous metaplasia was present. Death of these animals was attributed to these pulmonary lesions. Pneumonia with bronchiolar/alveolar epithelial hyperplasia occurred commonly in vehicle control animals; the lesions were usually of minimal or mild severity but were extensive in one vehicle control animal. Unlike the lesions in the 40 and 60 mg/kg groups, those in vehicle control animals did not exhibit degenerative, hyperplastic, or metaplastic changes higher in the bronchiolar tree and did not cause death. Microscopically, the lung lesions were typical of those produced by Sendai virus infection in mice.

Dose Selection Rationale: Based on microscopic lesions in the liver and reduced body weight gain, THPS doses selected for mice for the 2-year studies were 5 and 10 mg/kg administered by gavage in water 5 days per week.

TABLE 23. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF THPS

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams)			Final Weight Relative to Vehicle Controls (percent)
		Initial (b)	Final	Change (c)	
MALE					
0	10/10	22.5	32.2	+9.7	--
5	10/10	22.7	33.2	+10.5	103.1
10	10/10	22.9	33.3	+10.4	103.4
20	10/10	23.8	30.9	+7.1	96.0
40	(d) 8/10	24.9	29.9	+5.0	92.9
60	10/10	23.5	28.5	+5.0	88.5
FEMALE					
0	(e) 8/10	17.5	25.3	+7.8	--
5	10/10	17.0	25.2	+8.2	99.6
10	10/10	17.1	24.4	+7.3	96.4
20	10/10	18.3	24.5	+6.2	96.8
40	(f) 9/10	18.7	24.1	+5.4	95.3
60	(g) 9/10	18.8	22.5	+3.7	88.9

(a) Number surviving/number in group
(b) Initial mean group body weight
(c) Mean body weight change
(d) Week of death: 8, 9
(e) Two animals killed during week 2 because of inner ear infection
(f) Week of death: 6
(g) Week of death: 7

THPC

Seven of 10 males and 6/10 females that received 135 mg/kg died before the end of the studies (Table 24). Final mean body weights for mice that received 135 mg/kg THPC were 8% lower than that of the vehicle controls for males and 19% lower for females.

Paresis of the hindlegs and loss of coordination were observed in 10/10 males and 9/10 females that received 135 mg/kg but not in any other groups. Mice in the 135 mg/kg group had marked axonal degeneration that was characterized by swollen axon sheaths, missing or fragmented axons, and some proliferation of neurolemmal cells (Table 25). These changes were seen in the sciatic nerve, dorsal roots of the caudal spinal nerves, and tracts of the spinal cord, particularly in the dorsal column of the lumbar cord. Eosinophilic spherical intracytoplasmic vacuoles in periportal hepatocytes, which in some cells displaced the nucleus to one side, were seen in the 135 mg/kg group and to a lesser extent in the 45 and 15 mg/kg groups of mice. Some of these vacuolated cells contained a finely granular basophilic material, and some had pyknotic or missing nuclei. The hepatocytes in some dosed animals had a notably greater number of mitotic figures than was seen in the vehicle controls.

Dose Selection Rationale: Because hepatocellular necrosis was observed at higher doses, THPC doses selected for mice for the 2-year studies were 7.5 and 15 mg/kg in water by gavage for male mice and 15 and 30 mg/kg for female mice.

TABLE 24. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF THPS

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	24.2 ± 0.4	32.9 ± 0.9	+8.7 ± 0.7	--
1.5	10/10	24.8 ± 0.4	31.1 ± 1.2	+6.3 ± 1.0	94.5
4.5	10/10	24.6 ± 0.3	34.8 ± 0.9	+10.2 ± 0.9	105.8
15	10/10	24.7 ± 0.4	34.2 ± 0.4	+9.5 ± 0.6	104.0
45	10/10	24.8 ± 0.5	33.0 ± 0.9	+8.2 ± 0.9	100.3
135	(d) 3/10	25.1 ± 0.5	30.3 ± 1.8	+4.7 ± 1.8	92.1
FEMALE					
0	10/10	19.6 ± 0.5	25.6 ± 0.4	+6.0 ± 0.3	--
1.5	10/10	19.9 ± 0.4	25.7 ± 0.4	+5.8 ± 0.4	100.4
4.5	10/10	19.6 ± 0.4	25.9 ± 0.3	+6.3 ± 0.3	101.2
15	10/10	20.2 ± 0.4	26.4 ± 0.5	+6.2 ± 0.5	103.1
45	10/10	19.4 ± 0.4	24.8 ± 0.5	+5.4 ± 0.4	96.9
135	(e) 4/10	20.1 ± 0.3	20.8 ± 0.6	+1.0 ± 0.7	81.3

(a) Number surviving/number initially in the group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors of the group ± standard error of the mean
(d) Week of death: 6, 8, 11, 12, 13, 13, 13
(e) Week of death: 3, 8, 10, 11, 11, 13

TABLE 25. NUMBER OF MICE WITH COMPOUND-RELATED LESIONS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF THPC

Site/Lesion	Dose (mg/kg) 0	1.5	4.5	15	45	135
MALE (a)						
Liver, hepatocytes						
Cytoplasmic vacuolation, periportal	0	0	0	10	10	10
Liver						
Hepatocellular necrosis, periportal	0	0	0	0	10	8
Thymus, cortex						
Lymphoid depletion	0	--	--	--	0	4
Skeletal muscle						
Degeneration	0	0	0	0	0	6
Peripheral nerve						
Axonal degeneration	0	0	0	0	0	0
Sciatic nerve						
Axonal degeneration	0	0	0	0	0	8
Spinal nerve						
Axonal degeneration	0	0	0	0	0	10
Spinal cord						
Axonal degeneration	0	0	0	0	0	6
FEMALE (a)						
Liver, hepatocytes						
Cytoplasmic vacuolation, periportal	0	0	0	10	10	9
Liver						
Hepatocellular necrosis, periportal	0	0	0	0	0	7
Thymus, cortex						
Lymphoid depletion	0	--	--	--	0	4
Skeletal muscle						
Degeneration	0	0	0	0	0	2
Peripheral nerve						
Axonal degeneration	0	0	0	0	0	1
Sciatic nerve						
Axonal degeneration	0	0	0	0	0	8
Spinal nerve						
Axonal degeneration	0	0	0	0	0	9
Spinal cord						
Axonal degeneration	0	0	0	0	0	4

(a) Ten males and 10 females were examined in each group.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

THPS

Mean body weights of dosed and vehicle control female mice and high dose and vehicle control male mice were comparable throughout the studies (Table 26 and Figure 5). Compound-related clinical signs consisted primarily of rough hair coats and diarrhea.

THPC

Between week 50 and week 63, mean body weights of high dose male mice were 5% or more lower than those of the vehicle controls (Table 27 and Figure 6). Mean body weights of high dose female mice were comparable to or greater than those of the vehicle controls throughout the studies. Compound-related clinical signs consisted primarily of rough hair coats and diarrhea.

TABLE 26. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF THPS

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	5 mg/kg Av. Wt. (grams)	5 mg/kg Wt. (percent of veh. controls)	5 mg/kg No. of Survivors	10 mg/kg Av. Wt. (grams)	10 mg/kg Wt. (percent of veh. controls)	10 mg/kg No. of Survivors
MALE								
0	25.6	50	25.2	98	50	24.3	95	50
1	27.1	50	27.3	101	49	27.4	101	50
2	27.2	50	27.3	100	49	27.4	101	50
3	29.1	50	29.3	101	49	28.5	98	50
4	29.8	50	29.7	100	49	29.6	99	50
5	30.8	50	31.4	102	49	30.3	98	50
6	31.1	50	31.9	103	49	31.1	100	50
7	32.1	50	33.2	103	49	31.9	99	50
8	32.5	50	32.5	100	49	31.3	96	50
9	33.1	50	33.7	102	49	31.8	96	50
10	33.6	50	34.1	101	49	32.6	97	50
11	34.3	50	34.6	101	49	33.4	97	50
12	34.1	50	34.9	102	49	33.8	99	50
13	34.3	50	34.8	101	49	33.9	99	50
17	36.5	50	37.5	103	49	36.2	99	50
22	37.6	50	38.3	102	49	37.2	99	50
26	38.1	48	39.8	104	49	38.2	100	49
30	38.1	48	39.4	103	49	38.0	100	49
34	39.6	47	40.8	103	49	39.9	101	49
38	38.8	45	41.2	106	49	39.8	103	49
43	40.8	45	42.7	105	49	40.8	100	49
47	40.7	44	42.4	104	48	41.0	101	48
51	41.4	44	42.8	103	48	40.3	97	48
55	41.0	43	42.8	104	47	40.5	99	48
60	40.6	43	41.6	102	46	40.3	99	47
64	41.3	42	42.4	103	46	39.9	97	47
69	42.0	41	43.0	102	45	41.2	98	47
73	40.8	40	42.6	104	45	40.2	99	47
78	42.3	39	41.9	99	43	41.5	98	46
82	42.4	39	42.2	100	41	41.5	98	42
87	41.8	36	42.7	102	37	42.0	100	41
91	41.7	29	41.9	100	37	40.6	97	37
95	40.7	29	40.8	100	37	39.7	98	35
100	39.6	27	39.3	99	35	37.9	96	30
104	39.1	23	39.3	101	31	37.1	95	25
FEMALE								
0	20.1	50	20.3	101	50	20.1	100	50
1	20.2	49	20.7	102	50	20.0	99	50
2	21.1	48	21.9	104	50	21.3	101	50
3	21.5	48	22.2	103	50	21.7	101	49
4	22.5	48	23.2	103	50	23.2	103	49
5	23.1	48	24.0	104	50	23.3	101	49
6	23.1	48	23.9	103	50	23.8	103	49
7	23.8	48	24.2	102	50	24.2	102	49
8	23.7	48	23.7	100	50	23.6	100	49
9	24.3	48	24.8	102	50	24.2	100	49
10	24.4	48	24.1	99	50	24.4	100	48
11	25.1	48	25.4	101	50	25.0	100	48
12	25.1	48	25.3	101	50	24.8	99	48
13	25.5	48	25.6	100	50	25.0	98	48
17	26.6	47	27.1	102	50	27.2	102	48
22	27.8	47	27.9	100	50	28.0	101	48
26	29.3	47	28.9	99	50	28.6	98	48
30	30.0	47	29.1	97	50	28.9	96	48
34	30.6	46	31.0	101	50	30.8	101	48
38	31.1	46	30.6	98	50	30.7	99	48
43	32.8	46	33.3	102	50	33.2	101	48
47	33.3	46	33.7	101	50	33.8	102	48
51	34.1	46	34.9	102	50	33.5	98	48
55	35.5	46	36.0	101	50	35.5	100	48
60	35.2	44	36.7	104	50	35.0	99	48
64	37.9	43	38.9	103	50	38.1	101	48
69	39.1	42	40.3	103	47	39.1	100	48
73	39.0	42	40.3	103	45	39.8	102	47
78	41.2	40	41.5	101	40	42.4	103	43
82	42.3	36	41.8	99	39	42.7	101	42
87	42.1	36	41.7	99	39	42.1	100	41
91	42.6	35	42.6	100	38	42.4	100	39
95	42.5	35	43.0	101	35	42.8	101	38
100	39.3	31	40.0	102	34	40.0	102	35
104	41.1	28	40.5	99	33	41.0	100	33

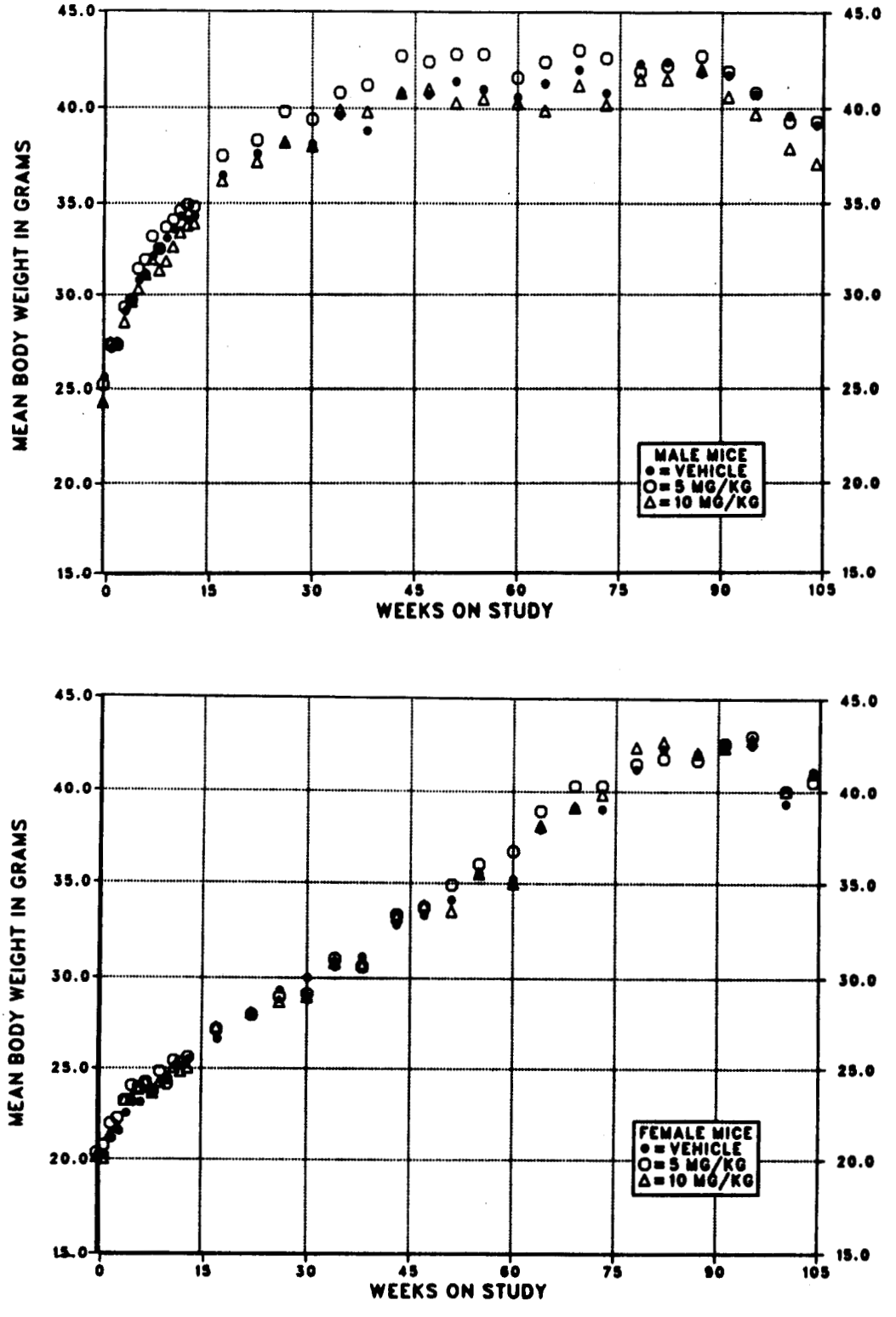


FIGURE 5. GROWTH CURVES FOR MICE ADMINISTERED THPS IN WATER BY GAVAGE FOR TWO YEARS

TABLE 27. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF THPC

Weeks on Study	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors
MALE	**Vehicle Control**			**7.5 mg/kg**			**15 mg/kg**	
0	24.6	50	23.7	96	49	23.5	96	50
1	25.2	50	24.5	97	49	24.2	96	50
2	25.2	50	26.0	103	49	25.0	99	50
3	26.3	50	26.3	100	49	25.7	98	50
4	27.0	50	27.8	103	49	27.1	100	50
5	28.6	50	28.7	100	49	28.0	98	50
6	28.5	50	28.3	99	49	27.5	96	50
7	28.9	50	30.0	104	49	29.0	100	50
8	31.9	50	30.9	97	49	31.8	100	50
9	33.1	50	32.3	98	49	32.0	97	50
11	33.1	50	32.8	99	49	32.7	99	50
12	32.9	50	32.1	98	48	31.3	95	50
13	33.7	50	33.3	99	48	33.2	99	50
17	33.5	50	33.1	99	47	32.7	98	50
20	35.0	50	34.6	99	47	34.3	98	50
25	36.7	50	36.4	99	47	35.5	97	50
29	36.4	50	36.0	99	47	35.4	97	50
32	38.0	50	38.4	101	47	36.5	96	50
36	38.4	50	38.6	101	47	37.4	97	50
40	39.8	50	39.7	100	47	37.5	94	50
45	40.0	50	39.5	99	46	38.7	97	50
50	41.5	50	40.8	98	46	39.6	95	50
54	41.4	50	41.0	99	46	38.8	94	49
58	41.9	50	41.5	99	46	39.3	94	49
63	43.4	50	39.5	91	46	39.6	91	48
67	40.7	48	39.5	97	44	39.3	97	47
72	40.7	44	39.6	97	40	40.3	99	43
77	41.8	42	39.8	95	39	40.1	96	42
81	40.1	36	40.2	100	38	39.2	98	42
85	41.6	36	40.8	98	38	40.5	97	41
90	40.7	34	40.4	99	36	39.9	98	40
95	42.0	29	41.4	99	33	40.5	96	37
99	39.5	28	39.9	101	32	38.9	98	36
103	40.1	25	38.2	95	31	37.5	94	35
FEMALE	**Vehicle Control**			**15 mg/kg**			**30 mg/kg**	
0	19.8	50	19.9	101	50	19.7	99	50
1	20.8	50	20.5	99	50	20.9	100	50
2	21.4	50	21.1	99	50	21.4	100	50
3	21.5	50	21.7	101	50	22.0	102	50
4	21.9	50	21.8	100	50	22.3	102	50
5	22.8	50	22.5	99	50	23.1	101	50
6	22.7	50	23.7	104	50	23.3	103	50
7	22.7	50	23.6	104	50	23.5	104	50
8	23.6	50	24.6	104	50	24.4	103	50
9	23.8	50	25.9	109	50	24.7	104	50
11	25.1	50	25.9	103	50	25.4	101	50
12	24.4	50	25.2	103	50	25.1	103	50
13	24.2	50	25.1	104	50	25.6	106	50
17	25.9	50	26.5	102	50	27.0	104	50
20	25.9	50	27.8	107	50	27.2	105	50
25	27.9	50	28.7	103	50	28.7	103	50
29	28.8	50	29.4	102	50	29.7	103	50
32	29.9	50	30.8	103	50	31.1	104	50
36	30.7	50	31.4	102	50	30.8	100	50
40	31.3	50	33.3	106	50	32.5	104	50
45	31.7	50	34.6	109	50	33.5	106	50
50	34.9	50	36.0	103	50	35.3	101	50
54	35.0	50	36.3	104	50	36.3	104	50
58	36.7	49	37.6	103	50	37.3	102	50
63	35.3	49	38.1	108	50	35.4	100	50
67	35.3	48	36.3	103	50	36.4	103	48
72	36.5	47	37.2	102	48	37.9	104	48
77	36.8	46	36.3	99	46	37.5	102	46
81	36.2	46	36.4	101	46	37.2	103	46
85	37.0	45	38.5	104	45	39.0	105	44
90	37.6	44	39.3	105	45	39.2	104	41
95	39.5	42	39.7	101	44	40.9	104	40
99	39.3	41	38.5	98	43	38.0	97	40
103	37.5	37	37.7	101	40	36.8	98	38

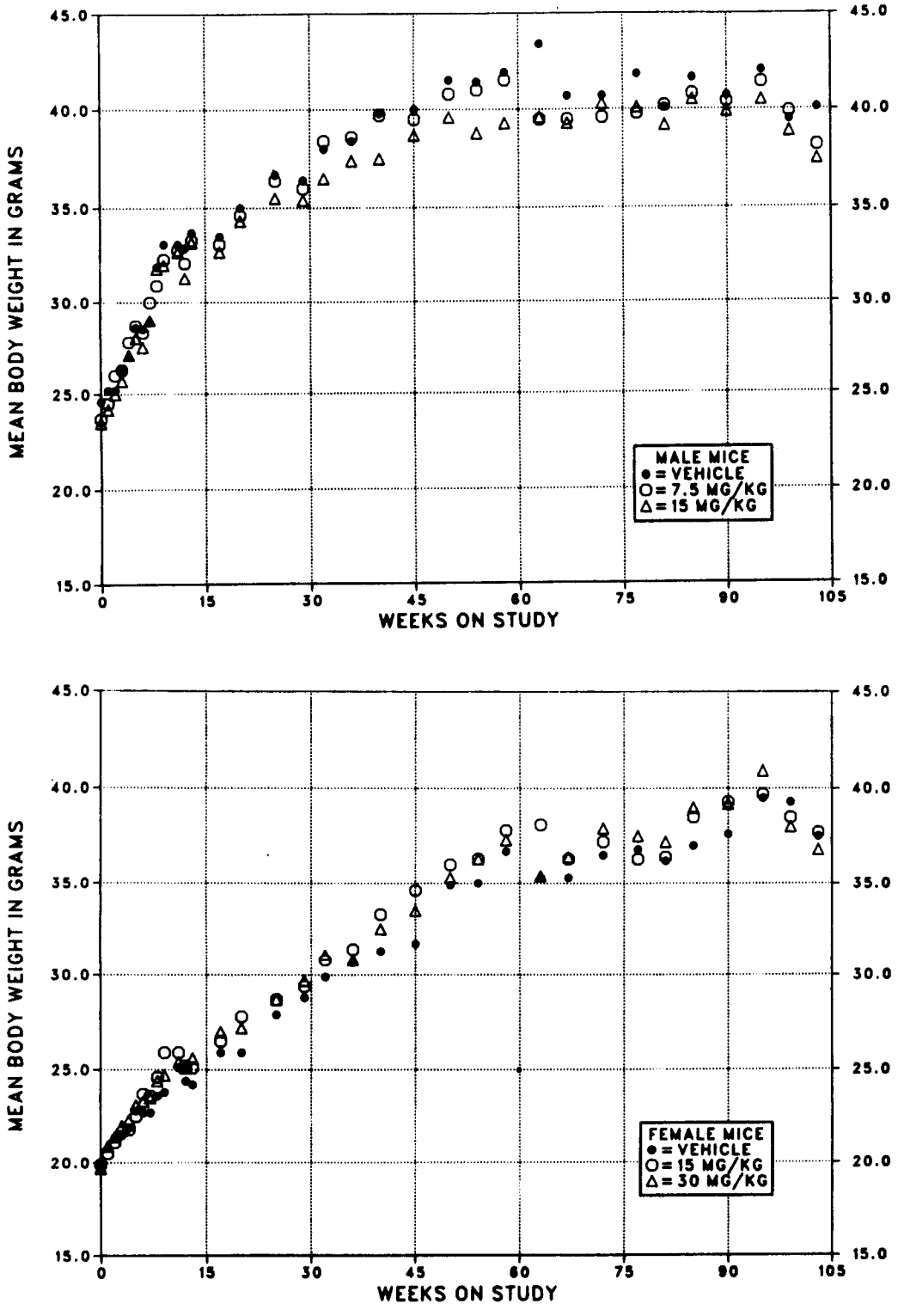


FIGURE 6. GROWTH CURVES FOR MICE ADMINISTERED THPC IN WATER BY GAVAGE FOR TWO YEARS

Survival

THPS

Estimates of the probabilities of survival for male and female mice administered THPS at the doses used in these studies and for vehicle controls are shown in the Kaplan and Meier curves in Figure 7. No significant differences in survival were observed between any groups of mice of either sex (Table 28).

THPC

Estimates of the probabilities of survival for male and female mice administered THPC at the doses used in these studies and for vehicle controls are shown in the Kaplan and Meier curves in Figure 8. No significant differences in survival were observed between any groups of either sex (Table 29).

TABLE 28. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF THPS

	Vehicle Control	5 mg/kg	10 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	27	19	26
Killed at termination	23	31	23
Died during termination period	0	0	1
Survival P values (c)	0.629	0.144	0.649
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	20	20	16
Accidentally killed	2	0	0
Animals missing	0	0	1
Killed at termination	28	30	33
Survival P values (c)	0.376	0.896	0.444

(a) Terminal-kill period: week 106
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

TABLE 29. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF THPC

MALE (a)	Vehicle Control	7.5 mg/kg	15 mg/kg
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	25	17	15
Accidentally killed	2	1	0
Animals missexed	0	1	0
Killed at termination	23	30	34
Died during termination period	0	1	1
Survival P values (c)	0.068	0.252	0.079
FEMALE (a)	**Vehicle Control**	**15 mg/kg**	**30 mg/kg**
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	12	10	11
Accidentally killed	1	0	1
Killed at termination	37	40	38
Survival P values (c)	0.939	0.755	0.867

(a) Terminal-kill period: week 104
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

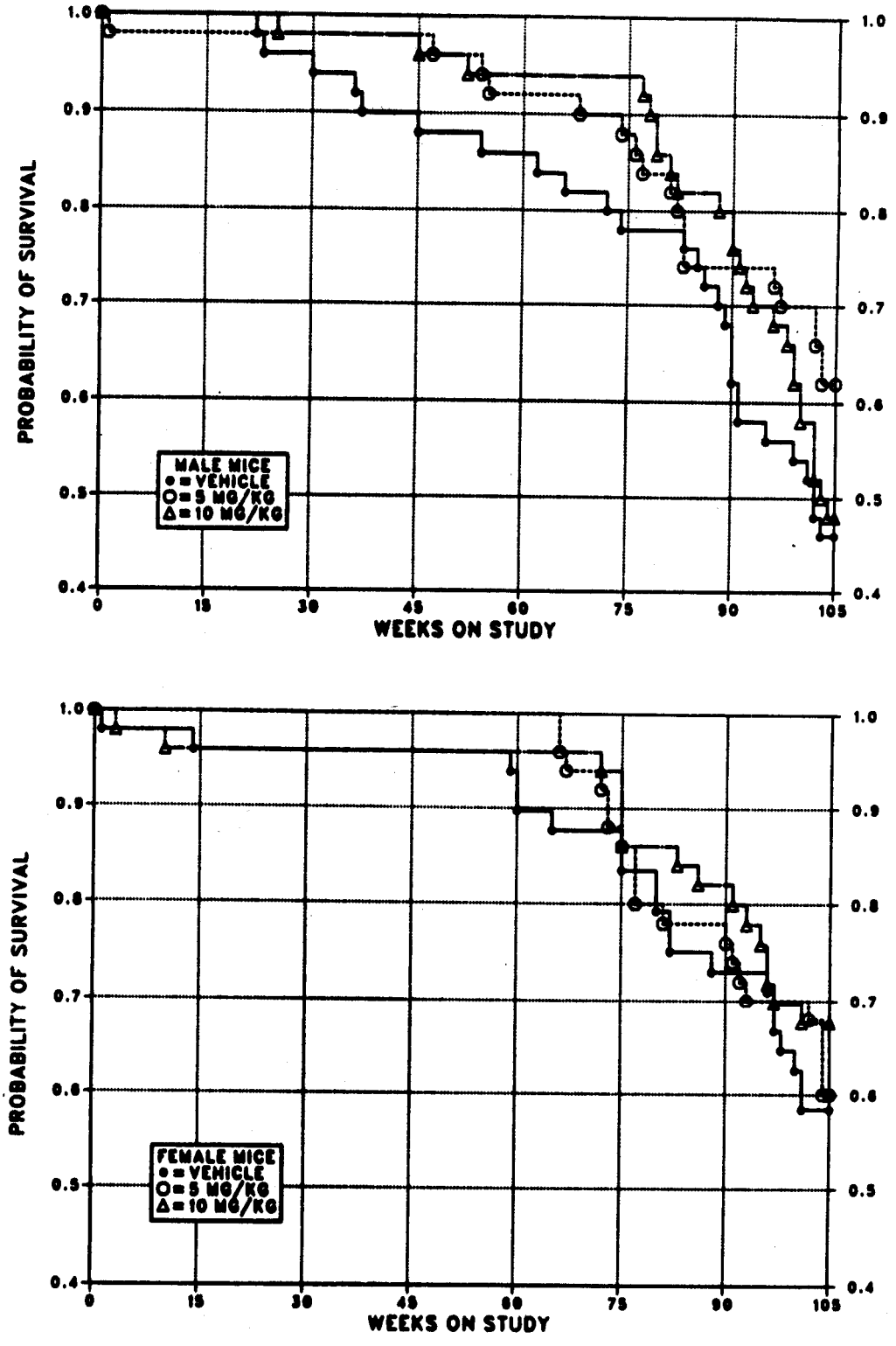


FIGURE 7. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED THPS IN WATER BY GAVAGE FOR TWO YEARS

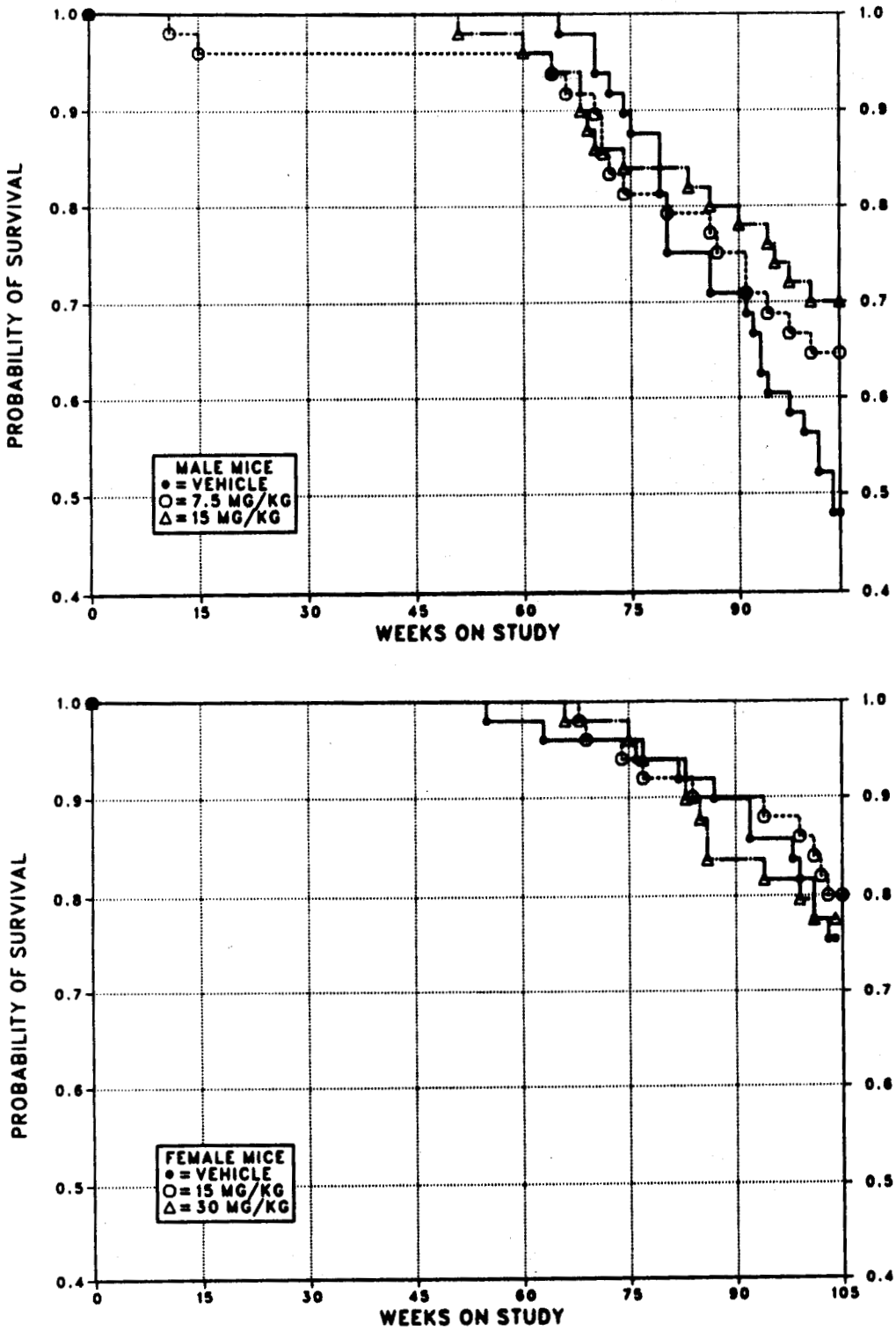


FIGURE 8. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED THPC IN WATER BY GAVAGE FOR TWO YEARS

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy increases in the incidences of mice with neoplastic or nonneoplastic lesions in the hematopoietic system, skin, adrenal gland, liver, and thyroid gland.

Histopathologic findings in the THPS studies on neoplasms in mice are summarized in Tables C1 and D1; Tables C2 and D2 give the survival and tumor status for individual male and female mice. Tables C3 and D3 contain the statistical analyses of those primary tumors in the THPS studies 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 Tables C3 and D3 (footnotes). The historical incidences of tumors in control male B6C3F$_1$ mice are listed in Table C4. Findings on nonneoplastic lesions in the THPS studies are summarized in Tables C5 and D4.

Histopathologic findings in the THPC studies on neoplasms in mice are summarized in Tables G1 and H1; Tables G2 and H2 give the survival and tumor status for individual male and female mice. Tables G3 and H3 contain the statistical analyses of those primary tumors in the THPC studies 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 Tables G3 and H3 (footnotes). Findings on nonneoplastic lesions in the THPC studies are summarized in Tables G4 and H4.

Hematopoietic System (THPS): Increased incidences of granulocytic hyperplasia of the bone marrow in dosed female mice and hematopoiesis of the splenic red pulp and liver in high dose male mice were observed (Table 30). These lesions are considered secondary to the subcutaneous and liver lesions observed in these animals. Malignant lymphomas (all types) occurred at a significantly increased incidence by the incidental tumor test in low dose male mice but not in high dose mice (Table 31).

TABLE 30. INCIDENCES OF HEMATOPOIETIC SYSTEM LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF THPS

	Vehicle Control	5 mg/kg	10 mg/kg
MALE			
Bone marrow granulocytic hyperplasia	6/49	4/49	9/50
All malignant lymphomas	2/50	9/50	0/50
Splenic red pulp hematopoiesis	14/48	10/49	24/49
Liver hematopoiesis	1/48	4/49	6/50
Thymus lymphoid depletion	1/27	8/38	9/32
FEMALE			
Bone marrow granulocytic hyperplasia	0/50	6/49	6/49
All malignant lymphomas	16/50	17/50	18/49
Splenic red pulp hematopoiesis	5/50	6/50	9/49
Liver hematopoiesis	2/50	5/50	6/49
Thymus lymphoid depletion	5/41	3/44	2/41

TABLE 31. ANALYSIS OF MALIGNANT LYMPHOMAS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS (a,b)

	Vehicle Control	5 mg/kg	10 mg/kg
Overall Rates	2/50 (4%)	9/50 (18%)	0/50 (0%)
Adjusted Rates	6.3%	23.1%	0.0%
Terminal Rates	1/23 (4%)	4/31 (13%)	0/24 (0%)
Week of First Observation	23	54	--
Life Table Tests	P=0.253N	P=0.063	P=0.233N
Incidental Tumor Tests	P=0.350N	P=0.023	P=0.308N

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix C, Table C3 (footnotes).
(b) Historical incidence in water gavage vehicle controls (mean ± SD): 24/200 (12% ± 7%); historical incidence in untreated controls: 217/1,791 (12% ± 7%)

Skin (THPS): The incidences of hyperkeratosis and acanthosis of the skin were increased in low dose male mice (hyperkeratosis: vehicle control, 0/50; low dose, 9/50; high dose, 3/50; acanthosis: 1/50; 12/50; 3/50). Some of these lesions were associated with ulcerated subcutaneous tumors, and others are possibly the result of fighting. Hyperkeratosis and acanthosis were not observed in the skin of female mice.

Adrenal Gland (THPS): The incidences of focal hyperplasia of the adrenal capsule were increased in dosed mice of each sex (male: vehicle control, 18/49; low dose, 26/48; high dose, 26/49; female: 29/50; 43/50; 44/49).

The incidence of focal hyperplasia of the adrenal medulla was increased in dosed male mice (male: vehicle control, 3/49; low dose, 5/48; high dose, 10/49; female: 2/50; 0/50; 2/49). The incidences of pheochromocytomas were increased in high dose male mice and dosed female mice, but the incidences in the dosed groups were not significantly greater than those in the vehicle controls (male: 4/49; 1/48; 7/49; female: 0/50; 3/50; 2/49).

Liver (THPC): Cytoplasmic vacuolization was observed at increased incidences in dosed male and dosed female mice (male: vehicle control, 0/49; low dose, 39/49; high dose, 44/50; female: 0/49; 42/50; 48/50). Affected hepatocytes were periportal and had large cytoplasmic vacuoles. In some cells, the nuclei were displaced to one side by the vacuoles.

Thyroid Gland (THPC): Follicular cell hyperplasia was observed at an increased incidence in high dose female mice (vehicle control, 3/48; low dose, 5/50; high dose, 11/49). A follicular cell adenoma was observed in one vehicle control and one low dose female mouse.

IV. DISCUSSION AND CONCLUSIONS

IV. DISCUSSION AND CONCLUSIONS

Thirteen-week studies with THPS and THPC were conducted to identify affected organs, characterize toxic effects, and determine doses to be used for the 2-year studies. Doses for the THPS studies ranged from 5 to 60 mg/kg for both rats and mice. Doses for the THPC studies ranged from 3.75 to 60 mg/kg for rats and 1.5 to 135 mg/kg for mice. Clinical signs, which included rough hair coats, labored breathing, swollen abdomens, tremors, arched backs, hind limb paralysis, and diarrhea, occurred in rats and mice dosed with THPS or THPC. Most of these effects occurred in the groups receiving the higher doses. In earlier studies, paralysis of the back muscles occurred in mice receiving lethal doses of THPS or THPC by the dermal route (Connor et al., 1980; Afansa'eva and Evseenko, 1971). In the present 13-week studies, the clinical neurotoxicity was confirmed by evidence of histopathologic changes in the central and peripheral nervous systems of female rats and both sexes of mice dosed with THPC. The lesions consisted of axonal degeneration of the spinal cord and sciatic nerve in animals from the high dose groups. Similar histopathologic changes were not present in animals receiving THPS.

In the 14-day and 13-week studies of THPS and THPC, the liver was the primary site affected in both rats and mice. Cytoplasmic vacuolization and necrosis of hepatocytes in the periportal region progressed to vacuolar degeneration. Earlier investigators reported elevated serum transaminase enzyme activity in rats and elevated liver mucopolysaccharide levels in mice administered THPC in drinking water, indicating hepatocellular toxicity (Ishizu, 1975).

Doses for the 2-year studies were selected on the bases of mortality, decreased body weight, and hepatocellular lesions that occurred in the three highest dose groups in the 13-week studies. The observed toxicity varied with species and sex, resulting in a fourfold range in dose selection for the 2-year studies of THPS and THPC. THPS doses in rats and mice of each sex were 0, 5, and 10 mg/kg. THPC doses for rats of each sex were 0, 3.75, and 7.5 mg/kg. THPC doses in male mice were 0, 7.5, and 15 mg/kg and in female mice, 0, 15, and 30 mg/kg.

Neither THPS nor THPC significantly affected body weight gains of either rats or mice (see Figures 1, 2, 5, and 6). Compound-related signs of toxicity in rats and mice consisted primarily of rough hair coats and diarrhea. None of the neurotoxic clinical signs seen at higher doses in the 13-week studies was observed. Earlier dermal studies in rats (Ulsamer et al., 1980) and rats and rabbits (Aoyama, 1975) reported erythema and edema at lower doses and body weight loss, severe skin lesions, and death at higher doses.

Survival of the male rats given the low dose (after week 102) or the high dose (after week 67) of THPS was lower than that of the vehicle controls (survival at terminal kill: vehicle control, 28/50; low dose, 13/50; high dose, 16/50). Survival of the high dose group of female rats given THPC was also lower (after week 70) than that of vehicle controls (survival at terminal kill: 36/50; 33/50; 21/50). There were no significant differences in survival between the vehicle controls and mice dosed with THPS or THPC (see Tables 26 and 27; Figures 7 and 8). The survival of rats and mice in these studies was considered adequate to assess the carcinogenic potential of THPS and THPC.

Organ toxicity was mainly restricted to the liver, and the predominant nonneoplastic lesions were similar to those observed in the 13-week studies. Increased incidences of hepatocellular cytoplasmic vacuolization were observed in rats and mice dosed with THPS or THPC (Table 32).

Low dose male rats administered THPS or THPC had marginally increased incidences of mononuclear cell leukemia when compared with the concurrent vehicle controls (Table 33). These incidences were statistically significant by the life table test ($P<0.05$). Survival in low dose males in each study was similar until week 94, which is well within the period of greatest risk for development of mononuclear cell leukemia. The lack of similar dose-related increases of mononuclear cell leukemia in the high dose groups suggests that the increases in low dose male rats were not chemically related. Although mononuclear cell leukemia is generally considered a life-threatening tumor, the data indicate that these tumors were not the primary contributing cause of death in some of the low dose male rats with these tumors. Low dose male mice receiving THPS had an increased incidence of malignant lymphomas (all types) when compared with vehicle controls (Table 34).

TABLE 32. COMPARISON OF INCIDENCES OF CYTOPLASMIC VACUOLIZATION OF THE LIVER IN THE TWO-YEAR GAVAGE STUDIES OF THPS AND THPC

	THPS				THPC		
RATS	**Vehicle Control**	**5 mg/kg**	**10 mg/kg**		**Vehicle Control**	**3.75 mg/kg**	**7.5 mg/kg**
Male	2/50	4/50	9/49	Male	0/50	9/50	23/49
Female	1/49	3/50	8/49	Female	3/50	11/50	25/50
MICE						**7.5 mg/kg**	**15 mg/kg**
Male	0/48	1/49	0/50	Male	0/49	39/49	44/50
						15 mg/kg	**30 mg/kg**
Female	6/50	13/50	7/49	Female	0/49	42/50	48/50

TABLE 33. COMPARISON OF INCIDENCES OF LEUKEMIA IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF THPS AND THPC

	THPS				THPC		
	Vehicle Control	**5 mg/kg**	**10 mg/kg**		**Vehicle Control**	**3.75 mg/kg**	**7.5 mg/kg**
Male	30/50	(a) 36/50	20/50	Male	19/50	(a) 25/50	16/50
Female	23/49	20/50	22/50	Female	4/50	8/50	7/50

(a) Statistically significant; $P < 0.05$ by life table test.

TABLE 34. COMPARISON OF INCIDENCES OF MALIGNANT LYMPHOMAS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF THPS AND THPC

	THPS				THPC		
	Vehicle Control	**5 mg/kg**	**10 mg/kg**		**Vehicle Control**	**7.5 mg/kg**	**15 mg/kg**
Male	2/50	9/50	0/50	Male	9/50	4/49	8/50
						15 mg/kg	**30 mg/kg**
Female	16/50	17/50	18/49	Female	21/50	14/50	19/50

These increased incidences were not present in female mice dosed with THPS or in male or female mice administered THPC. The increased incidences of hematopoietic system lesions observed in these studies were not considered biologically related to chemical exposure because the increases were marginal, no dose-response relationship was observed, and the incidences of these lesions are highly variable in untreated rats and mice (Haseman et al., 1984; Tables A4 and C4).

The incidence of adenomas of the anterior pituitary gland in low dose male rats given THPS was marginally increased relative to that of the vehicle controls (see Table 16). Although statistically significant by the life table test, many of these tumors were not life threatening and are not considered to be the primary contributing cause of death in rats. The result was not significant by the incidental tumor test ($P = 0.334$), which is considered the more appropriate analysis. The elevated incidence of anterior pituitary gland adenomas in low dose rats is not believed to be chemically related.

Hyperplasia of the adrenal medulla occurred with an increased incidence in high dose male

mice given THPS (vehicle control, 3/49; low dose, 5/48; high dose, 10/49). Although the incidences of pheochromocytomas in the high dose and vehicle control groups were similar (4/49; 1/48; 7/49), the incidences of adrenal medullary hyperplasia or pheochromocytomas (combined) (7/49; 6/48; 15/49) suggest a marginal chemically related effect.

Follicular cell hyperplasia of the thyroid gland occurred with an increased incidence in high dose female mice given THPC (vehicle control, 3/48; low dose, 5/50; high dose, 11/49). No published data on the effect of THPC on the thyroid gland have been located. Since this is a common degenerative lesion in rodents, this increase is not considered to be clearly related to chemical administration.

Endometrial stromal polyps in female rats given THPS occurred with a positive trend, and the incidence in the high dose group was greater than that in the vehicle controls (see Table 18). This common lesion of female rats occurs with a relatively wide range of incidences. Since the incidence of polyps in the high dose group is similar to the mean for historical control rats (water, 18%; untreated, 22%; Table B4), this lesion is not considered to be compound related.

Concern about the possible chronic toxicity of THPC was due in part to the potential decomposition of this compound to formaldehyde and hydrochloric acid, which might react to form bis(chloromethyl)ether (BCME), a known carcinogen. BCME is carcinogenic in mice by the dermal route (Van Duuren et al., 1972), causing squamous cell carcinomas of the skin, and in rats and mice by the inhalation route (Laskin et al., 1971; Leong et al., 1971), causing squamous cell carcinomas of the lung.

However, Kallos and Solomon (1973) reported that 100 ppm each of hydrogen chloride and formaldehyde, when combined in air at ambient temperature and humidity, failed to form BCME at detection limits of 0.1 ppb. Therefore, occupational health problems from BCME exposure would not be expected when ambient hydrogen chloride and formaldehyde were present in the workplace, since reactant concentrations would have to be far above those that could be tolerated by humans. In addition, the industrial use of THPC to treat fabrics consists of the formation of THPC in polymer form (Hindersinn and Wagner, 1967) with extremely low concentrations of residual formaldehyde and hydrogen chloride. BCME could form only from the residual chemicals, and concentrations would have to be much higher than those found in the fabric treatment processes.

Although no mutagenic activity for THPS or THPC in bacteria has been reported, there is evidence for genotoxicity in mammalian cell cultures. Both compounds gave strongly positive responses in the mouse lymphoma L5178Y/TK$^{+/-}$ forward mutation assay without exogenous metabolic activation (Appendixes I and J) as well as in V79 hamster lung cells both with and without S9. THPC also produced increases in the frequency of chromosomal aberrations and sister-chromatid exchanges in cultured Chinese hamster ovary (CHO) cells with and without metabolic activation (Tables J3 and J4). The cytogenetic responses were more pronounced in the absence of exogenous metabolic activation. These results with mammalian cells suggest that the chemical is a direct-acting mutagen.

In vitro studies by Coutino (1979) indicate that THPS may produce the various anaphase anomalies observed in CHO cells by disrupting mitosis through interference with the spindle apparatus or chromosomal proteins. Whether this interference with the mitotic process leads to aneuploidy remains to be determined. In vivo assays of the cytogenetic effects of THPS in Swiss mice dosed orally or dermally with the chemical, however, have not revealed any increase in bone marrow micronuclei or chromosomal aberrations (Connor et al., 1980).

Conclusions: Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenicity** of THPS in either sex of F344/N rats or B6C3F$_1$ mice given 5 or 10 mg/kg. There was *no evidence of carcinogenicity* of THPC in either sex of F344/N rats given 3.75 or 7.5 mg/kg, in male B6C3F$_1$ mice given 7.5 or 15 mg/kg, or in female B6C3F$_1$ mice given 15 or 30 mg/kg.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 9.

V. REFERENCES

V. REFERENCES

1. Afansa'eva, L.; Evseenko, N. (1971) Hygienic evaluation of fireproof textiles processed with an organophosphorus impregnant based on tetrahydroxymethyl phosphonium chloride. Hyg. Sanit. 36:450-452.

2. Aoyama, M. (1975) Effect of anti-flame treating agents on the skin. Nagoya Med. J. 20:11-19.

3. Armitage, P. (1971) Statistical Methods in Medical Research. New York: John Wiley & Sons, Inc., pp. 362-365.

4. Berenblum, I., Ed. (1969) Carcinogenicity Testing: A Report of the Panel on Carcinogenicity of the Cancer Research Commission of UICC, Vol. 2. Geneva: International Union Against Cancer.

5. Boorman, G.; Montgomery, C., Jr.; Eustis, S.; Wolfe, M.; McConnell, E.; Hardisty, J. (1985) Quality assurance in pathology for rodent carcinogenicity studies. Milman, H.; Weisburger, E., Eds.: Handbook of Carcinogen Testing. Park Ridge, NJ: Noyes Publications, pp. 345-357.

6. Clive, D.; Johnson, K.; Spector, J.; Batson, A.; Brown, M. (1979) Validation and characterization of the L5178Y/TK$^{+/-}$ mouse lymphoma mutagen assay system. Mutat. Res. 59:61-108.

7. Connor, T.; Meyne, J.; Legator, M. (1980) The mutagenic evaluation of tetrakis (hydroxymethyl) phosphonium sulfate using a combined testing protocol approach. J. Environ. Pathol. Toxicol. 4:145-158.

8. Coutino, R. (1979) Analysis of anaphase in cell culture: An adequate test system for the distinction between compounds which selectively alter the chromosome structure or the mitotic apparatus. Environ. Health Perspect. 31:131-136.

9. Cox, D. (1972) Regression models and life tables. J. R. Stat. Soc. B34:187-220.

10. Ehrlich, K.; Hulett, A.; Turnham, T. (1980) Mammalian cell culture mutagenicity and carcinogenicity testing of dimethyl sulfoxide extracts of flame retardant-treated cotton fabrics. J. Toxicol. Environ. Health 6:259-271.

11. Frank, A. (1977) The iodometric determination of P(III) in flame retardants for cotton; Part IV: Reaction of THPS with iodate. Tex. Res. J., pp. 60-61.

12. Galloway, S.; Bloom, A.; Resnick, M.; Margolin, B.,; Nakamura, F.; Archer, P.; Zeiger, E. (1985) Development of a standard protocol for in vitro cytogenetic testing with Chinese hamster ovary cells: Comparison of results for 22 compounds in two laboratories. Environ. Mutagen. 7:1-51.

13. Gart, J.; Chu, K.; Tarone, R. (1979) Statistical issues in interpretation of chronic bioassay tests for carcinogenicity. J. Natl. Cancer Inst. 62:957-974.

14. Haseman, J. (1984) Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies. Environ. Health Perspect. 58:385-392.

15. Haseman, J; Huff, J.; Boorman, G. (1984) Use of historical control data in carcinogenicity studies in rodents. Toxicol. Pathol. 12:126-135.

16. Haseman, J.; Huff, J.; Rao, G.; Arnold, J.; Boorman, G.; McConnell, E. (1985) Neoplasms observed in untreated and corn oil gavage control groups of F344/N rats and (C57BL/6N $\times$ C3H/HeN)F_1 (B6C3F_1) mice. J. Natl. Cancer Inst. 75:975-984.

17. Haworth, S.; Lawlor, T.; Mortelmans, K.; Speck, W.; Zeiger, E. (1983) Salmonella mutagenicity test results for 250 chemicals. Environ. Mutagen. 5(Suppl. 1):3-142.

18. Hindersinn, R.; Wagner, G. (1967) Encyclopedia of Polymer Science and Technology. New York: John Wiley & Sons, Inc.

19. Ishizu, S. (1975) Toxicity of organophosphorus fire retardants. Kabunshi 24:788-792.

20. Kallos, G.; Solomon, R. (1973) Investigations of the formation of bis-chloromethyl ether in simulated hydrogen chloride-formaldehyde atmospheric environments. Am. Ind. Hyg. Assoc. J. 34:469-473.

21. Kaplan, E.; Meier, P. (1958) Nonparametric estimation of incomplete observations. J. Am. Stat. Assoc. 53:457-481.

22. Kawachi, T.; Komatsu, T.; Kada, T.; Ishidate, M.; Sasaki, M.; Sugiyama, T.; Tazima, Y. (1980a) Results of recent studies on the relevance of various short-term screening tests in Japan. The Predictive Value of Short-Term Screening Tests in Carcinogenicity Evaluation. Appl. Methods Oncol. 3:253-267.

23. Kawachi, T.; Yahagi, T.; Kada, T.; Tazima, Y.; Ishidate, M.; Sasaki, M.; Sugiyama, T. (1980b) Cooperative program on short-term assays for carcinogenicity in Japan. Montesano, R., et al., Eds.: Molecular and Cellular Aspects of Carcinogen Screening Tests. International Agency for Research on Cancer Sci. Publ. 27:323-330.

24. Kirk-Othmer Encyclopedia of Chemical Technology (1980) 3rd ed., Vol. 10. Grayson, M., Ed. New York: John Wiley & Sons, Inc., pp. 432-434.

25. Laskin, S.; Kuschner, M.; Drew, R.; Coppullo, V.; Nelson, N. (1971) Arch. Environ. Health 23:135.

26. Legator, M. (1977) Report to Hooker Chemicals and Plastic Corp.

27. Leong, B.; MacFarland, H; Reese, W. (1971) Arch. Environ. Health 22:663.

28. Linhart, M.; Cooper, J.; Martin, R.; Page, N.; Peters, J. (1974) Carcinogenesis bioassay data system. Comput. Biomed. Res. 7:230-248.

29. Loewengart, G.; Van Duuren, B. (1977) Evaluation of chemical flame retardants for carcinogenic potential. J. Toxicol. Environ. Health 2:539-546.

30. MacGregor, J.; Diamond, M.; Mazzeno, L., Jr.; Friedman, M. (1980) Mutagenicity tests of fabric-finishing agents in *Salmonella typhimurium:* Fiber-reactive wool dyes and cotton flame retardants. Environ. Mutagen. 2:405-418.

31. Mantel, N.; Haenszel, W. (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J. Natl. Cancer Inst. 22:719-748.

31. Maronpot, R.; Boorman, G. (1982) Interpretation of rodent hepatocellular proliferative alterations and hepatocellular tumors in chemical safety assessment. Toxicol. Pathol. 10:71-80.

32. McConnell, E.; Solleveld, H.; Swenberg, J; Boorman, G. (1986) Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. J. Natl. Cancer Inst. 76:283-289.

33. National Cancer Institute (NCI) (1976) Guidelines for Carcinogen Bioassay in Small Rodents. NCI Carcinogenesis Technical Report Series No. 1. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health.

34. National Institutes of Health (NIH) (1978) NIH Specification, NIH-11-133f, November 1.

35. Sadtler Research Laboratories, Sadtler Standard Spectra. IR No. 13510; NMR No. 11664M. Philadelphia, PA.

36. Tarone, R. (1975) Tests for trend in life table analysis. Biometrika 62:679-682.

37. Ulsamer, A.; Osterberg, R,; McLaughlin, J., Jr. (1980) Flame-retardant chemicals in textiles. Clin. Toxicol. 17:101-131.

38. Van Duuren, B.; Katz, C.; Goldschmidt, B.; Frenkel, K.; Sivak, A. (1972) Carcinogenicity of haloethers. II. Structure-activity relationships of analogs of bis(chloromethyl)ether. J. Natl. Cancer Inst. 48:1431-1439.

39. Van Duuren, B.; Loewengart, G.; Seidman, I.; Smith, A.; Melchionne, S. (1978) Mouse skin carcinogenicity tests of the flame retardants tris(2,3-dibromopropyl)phosphate, tetrakis(hydroxymethyl)phosphonium chloride, and polyvinyl bromide. Cancer Res. 38:3236-3240.

APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS

	Vehicle Control	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	3 (6%)	1 (2%)	1 (2%)
Basal cell tumor	1 (2%)	1 (2%)	
Keratoacanthoma	2 (4%)	2 (4%)	1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma			2 (4%)
Fibrosarcoma	1 (2%)	1 (2%)	
Fibrous histiocytoma, malignant		1 (2%)	
Lipoma			1 (2%)
Neurofibrosarcoma	2 (4%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(49)
Squamous cell carcinoma	1 (2%)		
Alveolar/bronchiolar carcinoma			1 (2%)
Pheochromocytoma, metastatic			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	30 (60%)	36 (72%)	20 (40%)
#Lymph node	(48)	(49)	(46)
Fibrous histiocytoma, metastatic		1 (2%)	
#Mediastinal lymph node	(48)	(49)	(46)
Squamous cell carcinoma, metastatic	1 (2%)		
CIRCULATORY SYSTEM			
#Endocardium	(50)	(50)	(50)
Neurilemoma, malignant			1 (2%)
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(50)	(48)
Neurilemoma, malignant			1 (2%)
#Liver	(50)	(50)	(49)
Neoplastic nodule	3 (6%)	5 (10%)	1 (2%)
#Pancreas	(48)	(50)	(47)
Acinar cell adenoma			1 (2%)
URINARY SYSTEM			
#Urinary bladder/serosa	(47)	(48)	(45)
Mesothelioma, NOS		1 (2%)	1 (2%)
ENDOCRINE SYSTEM			
#Pituitary intermedia	(50)	(49)	(48)
Adenoma, NOS			1 (2%)
#Anterior pituitary	(50)	(49)	(48)
Carcinoma, NOS		1 (2%)	
Adenoma, NOS	21 (42%)	26 (53%)	14 (29%)
#Adrenal	(50)	(49)	(50)
Cortical adenoma	3 (6%)	1 (2%)	

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Adrenal medulla	(50)	(49)	(50)
Pheochromocytoma	22 (44%)	19 (39%)	16 (32%)
Pheochromocytoma, malignant	1 (2%)		2 (4%)
Ganglioneuroma		1 (2%)	
#Thyroid	(47)	(47)	(49)
Follicular cell carcinoma	1 (2%)		
C-cell adenoma	2 (4%)	4 (9%)	4 (8%)
C-cell carcinoma	1 (2%)	3 (6%)	2 (4%)
#Parathyroid	(41)	(46)	(44)
Adenoma, NOS	2 (5%)	1 (2%)	
#Pancreatic islets	(48)	(50)	(47)
Islet cell adenoma	4 (8%)		1 (2%)
Islet cell carcinoma	1 (2%)		1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS			1 (2%)
Adenocarcinoma, NOS		1 (2%)	
Fibroadenoma	2 (4%)	1 (2%)	
*Preputial gland	(50)	(50)	(50)
Adenoma, NOS			1 (2%)
Adenocarcinoma, NOS		3 (6%)	1 (2%)
#Testis	(50)	(49)	(50)
Interstitial cell tumor	40 (80%)	35 (71%)	33 (66%)
NERVOUS SYSTEM			
#Cerebrum	(50)	(49)	(50)
Carcinoma, NOS, invasive		1 (2%)	
#Brain	(50)	(49)	(50)
Astrocytoma		1 (2%)	
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS		1 (2%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
*Mandible	(50)	(50)	(50)
Squamous cell carcinoma			1 (2%)
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Neurilemoma, metastatic			1 (2%)
*Peritoneum	(50)	(50)	(50)
Mesothelioma, NOS	1 (2%)		
*Tunica vaginalis	(50)	(50)	(50)
Mesothelioma, NOS	1 (2%)	2 (4%)	2 (4%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Sarcoma, NOS, unclear primary or metastatic			1 (2%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	6	8	17
Moribund sacrifice	15	25	16
Terminal sacrifice	28	13	16
Dosing accident	1		
Accidentally killed, NDA		4	
Accidentally killed, NOS			1
TUMOR SUMMARY			
Total animals with primary tumors**	48	49	39
Total primary tumors	145	148	113
Total animals with benign tumors	48	48	39
Total benign tumors	102	92	77
Total animals with malignant tumors	32	40	26
Total malignant tumors	38	48	31
Total animals with secondary tumors##	1	2	2
Total secondary tumors	1	2	2
Total animals with tumors uncertain-- benign or malignant	4	7	3
Total uncertain tumors	5	8	4
Total animals with tumors uncertain-- primary or metastatic			1
Total uncertain tumors			1

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS: VEHICLE CONTROL

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	106	082	105	106	106	106	106	106	106	106	106	106	106	097	106	080	094	104	106	106	072	106	033	097	106
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma							X						X												
Basal cell tumor															X										
Keratoscanthoma						X											X								
Subcutaneous tissue	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Neurofibrosarcoma			X																						
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																					X				
Trachea	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic																					X				
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule					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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	–	–	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	–	–	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	–	–	+
URINARY SYSTEM																									
Kidney	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	–	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS		X		X							X			X				X			X	X		X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																		X							
Pheochromocytoma	X			X	X	X				X	X		X		X			X		X					X
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+
Follicular cell carcinoma																									
C-cell adenoma																					X				
C-cell carcinoma																									
Parathyroid	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	–	–	+
Adenoma, NOS																									
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
Islet cell adenoma	X																								
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	N	+	+	N	+	N	+	N	+	N	N	N	N	N	N	N	N	+	N	+	+	+
Fibroadenoma	X																								
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor	X		X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X		X			X
Prostate	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BODY CAVITIES																									
Peritoneum	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																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
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, mononuclear cell		X	X			X		X			X	X		X	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 missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE A2. 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: TISSUES TUMORS
WEEKS ON STUDY	083	106	092	106	106	106	106	084	106	106	105	100	097	100	094	106	089	094	083	106	106	106	034	091	106	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																				X						3
Basal cell tumor																										1
Keratoacanthoma																										2
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma									X																	1
Neurofibrosarcoma					X																					2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	48
Squamous cell carcinoma, metastatic																										1
Thymus	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule			X																	X						3
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	46
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	45
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS	X	X	X	X	X		X		X			X				X				X				X	X	21
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma											X					X										3
Pheochromocytoma			X						X	X	X	X	X	X		X				X	X	X				22
Pheochromocytoma, malignant							X																			1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	47
Follicular cell carcinoma				X																						1
C-cell adenoma								X																		2
C-cell carcinoma													X													1
Parathyroid	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	41
Adenoma, NOS																			X					X		2
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	48
Islet cell adenoma	X				X							X														4
Islet cell carcinoma							X																			1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	N	+	N	+	+	N	+	+	N	+	N	+	+	N	N	+	N	+	N	+	+	+	*50
Fibroadenoma																										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	40
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BODY CAVITIES																										
Peritoneum	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
Mesothelioma, NOS																			X							1
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS																			X							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				X	X	X	X	X	X	X	X		X	X			X	X		X	X	30

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS: LOW DOSE

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0110	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	1010	0889	0887	0997	0880	1006	1006	1006	0990	1006	1011	0881	0994	1006	0996	0990	1006	1006	1000	0991	0993	0889	1006	0995	1001
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+
Squamous cell papilloma										X															
Basal cell tumor																									
Keratoacanthoma								X																	
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+
Fibrosarcoma																									
Fibrous histiocytoma, malignant		X																							
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic		X																							
Thymus	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule						X																			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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Small intestine	+	+	−	−	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+
Large intestine	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS									X																
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS	X		X		X	X		X			X		X						X	X	X		X		X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma	X					X		X	X		X						X		X	X		X	X	X
Ganglioneuroma																						X			
Thyroid	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+
C-cell adenoma														X						X					
C-cell carcinoma		X					X																		
Parathyroid	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+
Adenoma, NOS																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	N	+	+	+	+	N	+	N	N	N	N	N	N	N	N	+	+	+	N	+	N	N
Adenocarcinoma, NOS																									
Fibroadenoma							X																		
Testis	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor		X		X		X	X	X	X	X	X		X	X	X	X	X	X				X		X	X
Prostate	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Adenocarcinoma, NOS				X																		X			
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																									
Astrocytoma		X																							
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
Carcinoma, NOS											X														
BODY CAVITIES																									
Tunica vaginalis	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, 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
Leukemia, mononuclear cell	X		X		X		X	X		X		X		X	X	X	X	X	X			X	X	X	X

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW 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	096	106	073	099	106	044	103	099	104	104	083	104	104	103	068	101	079	089	094	102	091	106	102	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	*50
Squamous cell papilloma																										1
Basal cell tumor															X											1
Keratoacanthoma												X														2
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	*50
Fibrosarcoma																						X				1
Fibrous histiocytoma, malignant																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	49
Fibrous histiocytoma, metastatic																										1
Thymus	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	45
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule		X				X																	X			5
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	47
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	44
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesothelioma, NOS																										1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS																									X	1
Adenoma, NOS		X		X	X				X	X		X		X	X	X	X	X				X	X	X		26
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma									X																	1
Pheochromocytoma	X						X			X		X	X	X										X	X	19
Ganglioneuroma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
C-cell adenoma											X														X	4
C-cell carcinoma														X												3
Parathyroid	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma, NOS	X																									1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	+	+	+	N	+	+	+	+	N	N	+	N	N	+	+	N	N	N	N	+	N	+	+	*50
Adenocarcinoma, NOS																									X	1
Fibroadenoma																										1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor	X	X	X	X		X	X				X	X	X	X	X	X			X	X	X		X	X	X	35
Prostate	–	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	46
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	*50
Adenocarcinoma, NOS																			X							3
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS, invasive																									X	1
Astrocytoma																										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
Carcinoma, NOS																										1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
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	*50
Leukemia, mononuclear cell	X	X	X	X		X	X		X	X	X	X		X		X		X		X	X	X	X	X	X	36

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS: 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	091	101	080	092	002	106	106	004	005	106	106	089	061	089	094	056	093	005	106	057	090	105	106	103	081
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma														X											
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									X
Lipoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma											X														
Pheochromocytoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+
Thymus	−	−	−	−	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	−	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, malignant												X													
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Neurilemoma, malignant																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Neoplastic nodule																									
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						
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+
Small intestine	+	+	+	+	−	+	+	+	−	+	+	+	+	+	−	+	+	−	+	−	+	−	+	+	+
Large intestine	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+
Mesothelioma, NOS																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS		X		X			X				X											X	X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma	X	X								X				X			X					X	X	X	
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
C-cell adenoma														X									X		
C-cell carcinoma																								X	
Parathyroid	−	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Islet cell adenoma		X																							
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	+	+	+	+	N	N	+	N	+	N	N	N	N	N	N	+	N	N	+	N	N
Adenoma, NOS							X																		
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor		X	X			X	X				X	X		X	X		X		X		X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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																							
Adenocarcinoma, NOS														X											
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Carcinoma, NOS																									
MUSCULOSKELETAL SYSTEM																									
Bone	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
Squamous cell carcinoma																									
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
Neurilemoma, metastatic												X													
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
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, unclear primary or metastatic			X																						
Leukemia, mononuclear cell	X	X		X		X				X					X						X		X	X	

TABLE A2. 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	100	070	089	061	104	106	066	071	106	106	106	102	106	078	097	004	090	068	082	106	106	106	081	106	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	*50
Squamous cell papilloma																										1
Keratoacanthoma													X													1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	*50
Fibroma	X																									2
Lipoma																				X						1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma																										1
Pheochromocytoma, metastatic																									X	1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	46
Thymus	+	+	+	−	+	−	+	+	−	−	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	37
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma, malignant																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	48
Neurilemoma, malignant															X											1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule										X																1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	47
Acinar cell adenoma																										1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	−	+	+	+	+	−	−	+	+	+	+	+	−	+	−	+	−	+	+	+	+	+	+	41
Small intestine	+	+	−	+	−	+	+	−	−	+	+	+	+	+	−	+	+	+	−	+	+	+	+	−	+	37
Large intestine	+	+	−	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	43
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	45
Mesothelioma, NOS																									X	1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS				X			X				X	X	X	X		X							X		X	15
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma				X		X	X				X		X					X					X		X	16
Pheochromocytoma, malignant																				X					X	2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell adenoma										X															X	4
C-cell carcinoma																							X			2
Parathyroid	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Pancreatic islets	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	47
Islet cell adenoma																										1
Islet cell carcinoma												X														1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	+	N	N	N	N	N	+	N	+	N	+	+	N	+	N	N	+	N	N	+	+	N	*50
Adenoma, NOS																										1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X				X	X	X	X	X	X	X	X	X	X		X		X	X	X			X	33
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	*50
Adenoma, NOS																										1
Adenocarcinoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	*50
Carcinoma, NOS							X																			1
MUSCULOSKELETAL SYSTEM																										
Bone	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
Squamous cell carcinoma													X													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	*50
Neurilemoma, metastatic																										1
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, 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	*50
Sarcoma, NOS, unclear primary or meta																										1
Leukemia, mononuclear cell		X				X	X			X	X	X		X						X	X	X			X	20

* Animals necropsied

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS

	Vehicle Control	5 mg/kg	10 mg/kg
Skin: Squamous Cell Papilloma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	10.7%	7.7%	3.1%
Terminal Rates (c)	3/28 (11%)	1/13 (8%)	0/16 (0%)
Week of First Observation	106	106	89
Life Table Tests (d)	P=0.378N	P=0.602N	P=0.490N
Incidental Tumor Tests (d)	P=0.340N	P=0.602N	P=0.429N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test		P=0.309N	P=0.309N
Subcutaneous Tissue: Fibrosarcoma or Neurofibrosarcoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	10.2%	4.8%	0.0%
Terminal Rates (c)	2/28 (7%)	0/13 (0%)	0/16 (0%)
Week of First Observation	105	102	--
Life Table Tests (d)	P=0.156N	P=0.568N	P=0.238N
Incidental Tumor Tests (d)	P=0.098N	P=0.306N	P=0.209N
Cochran-Armitage Trend Test (d)	P=0.060N		
Fisher Exact Test		P=0.309N	P=0.121N
Subcutaneous Tissue: Fibroma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	10.2%	4.8%	8.9%
Terminal Rates (c)	2/28 (7%)	0/13 (0%)	1/16 (6%)
Week of First Observation	105	102	81
Life Table Tests (d)	P=0.580	P=0.568N	P=0.641
Incidental Tumor Tests (d)	P=0.527N	P=0.306N	P=0.638N
Cochran-Armitage Trend Test (d)	P=0.399N		
Fisher Exact Test		P=0.309N	P=0.500N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	30/50 (60%)	36/50 (72%)	20/50 (40%)
Adjusted Rates (b)	66.3%	97.0%	78.9%
Terminal Rates (c)	13/28 (46%)	12/13 (92%)	11/16 (69%)
Week of First Observation	72	80	82
Life Table Tests (d)	P=0.267	P=0.003	P=0.437
Incidental Tumor Tests (d)	P=0.265N	P=0.304	P=0.225N
Cochran-Armitage Trend Test (d)	P=0.027N		
Fisher Exact Test		P=0.146	P=0.036N
Liver: Neoplastic Nodule			
Overall Rates (a)	3/50 (6%)	5/50 (10%)	1/49 (2%)
Adjusted Rates (b)	9.5%	28.1%	6.3%
Terminal Rates (c)	2/28 (7%)	3/13 (23%)	1/16 (6%)
Week of First Observation	92	91	106
Life Table Tests (d)	P=0.527N	P=0.122	P=0.506N
Incidental Tumor Tests (d)	P=0.436N	P=0.207	P=0.429N
Cochran-Armitage Trend Test (d)	P=0.272N		
Fisher Exact Test		P=0.357	P=0.316N
Pituitary: Adenoma			
Overall Rates (a)	21/50 (42%)	26/49 (53%)	14/48 (29%)
Adjusted Rates (b)	54.9%	75.9%	65.1%
Terminal Rates (c)	12/28 (43%)	6/13 (46%)	9/16 (56%)
Week of First Observation	72	68	89
Life Table Tests (d)	P=0.309	P=0.012	P=0.455
Incidental Tumor Tests (d)	P=0.278N	P=0.334	P=0.385N
Cochran-Armitage Trend Test (d)	P=0.122N		
Fisher Exact Test		P=0.184	P=0.132N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Pituitary: Adenoma or Carcinoma			
Overall Rates (a)	21/50 (42%)	27/49 (55%)	14/48 (29%)
Adjusted Rates (b)	54.9%	77.1%	65.1%
Terminal Rates (c)	12/28 (43%)	6/13 (46%)	9/16 (56%)
Week of First Observation	72	68	89
Life Table Tests (d)	P=0.301	P=0.008	P=0.455
Incidental Tumor Tests (d)	P=0.281N	P=0.282	P=0.385N
Cochran-Armitage Trend Test (d)	P=0.124N		
Fisher Exact Test		P=0.135	P=0.132N
Adrenal: Cortical Adenoma			
Overall Rates (a)	3/50 (6%)	1/49 (2%)	0/50 (0%)
Adjusted Rates (b)	9.8%	5.3%	0.0%
Terminal Rates (c)	1/28 (4%)	0/13 (0%)	0/16 (0%)
Week of First Observation	104	103	--
Life Table Tests (d)	P=0.157N	P=0.562N	P=0.239N
Incidental Tumor Tests (d)	P=0.070N	P=0.197N	P=0.181N
Cochran-Armitage Trend Test (d)	P=0.061N		
Fisher Exact Test		P=0.316N	P=0.121N
Adrenal: Pheochromocytoma			
Overall Rates (a)	22/50 (44%)	19/49 (39%)	16/50 (32%)
Adjusted Rates (b)	64.3%	71.0%	60.2%
Terminal Rates (c)	16/28 (57%)	7/13 (54%)	6/16 (38%)
Week of First Observation	92	83	89
Life Table Tests (d)	P=0.248	P=0.091	P=0.315
Incidental Tumor Tests (d)	P=0.531	P=0.558	P=0.562
Cochran-Armitage Trend Test (d)	P=0.129N		
Fisher Exact Test		P=0.373N	P=0.152N
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant			
Overall Rates (a)	23/50 (46%)	19/49 (39%)	17/50 (34%)
Adjusted Rates (b)	67.3%	71.0%	61.4%
Terminal Rates (c)	17/28 (61%)	7/13 (54%)	6/16 (38%)
Week of First Observation	92	83	82
Life Table Tests (d)	P=0.232	P=0.112	P=0.289
Incidental Tumor Tests (d)	P=0.520	P=0.564N	P=0.551
Cochran-Armitage Trend Test (d)	P=0.130N		
Fisher Exact Test		P=0.300N	P=0.154N
Thyroid: C-Cell Adenoma			
Overall Rates (a)	2/47 (4%)	4/47 (9%)	4/49 (8%)
Adjusted Rates (b)	4.4%	19.5%	21.3%
Terminal Rates (c)	0/28 (0%)	1/13 (8%)	3/16 (19%)
Week of First Observation	72	91	89
Life Table Tests (d)	P=0.116	P=0.214	P=0.173
Incidental Tumor Tests (d)	P=0.279	P=0.483	P=0.375
Cochran-Armitage Trend Test (d)	P=0.293		
Fisher Exact Test		P=0.339	P=0.359
Thyroid: C-Cell Carcinoma			
Overall Rates (a)	1/47 (2%)	3/47 (6%)	2/49 (4%)
Adjusted Rates (b)	2.9%	15.2%	11.2%
Terminal Rates (c)	0/28 (0%)	1/13 (8%)	1/16 (6%)
Week of First Observation	97	89	103
Life Table Tests (d)	P=0.227	P=0.186	P=0.334
Incidental Tumor Tests (d)	P=0.315	P=0.386	P=0.411
Cochran-Armitage Trend Test (d)	P=0.416		
Fisher Exact Test		P=0.308	P=0.516

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Thyroid: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	3/47 (6%)	7/47 (15%)	6/49 (12%)
Adjusted Rates (b)	7.1%	32.5%	31.2%
Terminal Rates (c)	0/28 (0%)	2/13 (15%)	4/16 (25%)
Week of First Observation	72	89	89
Life Table Tests (d)	P=0.058	P=0.066	P=0.085
Incidental Tumor Tests (d)	P=0.172	P=0.284	P=0.224
Cochran-Armitage Trend Test (d)	P=0.231		
Fisher Exact Test		P=0.158	P=0.264
Pancreatic Islets: Islet Cell Adenoma			
Overall Rates (a)	4/48 (8%)	0/50 (0%)	1/47 (2%)
Adjusted Rates (b)	12.0%	0.0%	4.8%
Terminal Rates (c)	2/28 (7%)	0/13 (0%)	0/16 (0%)
Week of First Observation	83	--	101
Life Table Tests (d)	P=0.176N	P=0.132N	P=0.340N
Incidental Tumor Tests (d)	P=0.116N	P=0.068N	P=0.264N
Cochran-Armitage Trend Test (d)	P=0.083N		
Fisher Exact Test		P=0.054N	P=0.187N
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (a)	5/48 (10%)	0/50 (0%)	2/47 (4%)
Adjusted Rates (b)	15.3%	0.0%	10.7%
Terminal Rates (c)	3/28 (11%)	0/13 (0%)	1/16 (6%)
Week of First Observation	83	--	101
Life Table Tests (d)	P=0.277N	P=0.094N	P=0.445N
Incidental Tumor Tests (d)	P=0.215N	P=0.049N	P=0.372N
Cochran-Armitage Trend Test (d)	P=0.120N		
Fisher Exact Test		P=0.025N	P=0.226N
Preputial Gland: Adenocarcinoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	0.0%	7.6%	3.1%
Terminal Rates (c)	0/28 (0%)	0/13 (0%)	0/16 (0%)
Week of First Observation	--	79	89
Life Table Tests (d)	P=0.285	P=0.113	P=0.446
Incidental Tumor Tests (d)	P=0.431	P=0.221	P=0.564
Cochran-Armitage Trend Test (d)	P=0.378		
Fisher Exact Test		P=0.121	P=0.500
Preputial Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	0.0%	7.6%	7.7%
Terminal Rates (c)	0/28 (0%)	0/13 (0%)	0/16 (0%)
Week of First Observation	--	79	89
Life Table Tests (d)	P=0.127	P=0.113	P=0.171
Incidental Tumor Tests (d)	P=0.210	P=0.221	P=0.251
Cochran-Armitage Trend Test (d)	P=0.202		
Fisher Exact Test		P=0.121	P=0.247
Testis: Interstitial Cell Tumor			
Overall Rates (a)	40/50 (80%)	35/49 (71%)	33/50 (66%)
Adjusted Rates (b)	100.0%	96.8%	93.9%
Terminal Rates (c)	28/28 (100%)	12/13 (92%)	14/16 (88%)
Week of First Observation	80	79	66
Life Table Tests (d)	P=0.034	P=0.015	P=0.048
Incidental Tumor Tests (d)	P=0.427	P=0.587	P=0.517
Cochran-Armitage Trend Test (d)	P=0.073N		
Fisher Exact Test		P=0.224N	P=0.088N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle 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 vehicle 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 exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE A4a. HISTORICAL INCIDENCE OF LEUKEMIA IN MALE F344/N RATS (a)

Study	Incidence in Controls
Historical Incidence in All Water Controls	
THPS (b)	30/50
THPC (b)	19/50
Chlorpheniramine maleate (b)	25/50
TOTAL	74/150 (49.3%)
SD	11.02%
Overall Historical Incidence in Untreated Controls	
TOTAL	458/1,727 (26.5%)
SD (c)	8.83%
Range (d)	
High	23/50
Low	5/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Battelle Columbus Laboratories
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE A4b. HISTORICAL INCIDENCE OF PITUITARY GLAND TUMORS IN MALE F344/N RATS (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence in All Water Vehicle Controls			
THPS (b)	21/50	0/50	21/50
THPC (b)	17/50	1/50	18/50
Chlorpheniramine maleate (b)	12/50	0/50	12/50
TOTAL	50/150 (33.3%)	1/150 (0.7%)	51/150 (34.0%)
SD (c)	9.02%	1.15%	9.17%
Range (d)			
High	21/50	1/50	21/50
Low	12/50	0/50	12/50
Overall Historical Incidence in Untreated Controls			
TOTAL	(e) 325/1,614 (20.1%)	(f) 38/1,614 (2.4%)	(e,f) 363/1,614 (22.5%)
SD (c)	11.14%	3.04%	10.98%
Range (d)			
High	24/46	5/45	25/46
Low	2/39	0/50	2/39

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Battelle Columbus Laboratories
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes 39 chromophobe adenomas and 3 acidophil adenomas
(f) Includes eight chromophobe adenomas

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS

	Vehicle Control	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, active chronic		1 (2%)	
Hyperkeratosis		1 (2%)	
Acanthosis		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Hemorrhage			1 (2%)
Inflammation, active chronic	2 (4%)		
RESPIRATORY SYSTEM			
#Trachea	(49)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
#Peritracheal tissue	(49)	(50)	(50)
Inflammation, necrotizing granulomatous		1 (2%)	
#Bronchus/muscularis	(50)	(50)	(49)
Hyperplasia, focal			1 (2%)
#Lung/bronchiole	(50)	(50)	(49)
Inflammation, chronic focal		1 (2%)	
#Lung	(50)	(50)	(49)
Aspiration, foreign body		4 (8%)	1 (2%)
Congestion, NOS	1 (2%)		3 (6%)
Congestion, acute	1 (2%)	3 (6%)	3 (6%)
Edema, NOS			7 (14%)
Edema, interstitial	1 (2%)		
Hemorrhage	2 (4%)		
Inflammation, interstitial	3 (6%)		
Inflammation, active chronic	1 (2%)		
Inflammation, acute/chronic			4 (8%)
Pneumonia, interstitial chronic	2 (4%)	3 (6%)	7 (14%)
Inflammation, granulomatous focal		7 (14%)	1 (2%)
Alveolar macrophages	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, alveolar epithelium	2 (4%)	5 (10%)	
#Lung/alveoli	(50)	(50)	(49)
Edema, NOS			1 (2%)
Hemorrhage		1 (2%)	1 (2%)
Hemorrhage, chronic	1 (2%)		
Crystals, NOS			1 (2%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(48)	(50)	(48)
Myelofibrosis	1 (2%)	1 (2%)	2 (4%)
Hyperplasia, granulocytic		3 (6%)	3 (6%)
Aplasia, hematopoietic			1 (2%)
#Spleen	(49)	(50)	(49)
Hemorrhage	1 (2%)		
Infarct, hemorrhagic	1 (2%)		
Depletion, lymphoid		1 (2%)	4 (8%)
#Splenic red pulp	(49)	(50)	(49)
Congestion, NOS			1 (2%)
Inflammation, chronic focal			1 (2%)
Fibrosis, focal		1 (2%)	
Necrosis, focal		1 (2%)	
Necrosis, ischemic	1 (2%)		
Infarct, NOS		1 (2%)	

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
#Splenic red pulp (Continued)	(49)	(50)	(49)
Infarct, acute		1 (2%)	
Infarct, hemorrhagic			1 (2%)
Hematopoiesis		1 (2%)	1 (2%)
#Splenic trabeculae	(49)	(50)	(49)
Hyperplasia, focal		2 (4%)	
#Mandibular lymph node	(48)	(49)	(46)
Dilatation, NOS			1 (2%)
Dilatation/sinus	1 (2%)		
Cyst, NOS	2 (4%)	10 (20%)	3 (7%)
Multiple cysts	1 (2%)		
Hemorrhage	2 (4%)	1 (2%)	2 (4%)
Inflammation, multifocal			1 (2%)
Inflammation, chronic	1 (2%)		
Inflammation, granulomatous focal	1 (2%)		
Depletion, lymphoid			2 (4%)
Plasmacytosis	31 (65%)	37 (76%)	29 (63%)
#Thoracic lymph node	(48)	(49)	(46)
Pigmentation, NOS	1 (2%)		
Histiocytosis	1 (2%)		
Plasmacytosis			1 (2%)
#Mediastinal lymph node	(48)	(49)	(46)
Inflammation, chronic focal		1 (2%)	
Inflammation, granulomatous		1 (2%)	
#Pancreatic lymph node	(48)	(49)	(46)
Inflammation, granulomatous focal			2 (4%)
Depletion, lymphoid			1 (2%)
#Mesenteric lymph node	(48)	(49)	(46)
Dilatation/sinus		1 (2%)	
Cyst, NOS		1 (2%)	
Multiple cysts	2 (4%)	1 (2%)	
Inflammation, chronic focal			1 (2%)
Depletion, lymphoid		1 (2%)	
#Renal lymph node	(48)	(49)	(46)
Dilatation, NOS			1 (2%)
Hemorrhage			1 (2%)
Inflammation, active chronic			1 (2%)
Inflammation, granulomatous focal			2 (4%)
Depletion, lymphoid			1 (2%)
#Inguinal lymph node	(48)	(49)	(46)
Inflammation, chronic		1 (2%)	
#Thymic lymph node	(48)	(49)	(46)
Dilatation/sinus		1 (2%)	
Congestion, NOS			1 (2%)
Hemorrhage	1 (2%)	3 (6%)	
Inflammation, active chronic		2 (4%)	1 (2%)
Inflammation, chronic		1 (2%)	
Inflammation, chronic focal	1 (2%)		1 (2%)
Inflammation, granulomatous focal	1 (2%)	2 (4%)	2 (4%)
Depletion, lymphoid		2 (4%)	1 (2%)
Plasmacytosis		2 (4%)	
#Liver	(50)	(50)	(49)
Hematopoiesis			1 (2%)
#Hepatic sinusoid	(50)	(50)	(49)
Leukocytosis, NOS	1 (2%)		
#Thymus	(47)	(45)	(37)
Hemorrhage	2 (4%)		1 (3%)
Depletion, lymphoid		1 (2%)	2 (5%)
#Thymic cortex	(47)	(45)	(37)
Depletion, lymphoid			3 (8%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Thymic lymphocytes	(47)	(45)	(37)
Necrosis, diffuse			1 (3%)
CIRCULATORY SYSTEM			
#Thymic lymph node	(48)	(49)	(46)
Lymphangiectasis	1 (2%)		
#Lung	(50)	(50)	(49)
Perivasculitis	1 (2%)		
#Heart/atrium	(50)	(50)	(50)
Dilatation, NOS		2 (4%)	3 (6%)
Thrombosis, NOS	1 (2%)		1 (2%)
#Right atrium	(50)	(50)	(50)
Dilatation, NOS	1 (2%)		1 (2%)
#Left atrium	(50)	(50)	(50)
Thrombosis, NOS	3 (6%)	3 (6%)	
Thrombus, fibrin	1 (2%)		
#Myocardium	(50)	(50)	(50)
Mineralization			1 (2%)
Degeneration, NOS	45 (90%)	48 (96%)	34 (68%)
#Cardiac valve	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)
*Splenic artery	(50)	(50)	(50)
Thrombus, mural			1 (2%)
#Hepatic sinusoid	(50)	(50)	(49)
Congestion, NOS			1 (2%)
Hemorrhagic cyst	1 (2%)		
#Pancreas	(48)	(50)	(47)
Periarteritis	1 (2%)		
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(50)	(48)
Atrophy, focal	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, focal	1 (2%)		
#Liver	(50)	(50)	(49)
Congestion, NOS			1 (2%)
Inflammation, acute focal		1 (2%)	
Inflammation, granulomatous	1 (2%)		
Inflammation, granulomatous focal	8 (16%)	6 (12%)	14 (29%)
Degeneration, cystic	7 (14%)	15 (30%)	14 (29%)
Necrosis, focal		1 (2%)	
Basophilic cyto change	11 (22%)	16 (32%)	10 (20%)
Eosinophilic cyto change	1 (2%)	2 (4%)	
Clear cell change	2 (4%)	2 (4%)	5 (10%)
Hyperplasia, focal	1 (2%)		1 (2%)
Angiectasis	1 (2%)	5 (10%)	2 (4%)
#Hepatic capsule	(50)	(50)	(49)
Hemorrhage			1 (2%)
#Liver/centrilobular	(50)	(50)	(49)
Congestion, chronic passive	1 (2%)		
Necrosis, focal	3 (6%)	2 (4%)	6 (12%)
Cytoplasmic vacuolization	1 (2%)	2 (4%)	1 (2%)
#Liver/periportal	(50)	(50)	(49)
Cytoplasmic vacuolization	1 (2%)	1 (2%)	6 (12%)
#Liver/hepatocytes	(50)	(50)	(49)
Necrosis, focal		1 (2%)	
Cytoplasmic change, NOS		1 (2%)	
Cytoplasmic vacuolization		1 (2%)	2 (4%)
Cell size alteration		1 (2%)	
#Bile duct	(50)	(50)	(49)
Hyperplasia, focal	46 (92%)	46 (92%)	25 (51%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Pancreas	(48)	(50)	(47)
Dilatation/ducts		4 (8%)	
Cystic ducts	1 (2%)		
Inflammation, chronic focal	1 (2%)		
#Pancreatic acinus	(48)	(50)	(47)
Atrophy, focal	18 (38%)	17 (34%)	16 (34%)
Hyperplasia, focal			1 (2%)
#Esophagus	(50)	(50)	(50)
Lacerated wound	1 (2%)		
Dilatation, NOS		1 (2%)	
Inflammation, necrotizing granulomatous		1 (2%)	
#Periesophageal tissue	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
#Stomach	(46)	(47)	(41)
Mineralization			2 (5%)
#Cardiac stomach	(46)	(47)	(41)
Ulcer, acute	1 (2%)		
Inflammation, active chronic		1 (2%)	
Hyperkeratosis	1 (2%)	3 (6%)	
Acanthosis	1 (2%)	2 (4%)	
#Gastric fundus	(46)	(47)	(41)
Necrosis, focal	1 (2%)	1 (2%)	
#Duodenum	(45)	(44)	(37)
Hyperplasia, epithelial		1 (2%)	
#Colon	(46)	(46)	(43)
Inflammation, chronic focal			1 (2%)
Parasitism	1 (2%)	2 (4%)	
URINARY SYSTEM			
#Kidney	(48)	(50)	(48)
Congestion, NOS			1 (2%)
Lymphocytic inflammatory infiltrate	1 (2%)		
Nephropathy	45 (94%)	49 (98%)	41 (85%)
Nephrosis, NOS	1 (2%)		1 (2%)
#Kidney/cortex	(48)	(50)	(48)
Cyst, NOS	4 (8%)	2 (4%)	2 (4%)
Multiple cysts		3 (6%)	2 (4%)
Granuloma, NOS			1 (2%)
#Kidney/medulla	(48)	(50)	(48)
Hyperplasia, epithelial		2 (4%)	
#Kidney/glomerulus	(48)	(50)	(48)
Cyst, NOS	1 (2%)		
#Kidney/tubule	(48)	(50)	(48)
Pigmentation, NOS	1 (2%)		1 (2%)
#Kidney/pelvis	(48)	(50)	(48)
Hyperplasia, epithelial	1 (2%)		
#Urinary bladder	(47)	(48)	(45)
Calculus, microscopic examination	1 (2%)		1 (2%)
Inflammation, active chronic			1 (2%)
Hyperplasia, epithelial		1 (2%)	1 (2%)
ENDOCRINE SYSTEM			
#Pituitary intermedia	(50)	(49)	(48)
Hyperplasia, focal		1 (2%)	
#Anterior pituitary	(50)	(49)	(48)
Embryonal duct cyst	5 (10%)	1 (2%)	1 (2%)
Cyst, NOS			1 (2%)
Multiple cysts		1 (2%)	1 (2%)
Hemorrhagic cyst		1 (2%)	
Hemorrhage, chronic	1 (2%)		

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Anterior pituitary (Continued)	(50)	(49)	(48)
Fibrosis, diffuse	1 (2%)		
Hyperplasia, NOS	1 (2%)		
Hyperplasia, focal	7 (14%)	3 (6%)	5 (10%)
#Adrenal/capsule	(50)	(49)	(50)
Fibrosis, multifocal		1 (2%)	
#Adrenal cortex	(50)	(49)	(50)
Cyst, NOS	1 (2%)		
Congestion, NOS			1 (2%)
Hemorrhage		1 (2%)	
Degeneration, NOS	1 (2%)		
Degeneration, cystic			3 (6%)
Necrosis, focal	1 (2%)		1 (2%)
Cytoplasmic vacuolization	12 (24%)	20 (41%)	11 (22%)
Focal cellular change	2 (4%)	5 (10%)	
Hyperplasia, focal	6 (12%)	7 (14%)	3 (6%)
#Adrenal medulla	(50)	(49)	(50)
Necrosis, NOS		1 (2%)	
Necrosis, focal	1 (2%)		
Cytoplasmic vacuolization	1 (2%)		
Hyperplasia, NOS	1 (2%)		
Hyperplasia, focal	8 (16%)	3 (6%)	6 (12%)
Hyperplasia, diffuse	1 (2%)		
#Thyroid	(47)	(47)	(49)
Embryonal duct cyst	1 (2%)	1 (2%)	1 (2%)
Follicular cyst, NOS			1 (2%)
Atrophy, NOS		1 (2%)	
Hyperplasia, C-cell	30 (64%)	17 (36%)	8 (16%)
#Thyroid follicle	(47)	(47)	(49)
Multiple cysts	1 (2%)	1 (2%)	
#Parathyroid	(41)	(46)	(44)
Hyperplasia, NOS	2 (5%)		4 (9%)
Hyperplasia, focal		3 (7%)	
#Pancreatic islets	(48)	(50)	(47)
Hyperplasia, focal	1 (2%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Dilatation, NOS		2 (4%)	
Dilatation/ducts		5 (10%)	
Galactocele	3 (6%)	3 (6%)	
Inflammation, granulomatous focal		1 (2%)	
Hyperplasia, focal	2 (4%)	1 (2%)	1 (2%)
Hyperplasia, cystic	7 (14%)	6 (12%)	7 (14%)
*Epididymal cytologic material	(50)	(50)	(50)
Mineralization	1 (2%)		
*Preputial gland	(50)	(50)	(50)
Cystic ducts	1 (2%)	1 (2%)	
Inflammation, active chronic	4 (8%)	1 (2%)	2 (4%)
Inflammation, chronic focal	10 (20%)		5 (10%)
Inflammation, granulomatous			1 (2%)
Inflammation, granulomatous focal	4 (8%)	9 (18%)	6 (12%)
Hyperplasia, NOS	1 (2%)		
Hyperplasia, focal	1 (2%)		
#Prostate	(48)	(46)	(50)
Inflammation, acute focal	1 (2%)		1 (2%)
Inflammation, acute diffuse		1 (2%)	
Inflammation, active chronic	1 (2%)	5 (11%)	2 (4%)
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic focal	9 (19%)	8 (17%)	3 (6%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM			
#Prostate (Continued)	(48)	(46)	(50)
Abscess, chronic			1 (2%)
Inflammation, granulomatous focal		1 (2%)	
Hyperplasia, epithelial		3 (7%)	
Hyperplasia, focal	1 (2%)		
*Seminal vesicle	(50)	(50)	(50)
Dilatation, NOS		1 (2%)	
#Testis	(50)	(49)	(50)
Inflammation, chronic focal	1 (2%)		
Atrophy, focal	1 (2%)		
Aspermatogenesis		1 (2%)	
Hyperplasia, interstitial cell	3 (6%)	1 (2%)	3 (6%)
#Testis/tubule	(50)	(49)	(50)
Degeneration, NOS		1 (2%)	
Atrophy, focal	14 (28%)	12 (24%)	6 (12%)
Atrophy, pressure	14 (28%)	10 (20%)	14 (28%)
Atrophy, diffuse			1 (2%)
*Epididymis	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
NERVOUS SYSTEM			
#Brain/meninges	(50)	(49)	(50)
Hemorrhage		1 (2%)	
#Lateral ventricle	(50)	(49)	(50)
Hydrocephalus, NOS		1 (2%)	
#Cerebrum	(50)	(49)	(50)
Atrophy, pressure	2 (4%)	2 (4%)	1 (2%)
#Brain	(50)	(49)	(50)
Hemorrhage	1 (2%)		2 (4%)
#Cerebellum	(50)	(49)	(50)
Hemorrhage		1 (2%)	
#Medulla oblongata	(50)	(49)	(50)
Hemorrhage			1 (2%)
SPECIAL SENSE ORGANS			
*Eye, posterior chamber	(50)	(50)	(50)
Hemorrhage		2 (4%)	
*Eye/cornea	(50)	(50)	(50)
Inflammation, chronic focal		2 (4%)	
*Eye/retina	(50)	(50)	(50)
Degeneration, NOS		3 (6%)	
Atrophy, focal		2 (4%)	1 (2%)
Atrophy, diffuse	3 (6%)		1 (2%)
*Eye/crystalline lens	(50)	(50)	(50)
Cataract	3 (6%)	3 (6%)	2 (4%)
Cytoplasmic vacuolization	1 (2%)		
*Harderian gland	(50)	(50)	(50)
Hemorrhage			1 (2%)
Inflammation, chronic focal			1 (2%)
Hyperplasia, epithelial	1 (2%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
*Femur	(50)	(50)	(50)
Osteosclerosis	1 (2%)	2 (4%)	2 (4%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	
*Mediastinal pleura	(50)	(50)	(50)
Inflammation, chronic diffuse	1 (2%)		
*Epicardium	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic focal	1 (2%)		
*Mesentery	(50)	(50)	(50)
Inflammation, granulomatous focal	2 (4%)	3 (6%)	3 (6%)
Hyperplasia, focal		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Inflammation, active chronic	1 (2%)		1 (2%)
SPECIAL MORPHOLOGY SUMMARY			
None			

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS

	Vehicle Control	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)
Squamous cell papilloma		3 (6%)	1 (2%)
Basal cell tumor	1 (2%)	1 (2%)	1 (2%)
*Subcutaneous tissue	(49)	(50)	(50)
Neurofibrosarcoma	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(49)	(50)	(49)
Alveolar/bronchiolar adenoma	1 (2%)	2 (4%)	
Alveolar/bronchiolar carcinoma	1 (2%)		1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(49)	(50)	(50)
Lymphocytic leukemia		1 (2%)	
Leukemia, mononuclear cell	23 (47%)	19 (38%)	22 (44%)
#Thymic medulla	(48)	(45)	(43)
Thymoma		1 (2%)	
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
#Liver	(49)	(50)	(49)
Neoplastic nodule	3 (6%)	2 (4%)	2 (4%)
#Cardiac stomach	(46)	(48)	(44)
Squamous cell papilloma			1 (2%)
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Anterior pituitary	(46)	(50)	(46)
Carcinoma, NOS			1 (2%)
Adenoma, NOS	23 (50%)	19 (38%)	16 (35%)
Adenocarcinoma, NOS		2 (4%)	
#Adrenal	(47)	(50)	(48)
Cortical adenoma	3 (6%)	3 (6%)	4 (8%)
Cortical carcinoma		1 (2%)	
#Adrenal medulla	(47)	(50)	(48)
Pheochromocytoma	4 (9%)	4 (8%)	3 (6%)
Pheochromocytoma, malignant		2 (4%)	
Ganglioneuroma	1 (2%)		
#Thyroid	(49)	(50)	(47)
Follicular cell adenoma		1 (2%)	1 (2%)
Follicular cell carcinoma	1 (2%)		
C-cell adenoma	2 (4%)	2 (4%)	
C-cell carcinoma	3 (6%)	2 (4%)	
#Parathyroid	(35)	(44)	(36)
Adenoma, NOS		1 (2%)	

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Pancreatic islets	(48)	(50)	(48)
Islet cell adenoma	1 (2%)		2 (4%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(49)	(50)	(50)
Adenoma, NOS	1 (2%)		
Adenocarcinoma, NOS		3 (6%)	1 (2%)
Papillary cystadenoma, NOS		1 (2%)	1 (2%)
Fibroadenoma	21 (43%)	11 (22%)	8 (16%)
*Mammary duct	(49)	(50)	(50)
Fibroadenoma		1 (2%)	
*Clitoral gland	(49)	(50)	(50)
Carcinoma, NOS	4 (8%)	1 (2%)	5 (10%)
Adenoma, NOS	4 (8%)	5 (10%)	4 (8%)
Adenocarcinoma, NOS		1 (2%)	1 (2%)
Cystadenoma, NOS		1 (2%)	
#Uterus	(49)	(50)	(49)
Carcinoma, NOS		1 (2%)	
Adenocarcinoma, NOS	1 (2%)	1 (2%)	
Endometrial stromal polyp	6 (12%)	9 (18%)	12 (24%)
#Ovary	(49)	(50)	(49)
Granulosa cell tumor			1 (2%)
NERVOUS SYSTEM			
#Cerebrum	(49)	(50)	(47)
Adenocarcinoma, NOS, invasive		1 (2%)	
Astrocytoma		1 (2%)	1 (2%)
#Medulla oblongata	(49)	(50)	(47)
Adenocarcinoma, NOS, invasive		1 (2%)	
SPECIAL SENSE ORGANS			
*External ear	(49)	(50)	(50)
Fibrosarcoma	1 (2%)		
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mediastinum	(49)	(50)	(50)
Lipoma			1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(49)	(50)	(50)
Adenocarcinoma, NOS, metastatic		1 (2%)	

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	8	4	9
Moribund sacrifice	4	8	11
Terminal sacrifice	37	38	29
Dosing accident	† 1		
Accidentally killed, NOS			1
TUMOR SUMMARY			
Total animals with primary tumors**	45	46	41
Total primary tumors	106	102	90
Total animals with benign tumors	39	38	32
Total benign tumors	68	65	55
Total animals with malignant tumors	29	27	25
Total malignant tumors	35	35	32
Total animals with secondary tumors##		3	
Total secondary tumors		3	
Total animals with tumors uncertain-- benign or malignant	3	2	3
Total uncertain tumors	3	2	3

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ
† One vehicle control female, removed after 73 weeks on study, was inadvertently dosed as part of the low dose group for an unknown period of time.

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS: VEHICLE CONTROL

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	106	106	106	106	090	106	094	106	104	106	106	099	106	106	106	106	081	106	106	106	106	085	106	106	073
INTEGUMENTARY SYSTEM																									
Skin	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B
Basal cell tumor																							X		
Subcutaneous tissue	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B
Neurofibrosarcoma																		X							
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B
Alveolar/bronchiolar adenoma		X																							
Alveolar/bronchiolar carcinoma															X										
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	B
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B
Neoplastic nodule			X														X								
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B
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	B
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B
Stomach	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B
Small intestine	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	B
Large intestine	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	B
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	B
Urinary bladder	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	B
Adenoma, NOS		X	X	X	X		X	X				X			X	X		X			X				
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B
Cortical adenoma																					X				
Pheochromocytoma											X														
Ganglioneuroma						X																			
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B
Follicular cell carcinoma				X																					
C-cell adenoma																				X					
C-cell carcinoma	X																								
Parathyroid	+	−	+	−	+	−	−	+	+	−	+	+	+	−	+	+	+	+	−	+	+	+	+	−	B
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	B
Adenoma, NOS																									
Fibroadenoma			X	X	X						X	X		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	B
Carcinoma, NOS							X						X							X					
Adenoma, NOS								X																	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B
Adenocarcinoma, NOS																			X						
Endometrial stromal polyp											X			X											
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B
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	B
Fibrosarcoma																							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	B
Leukemia, mononuclear cell			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 missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE 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	089	092	106	106	106	106	106	094	092	106	106	106	106	091	106	106	106	106	106	106	095	106	106	106	106	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Basal cell tumor																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Neurofibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Thymus	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule													X													3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	46
Small intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	45
Large intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	46
Adenoma, NOS		X					X		X				X		X	X		X		X	X		X	X	X	23
Adrenal	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	47
Cortical adenoma																				X		X				3
Pheochromocytoma				X																X		X				4
Ganglioneuroma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell carcinoma																										1
C-cell adenoma																				X						2
C-cell carcinoma									X					X												3
Parathyroid	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	−	−	−	35
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	48
Islet cell adenoma																									X	1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	*49
Adenoma, NOS										X																1
Fibroadenoma				X	X			X		X	X	X		X	X			X								21
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	*49
Carcinoma, NOS																									X	4
Adenoma, NOS				X	X													X								4
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS																										1
Endometrial stromal polyp											X		X				X			X						6
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	N	*49
Fibrosarcoma																										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	*49
Leukemia, mononuclear cell		X	X		X	X	X	X		X	X		X	X		X	X	X		X		X			X	23

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS: 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	106	106	102	106	106	089	106	106	106	106	106	106	106	073	106	106	106	106	106	106	106	094	106	106	106
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma	X			X																					
Basal cell tumor												X													
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X													
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Thymoma																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule				X															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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS		X			X	X		X		X	X		X							X					
Adenocarcinoma, NOS				X																					
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma								X															X	X	
Cortical carcinoma																									
Pheochromocytoma			X							X								X							
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																				X					
C-cell adenoma																						X		X	
C-cell carcinoma																									
Parathyroid	+	−	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS					X																				
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	+	+	+	+	N	+	+	+	+	N	+	+	N	+	+	+	+	+	+	N	+
Adenocarcinoma, NOS				X																					
Papillary cystadenoma, NOS											X														
Fibroadenoma		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
Carcinoma, NOS					X																				
Adenoma, NOS		X					X										X								
Adenocarcinoma, NOS											X														
Cystadenoma, NOS															X										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS			X																						
Adenocarcinoma, NOS																									
Endometrial stromal polyp	X		X				X			X					X				X					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, invasive				X																					
Astrocytoma																									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
Adenocarcinoma, NOS, metastatic																									
Lymphocytic leukemia														X											
Leukemia, mononuclear cell	X	X			X	X									X						X		X		

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	0026	0027	0028	0029	0030	0031	0032	0033	0034	0035	0036	0037	0038	0039	0040	0041	0042	0043	0044	0045	0046	0047	0048	0049	0050	TOTAL:
WEEKS ON STUDY	106	106	081	106	086	106	106	085	106	093	104	093	106	106	106	106	106	106	087	106	106	106	084	106	106	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																			X							3
Basal cell tumor																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma														X												2
Trachea	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	45
Thymoma								X																		1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										2
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	48
Small intestine	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	48
Large intestine	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS			X		X	X		X				X	X					X		X		X	X	X		19
Adenocarcinoma, NOS																					X					2
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										3
Cortical carcinoma								X																		1
Pheochromocytoma											X															4
Pheochromocytoma, malignant																						X	X			2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										1
C-cell adenoma																										2
C-cell carcinoma				X															X							2
Parathyroid	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	44
Adenoma, NOS																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS						X		X																		3
Papillary cystadenoma, NOS																										1
Fibroadenoma		X										X		X	X	X				X				X		12
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	*50
Carcinoma, NOS																										1
Adenoma, NOS		X														X										5
Adenocarcinoma, NOS																										1
Cystadenoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																										1
Adenocarcinoma, NOS																						X				1
Endometrial stromal polyp							X		X				X													9
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, invasive																					X					2
Astrocytoma																										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
Adenocarcinoma, NOS, metastatic																						X				1
Lymphocytic leukemia																										1
Leukemia, mononuclear cell	X					X		X			X		X		X	X	X		X	X	X			X		19

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS: 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	100	106	096	106	056	063	106	106	021	082	106	090	106	106	100	106	080	106	105	103	075	106	106	089	026
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Basal cell tumor																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																						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	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+
Squamous cell papilloma																									
Small intestine	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
Large intestine	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
Urinary bladder	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS	X			X						X	X			X								X	X	X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																X			X			X			
Pheochromocytoma								X																	
Thyroid	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	+	−	+	+	−	+	−	+	−	+	+	+	+	−	−	+	−	+	−	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma								X																	
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	N	N	+	N	N	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Papillary cystadenoma, NOS																						X			
Fibroadenoma							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
Carcinoma, NOS											X														
Adenoma, NOS													X			X									
Adenocarcinoma, NOS							X																		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp		X	X				X	X		X								X					X		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Granulosa cell tumor																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma																									
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
Lipoma													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, mononuclear cell	X		X								X	X	X		X		X	X	X	X	X			X	

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE 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:
WEEKS ON STUDY	105	106	037	106	106	106	106	094	106	106	100	106	092	102	100	106	106	106	106	106	106	106	106	106	106	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma							X																			1
Basal cell tumor				X																						1
RESPIRATORY SYSTEM																										
Lungs and bronchi	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma					X																					1
Trachea	A	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	45
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymus	A	−	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	43
CIRCULATORY SYSTEM																										
Heart	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	A	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	46
Liver	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule												X														2
Bile duct	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	A	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	A	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	44
Squamous cell papilloma				X																						1
Small intestine	A	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	45
Large intestine	A	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	45
URINARY SYSTEM																										
Kidney	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	45
ENDOCRINE SYSTEM																										
Pituitary	A	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	46
Carcinoma, NOS					X																					1
Adenoma, NOS		X						X			X	X		X	X						X				X	16
Adrenal	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cortical adenoma																						X				4
Pheochromocytoma							X									X										3
Thyroid	A	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular cell adenoma							X																			1
Parathyroid	A	−	−	+	+	−	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	36
Pancreatic islets	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma		X																								2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	*50
Adenocarcinoma, NOS												X														1
Papillary cystadenoma, NOS																										1
Fibroadenoma		X			X						X								X			X				8
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	*50
Carcinoma, NOS					X												X				X			X		5
Adenoma, NOS																				X			X			4
Adenocarcinoma, NOS																										1
Uterus	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endometrial stromal polyp											X					X	X			X			X			12
Ovary	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa cell tumor														X												1
NERVOUS SYSTEM																										
Brain	A	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	47
Astrocytoma		X																								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	*50
Lipoma																										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	X			X	X	X		X	X	X		X		22

* Animals necropsied

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS

	Vehicle Control	5 mg/kg	10 mg/kg
Skin: Squamous Cell Papilloma			
Overall Rates (a)	0/49 (0%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	0.0%	7.9%	3.4%
Terminal Rates (c)	0/37 (0%)	3/38 (8%)	1/29 (3%)
Week of First Observation	--	106	106
Life Table Tests (d)	P=0.303	P=0.126	P=0.451
Incidental Tumor Tests (d)	P=0.303	P=0.126	P=0.451
Cochran-Armitage Trend Test (d)	P=0.384		
Fisher Exact Test		P=0.125	P=0.505
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	23/49 (47%)	19/50 (38%)	22/50 (44%)
Adjusted Rates (b)	55.8%	44.8%	53.8%
Terminal Rates (c)	19/37 (51%)	15/38 (39%)	11/29 (38%)
Week of First Observation	91	85	75
Life Table Tests (d)	P=0.315	P=0.259N	P=0.341
Incidental Tumor Tests (d)	P=0.503	P=0.268N	P=0.580N
Cochran-Armitage Trend Test (d)	P=0.425N		
Fisher Exact Test		P=0.243N	P=0.464N
Hematopoietic System: Leukemia			
Overall Rates (a)	23/49 (47%)	20/50 (40%)	22/50 (44%)
Adjusted Rates (b)	55.8%	45.9%	53.8%
Terminal Rates (c)	19/37 (51%)	15/38 (39%)	11/29 (38%)
Week of First Observation	91	73	75
Life Table Tests (d)	P=0.315	P=0.327N	P=0.341
Incidental Tumor Tests (d)	P=0.518N	P=0.268N	P=0.580N
Cochran-Armitage Trend Test (d)	P=0.425N		
Fisher Exact Test		P=0.311N	P=0.464N
Liver: Neoplastic Nodule			
Overall Rates (a)	3/49 (6%)	2/50 (4%)	2/49 (4%)
Adjusted Rates (b)	7.3%	5.3%	6.9%
Terminal Rates (c)	2/37 (5%)	2/38 (5%)	2/29 (7%)
Week of First Observation	81	106	106
Life Table Tests (d)	P=0.501N	P=0.490N	P=0.600N
Incidental Tumor Tests (d)	P=0.514N	P=0.504N	P=0.618N
Cochran-Armitage Trend Test (d)	P=0.406N		
Fisher Exact Test		P=0.490N	P=0.500N
Pituitary: Adenoma			
Overall Rates (a)	23/46 (50%)	19/50 (38%)	16/46 (35%)
Adjusted Rates (b)	56.9%	42.3%	43.8%
Terminal Rates (c)	18/35 (51%)	13/38 (34%)	9/28 (32%)
Week of First Observation	90	81	82
Life Table Tests (d)	P=0.269N	P=0.219N	P=0.315N
Incidental Tumor Tests (d)	P=0.147N	P=0.206N	P=0.148N
Cochran-Armitage Trend Test (d)	P=0.084N		
Fisher Exact Test		P=0.164N	P=0.103N
Pituitary: Adenoma, Adenocarcinoma, or Carcinoma			
Overall Rates (a)	23/46 (50%)	21/50 (42%)	17/46 (37%)
Adjusted Rates (b)	56.9%	46.9%	46.8%
Terminal Rates (c)	18/35 (51%)	15/38 (39%)	10/28 (36%)
Week of First Observation	90	81	82
Life Table Tests (d)	P=0.352N	P=0.338N	P=0.394N
Incidental Tumor Tests (d)	P=0.217N	P=0.335N	P=0.210N
Cochran-Armitage Trend Test (d)	P=0.123N		
Fisher Exact Test		P=0.281N	P=0.146N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Adrenal: Cortical Adenoma			
Overall Rates (a)	3/47 (6%)	3/50 (6%)	4/48 (8%)
Adjusted Rates (b)	8.1%	7.9%	13.7%
Terminal Rates (c)	3/37 (8%)	3/38 (8%)	3/28 (11%)
Week of First Observation	106	106	105
Life Table Tests (d)	P=0.287	P=0.651N	P=0.356
Incidental Tumor Tests (d)	P=0.338	P=0.651N	P=0.429
Cochran-Armitage Trend Test (d)	P=0.431		
Fisher Exact Test		P=0.631N	P=0.512
Adrenal: Cortical Adenoma or Carcinoma			
Overall Rates (a)	3/47 (6%)	4/50 (8%)	4/48 (8%)
Adjusted Rates (b)	8.1%	9.9%	13.7%
Terminal Rates (c)	3/37 (8%)	3/38 (8%)	3/28 (11%)
Week of First Observation	106	85	105
Life Table Tests (d)	P=0.291	P=0.511	P=0.356
Incidental Tumor Tests (d)	P=0.337	P=0.512	P=0.429
Cochran-Armitage Trend Test (d)	P=0.435		
Fisher Exact Test		P=0.535	P=0.512
Adrenal: Pheochromocytoma			
Overall Rates (a)	4/47 (9%)	4/50 (8%)	3/48 (6%)
Adjusted Rates (b)	10.8%	10.0%	10.7%
Terminal Rates (c)	4/37 (11%)	2/38 (5%)	3/28 (11%)
Week of First Observation	106	102	106
Life Table Tests (d)	P=0.562N	P=0.625N	P=0.651N
Incidental Tumor Tests (d)	P=0.458N	P=0.602N	P=0.651N
Cochran-Armitage Trend Test (d)	P=0.412N		
Fisher Exact Test		P=0.607N	P=0.488N
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant			
Overall Rates (a)	4/47 (9%)	6/50 (12%)	3/48 (6%)
Adjusted Rates (b)	10.8%	14.3%	10.7%
Terminal Rates (c)	4/37 (11%)	3/38 (8%)	3/28 (11%)
Week of First Observation	106	84	106
Life Table Tests (d)	P=0.568	P=0.389	P=0.651N
Incidental Tumor Tests (d)	P=0.482N	P=0.411	P=0.651N
Cochran-Armitage Trend Test (d)	P=0.416N		
Fisher Exact Test		P=0.410	P=0.488N
Thyroid: C-Cell Carcinoma			
Overall Rates (a)	3/49 (6%)	2/50 (4%)	0/47 (0%)
Adjusted Rates (b)	7.5%	4.8%	0.0%
Terminal Rates (c)	2/37 (5%)	1/38 (3%)	0/29 (0%)
Week of First Observation	106	94	--
Life Table Tests (d)	P=0.109N	P=0.501N	P=0.161N
Incidental Tumor Tests (d)	P=0.122N	P=0.521N	P=0.176N
Cochran-Armitage Trend Test (d)	P=0.086N		
Fisher Exact Test		P=0.490N	P=0.129N
Thyroid: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	5/49 (10%)	4/50 (8%)	0/47 (0%)
Adjusted Rates (b)	12.8%	9.6%	0.0%
Terminal Rates (c)	4/37 (11%)	2/38 (5%)	0/29 (0%)
Week of First Observation	91	87	--
Life Table Tests (d)	P=0.048N	P=0.497N	P=0.056N
Incidental Tumor Tests (d)	P=0.043N	P=0.510N	P=0.062N
Cochran-Armitage Trend Test (d)	P=0.032N		
Fisher Exact Test		P=0.487N	P=0.031N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Mammary Gland: Fibroadenoma			
Overall Rates (a)	21/49 (43%)	12/50 (24%)	8/50 (16%)
Adjusted Rates (b)	48.1%	30.6%	26.2%
Terminal Rates (c)	15/37 (41%)	11/38 (29%)	7/29 (24%)
Week of First Observation	81	93	100
Life Table Tests (d)	P=0.014N	P=0.046N	P=0.026N
Incidental Tumor Tests (d)	P=0.008N	P=0.045N	P=0.015N
Cochran-Armitage Trend Test (d)	P=0.002N		
Fisher Exact Test		P=0.037N	P=0.003N
Mammary Gland: Fibroadenoma or Papillary Cystadenoma			
Overall Rates (a)	(e) 21/49 (43%)	13/50 (26%)	9/50 (18%)
Adjusted Rates (b)	48.1%	33.2%	29.5%
Terminal Rates (c)	15/37 (41%)	12/38 (32%)	8/29 (28%)
Week of First Observation	81	93	100
Life Table Tests (d)	P=0.028N	P=0.070N	P=0.046N
Incidental Tumor Tests (d)	P=0.016N	P=0.070N	P=0.028N
Cochran-Armitage Trend Test (d)	P=0.004N		
Fisher Exact Test (d)		P=0.060N	P=0.006N
Mammary Gland: Adenocarcinoma			
Overall Rates (a)	0/49 (0%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	0.0%	7.3%	3.4%
Terminal Rates (c)	0/37 (0%)	2/38 (5%)	1/29 (3%)
Week of First Observation	--	85	106
Life Table Tests (d)	P=0.312	P=0.125	P=0.451
Incidental Tumor Tests (d)	P=0.297	P=0.117	P=0.451
Cochran-Armitage Trend Test (d)	P=0.384		
Fisher Exact Test		P=0.125	P=0.505
Mammary Gland: Fibroadenoma, Papillary Cystadenoma, or Adenocarcinoma			
Overall Rates (a)	(e) 21/49 (43%)	15/50 (30%)	10/50 (20%)
Adjusted Rates (b)	48.1%	37.1%	32.9%
Terminal Rates (c)	15/37 (41%)	13/38 (34%)	9/29 (31%)
Week of First Observation	81	85	100
Life Table Tests (d)	P=0.054N	P=0.148N	P=0.076N
Incidental Tumor Tests (d)	P=0.035N	P=0.151N	P=0.050N
Cochran-Armitage Trend Test (d)	P=0.009N		
Fisher Exact Test (d)		P=0.131N	P=0.012N
Clitoral Gland: Adenoma			
Overall Rates (a)	4/49 (8%)	5/50 (10%)	4/50 (8%)
Adjusted Rates (b)	10.8%	13.2%	13.8%
Terminal Rates (c)	4/37 (11%)	5/38 (13%)	4/29 (14%)
Week of First Observation	106	106	106
Life Table Tests (d)	P=0.426	P=0.517	P=0.505
Incidental Tumor Tests (d)	P=0.426	P=0.517	P=0.505
Cochran-Armitage Trend Test (d)	P=0.558N		
Fisher Exact Test		P=0.513	P=0.631N
Clitoral Gland: Adenoma or Cystadenoma			
Overall Rates (a)	4/49 (8%)	6/50 (12%)	4/50 (8%)
Adjusted Rates (b)	10.8%	15.8%	13.8%
Terminal Rates (c)	4/37 (11%)	6/38 (16%)	4/29 (14%)
Week of First Observation	106	106	106
Life Table Tests (d)	P=0.418	P=0.385	P=0.505
Incidental Tumor Tests (d)	P=0.418	P=0.385	P=0.505
Cochran-Armitage Trend Test (d)	P=0.556N		
Fisher Exact Test		P=0.383	P=0.631N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Clitoral Gland: Carcinoma			
Overall Rates (a)	4/49 (8%)	1/50 (2%)	5/50 (10%)
Adjusted Rates (b)	10.3%	2.6%	17.2%
Terminal Rates (c)	3/37 (8%)	1/38 (3%)	5/29 (17%)
Week of First Observation	94	106	106
Life Table Tests (d)	P=0.308	P=0.177N	P=0.361
Incidental Tumor Tests (d)	P=0.349	P=0.175N	P=0.411
Cochran-Armitage Trend Test (d)	P=0.431		
Fisher Exact Test		P=0.175N	P=0.513
Clitoral Gland: Carcinoma or Adenocarcinoma			
Overall Rates (a)	4/49 (8%)	2/50 (4%)	6/50 (12%)
Adjusted Rates (b)	10.3%	5.3%	20.7%
Terminal Rates (c)	3/37 (8%)	2/38 (5%)	6/29 (21%)
Week of First Observation	94	106	106
Life Table Tests (d)	P=0.184	P=0.330N	P=0.236
Incidental Tumor Tests (d)	P=0.213	P=0.328N	P=0.275
Cochran-Armitage Trend Test (d)	P=0.300		
Fisher Exact Test		P=0.329N	P=0.383
Clitoral Gland: Adenoma, Cystadenoma, Adenocarcinoma, or Carcinoma			
Overall Rates (a)	8/49 (16%)	8/50 (16%)	10/50 (20%)
Adjusted Rates (b)	20.8%	21.1%	34.5%
Terminal Rates (c)	7/37 (19%)	8/38 (21%)	10/29 (34%)
Week of First Observation	94	106	106
Life Table Tests (d)	P=0.167	P=0.589N	P=0.201
Incidental Tumor Tests (d)	P=0.187	P=0.587N	P=0.229
Cochran-Armitage Trend Test (d)	P=0.363		
Fisher Exact Test		P=0.590N	P=0.416
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	6/49 (12%)	9/50 (18%)	12/49 (24%)
Adjusted Rates (b)	16.2%	23.0%	36.2%
Terminal Rates (c)	6/37 (16%)	8/38 (21%)	9/29 (31%)
Week of First Observation	106	102	82
Life Table Tests (d)	P=0.024	P=0.307	P=0.035
Incidental Tumor Tests (d)	P=0.035	P=0.304	P=0.045
Cochran-Armitage Trend Test (d)	P=0.075		
Fisher Exact Test		P=0.303	P=0.096

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle 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 vehicle 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 exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) An adenoma, NOS, was also observed in an animal with a fibroadenoma.

TABLE B4. HISTORICAL INCIDENCE OF UTERINE ENDOMETRIAL STROMAL TUMORS IN FEMALE F344/N RATS (a)

Study	Incidence in Controls		
	Polyp	Sarcoma	Polyp or Sarcoma
Historical Incidence in All Water Vehicle Controls			
THPS (b)	6/49	0/49	6/49
THPC (b)	10/50	0/50	10/50
Chlorpheniramine maleate (b)	11/49	0/49	11/49
TOTAL	27/148 (18.2%)	0/148 (0.0%)	27/148 (18.2%)
SD (c)	5.33%	0.0%	5.33%
Range (d)			
High	11/49	0/50	11/49
Low	6/49	0/50	6/49
Overall Historical Incidence in Untreated Controls			
TOTAL	383/1,750 (21.9%)	15/1/750 (0.9%)	396/1,750 (22.6%)
SD (c)	7.57%	1.58%	7.61%
Range (d)			
High	18/49	3/48	18/49
Low	4/50	0/87	4/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Battelle Columbus Laboratories
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS

	Vehicle Control	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)
Wound, NOS		1 (2%)	2 (4%)
Epidermal inclusion cyst			1 (2%)
Ulcer, NOS	1 (2%)		1 (2%)
Ulcer, acute		1 (2%)	
*Subcutaneous tissue	(49)	(50)	(50)
Inflammation, active chronic		1 (2%)	
Inflammation, chronic focal			1 (2%)
Necrosis, ischemic		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(49)	(50)	(49)
Aspiration, foreign body		2 (4%)	
Ectopia			1 (2%)
Emphysema, alveolar			1 (2%)
Congestion, NOS			1 (2%)
Congestion, acute	4 (8%)	4 (8%)	2 (4%)
Edema, NOS		1 (2%)	
Hemorrhage	1 (2%)		
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, interstitial	1 (2%)	1 (2%)	
Inflammation, acute/chronic			1 (2%)
Pneumonia, interstitial chronic	3 (6%)		
Inflammation, granulomatous focal	1 (2%)	3 (6%)	
Alveolar macrophages	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, alveolar epithelium	1 (2%)	2 (4%)	1 (2%)
#Lung/alveoli	(49)	(50)	(49)
Lymphocytic inflammatory infiltrate		1 (2%)	
HEMATOPOIETIC SYSTEM			
#Bone marrow	(49)	(50)	(48)
Necrosis, ischemic			1 (2%)
Myelofibrosis	2 (4%)	7 (14%)	4 (8%)
Hyperplasia, hematopoietic	1 (2%)		
Hyperplasia, granulocytic		4 (8%)	2 (4%)
Hyperplasia, reticulum cell	2 (4%)		
Aplasia, hematopoietic			1 (2%)
#Spleen	(49)	(50)	(49)
Hemorrhage, chronic	1 (2%)		
Inflammation, granulomatous focal	2 (4%)		
Depletion, lymphoid			1 (2%)
#Splenic capsule	(49)	(50)	(49)
Rupture	1 (2%)		
#Splenic follicles	(49)	(50)	(49)
Depletion, lymphoid	2 (4%)		
#Splenic red pulp	(49)	(50)	(49)
Inflammation, granulomatous focal		2 (4%)	
Fibrosis, multifocal			1 (2%)
Pigmentation, NOS			1 (2%)
#Perisplenic region	(49)	(50)	(49)
Hemorrhage, chronic	1 (2%)		
Inflammation, chronic focal	1 (2%)		

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Lymph node	(46)	(50)	(47)
Plasmacytosis		1 (2%)	
#Mandibular lymph node	(46)	(50)	(47)
Cyst, NOS	2 (4%)		
Multiple cysts		1 (2%)	
Congestion, NOS	1 (2%)		
Hemorrhage	5 (11%)	5 (10%)	8 (17%)
Inflammation, active chronic	1 (2%)		1 (2%)
Inflammation, granulomatous focal		1 (2%)	1 (2%)
Plasmacytosis	38 (83%)	37 (74%)	37 (79%)
#Pancreatic lymph node	(46)	(50)	(47)
Congestion, NOS	1 (2%)		
Inflammation, granulomatous focal	1 (2%)		
#Mesenteric lymph node	(46)	(50)	(47)
Inflammation, granulomatous focal	1 (2%)		1 (2%)
Plasmacytosis	1 (2%)		
Hematopoiesis		1 (2%)	
#Renal lymph node	(46)	(50)	(47)
Inflammation, granulomatous focal		1 (2%)	
#Inguinal lymph node	(46)	(50)	(47)
Cyst, NOS	1 (2%)		
#Thymic lymph node	(46)	(50)	(47)
Hemorrhage		3 (6%)	1 (2%)
Inflammation, chronic focal		1 (2%)	
Inflammation, granulomatous focal	2 (4%)	3 (6%)	2 (4%)
Plasmacytosis			2 (4%)
#Thymus	(48)	(45)	(43)
Necrosis, diffuse			1 (2%)
Depletion, lymphoid	1 (2%)	2 (4%)	
Hyperplasia, epithelial	1 (2%)		
#Thymic cortex	(48)	(45)	(43)
Necrosis, diffuse			1 (2%)
Depletion, lymphoid			2 (5%)
#Thymic medulla	(48)	(45)	(43)
Hyperplasia, epithelial	1 (2%)	1 (2%)	
CIRCULATORY SYSTEM			
#Right atrium	(49)	(50)	(49)
Dilatation, NOS	2 (4%)	2 (4%)	
#Left ventricle	(49)	(50)	(49)
Thrombus, mural	1 (2%)		
#Myocardium	(49)	(50)	(49)
Degeneration, NOS	44 (90%)	42 (84%)	37 (76%)
#Myocardium of right atrium	(49)	(50)	(49)
Degeneration, NOS	2 (4%)		
*Coronary artery	(49)	(50)	(50)
Perivasculitis		1 (2%)	
*Mesenteric artery	(49)	(50)	(50)
Aneurysm			1 (2%)
#Uterus	(49)	(50)	(49)
Thrombosis, NOS		1 (2%)	
#Uterine serosa	(49)	(50)	(49)
Aneurysm	1 (2%)		
Thrombus, organized	1 (2%)		

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM			
*Mucosa of tongue	(49)	(50)	(50)
Hyperkeratosis			1 (2%)
Acanthosis			1 (2%)
#Salivary gland	(49)	(50)	(46)
Dilatation/ducts			1 (2%)
Atrophy, focal		1 (2%)	
#Liver	(49)	(50)	(49)
Inflammation, granulomatous focal	26 (53%)	17 (34%)	19 (39%)
Necrosis, focal			1 (2%)
Basophilic cyto change	37 (76%)	39 (78%)	20 (41%)
Eosinophilic cyto change		1 (2%)	
Clear cell change	1 (2%)	1 (2%)	4 (8%)
Hyperplasia, focal	1 (2%)		
#Periportal bile duct	(49)	(50)	(49)
Inflammation, acute/chronic	1 (2%)		
#Liver/centrilobular	(49)	(50)	(49)
Congestion, chronic passive	1 (2%)		
Necrosis, focal		1 (2%)	
#Liver/periportal	(49)	(50)	(49)
Lymphocytic inflammatory infiltrate			1 (2%)
Cytoplasmic vacuolization		1 (2%)	6 (12%)
#Liver/hepatocytes	(49)	(50)	(49)
Necrosis, focal	1 (2%)	1 (2%)	1 (2%)
Cytoplasmic vacuolization	1 (2%)	2 (4%)	2 (4%)
#Bile duct	(49)	(50)	(49)
Inflammation, chronic focal		1 (2%)	1 (2%)
Hyperplasia, focal	27 (55%)	32 (64%)	25 (51%)
Hyperplasia, cystic			1 (2%)
#Pancreas	(48)	(50)	(48)
Inflammation, chronic focal	1 (2%)		
Atrophy, focal	2 (4%)		
#Pancreatic duct	(48)	(50)	(48)
Inflammation, acute/chronic			1 (2%)
#Pancreatic acinus	(48)	(50)	(48)
Atrophy, focal	11 (23%)	17 (34%)	11 (23%)
#Stomach	(46)	(48)	(44)
Inflammation, acute focal	1 (2%)		
#Gastric fundal gland	(46)	(48)	(44)
Hyperplasia, focal	1 (2%)		
#Gastric submucosa	(46)	(48)	(44)
Inflammation, active chronic	1 (2%)		
#Cardiac stomach	(46)	(48)	(44)
Hyperkeratosis		1 (2%)	1 (2%)
Acanthosis		1 (2%)	1 (2%)
#Gastric fundus	(46)	(48)	(44)
Ulcer, acute			1 (2%)
Inflammation, chronic focal	1 (2%)		
#Colon	(46)	(48)	(45)
Parasitism	3 (7%)		
#Cecum	(46)	(48)	(45)
Inflammation, active chronic			1 (2%)
URINARY SYSTEM			
#Kidney	(48)	(49)	(48)
Hydronephrosis		2 (4%)	
Inflammation, active chronic			1 (2%)
Nephropathy	41 (85%)	36 (73%)	37 (77%)
Nephrosis, NOS	1 (2%)		
Infarct, focal			1 (2%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM (Continued)			
#Kidney/cortex	(48)	(49)	(48)
Cyst, NOS			1 (2%)
Multiple cysts		1 (2%)	
#Kidney/medulla	(48)	(49)	(48)
Mineralization		1 (2%)	
#Kidney/tubule	(48)	(49)	(48)
Pigmentation, NOS			1 (2%)
*Ureter	(49)	(50)	(50)
Dilatation, NOS		1 (2%)	
Hyperplasia, epithelial		1 (2%)	
ENDOCRINE SYSTEM			
#Anterior pituitary	(46)	(50)	(46)
Embryonal duct cyst	1 (2%)		
Cyst, NOS		3 (6%)	4 (9%)
Multiple cysts	7 (15%)	11 (22%)	3 (7%)
Hemorrhage		1 (2%)	
Hemorrhagic cyst	4 (9%)	2 (4%)	4 (9%)
Necrosis, focal		1 (2%)	
Hyperplasia, focal	8 (17%)	15 (30%)	14 (30%)
Angiectasis	1 (2%)	1 (2%)	
#Adrenal/capsule	(47)	(50)	(48)
Ectopia		2 (4%)	
Cytoplasmic vacuolization	1 (2%)		
#Adrenal cortex	(47)	(50)	(48)
Congestion, NOS		1 (2%)	
Hemorrhage	1 (2%)		
Necrosis, focal		2 (4%)	4 (8%)
Necrosis, diffuse		1 (2%)	
Cytoplasmic vacuolization	10 (21%)	11 (22%)	12 (25%)
Basophilic cyto change	1 (2%)		
Focal cellular change	2 (4%)	2 (4%)	3 (6%)
Eosinophilic cyto change		1 (2%)	
Cytologic alteration, NOS			1 (2%)
Cell size alteration	1 (2%)	1 (2%)	
Hyperplasia, focal	12 (26%)	9 (18%)	7 (15%)
#Adrenal medulla	(47)	(50)	(48)
Hyperplasia, focal	2 (4%)	1 (2%)	5 (10%)
#Thyroid	(49)	(50)	(47)
Hyperplasia, C-cell	27 (55%)	23 (46%)	24 (51%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(49)	(50)	(50)
Dilatation/ducts		2 (4%)	1 (2%)
Galactocele	2 (4%)	2 (4%)	2 (4%)
Hyperplasia, cystic	27 (55%)	22 (44%)	27 (54%)
*Mammary acinus	(49)	(50)	(50)
Hyperplasia, stromal		1 (2%)	
*Clitoral gland	(49)	(50)	(50)
Cyst, NOS		1 (2%)	
Multiple cysts		1 (2%)	
Cystic ducts	1 (2%)	4 (8%)	1 (2%)
Ulcer, NOS	1 (2%)		
Inflammation, active chronic	4 (8%)	2 (4%)	3 (6%)
Inflammation, chronic focal	3 (6%)	1 (2%)	1 (2%)
Hyperplasia, NOS	1 (2%)		
Hyperplasia, focal		3 (6%)	2 (4%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
#Uterus	(49)	(50)	(49)
Dilatation, NOS	7 (14%)	8 (16%)	14 (29%)
Hemorrhage		1 (2%)	
Hyperplasia, epithelial		1 (2%)	
Angiectasis		1 (2%)	1 (2%)
#Cervix uteri	(49)	(50)	(49)
Diverticulum			2 (4%)
Fibrosis, multifocal			1 (2%)
#Endometrial gland	(49)	(50)	(49)
Dilatation, NOS	3 (6%)		
Cyst, NOS		2 (4%)	
Multiple cysts		3 (6%)	1 (2%)
Hyperplasia, cystic	17 (35%)	29 (58%)	23 (47%)
#Endometrial stroma	(49)	(50)	(49)
Inflammation, active chronic	1 (2%)		
#Fallopian tube	(49)	(50)	(49)
Dilatation, NOS		1 (2%)	
#Ovary	(49)	(50)	(49)
Follicular cyst, NOS	2 (4%)	1 (2%)	1 (2%)
Parovarian cyst		2 (4%)	2 (4%)
Congestion, NOS	1 (2%)		1 (2%)
Inflammation, granulomatous focal			1 (2%)
Pigmentation, NOS		1 (2%)	
#Ovary/follicle	(49)	(50)	(49)
Multiple cysts			1 (2%)
NERVOUS SYSTEM			
#Cerebral ventricle	(49)	(50)	(47)
Hydrocephalus, NOS		1 (2%)	1 (2%)
#Cerebrum	(49)	(50)	(47)
Hydrocephalus, NOS		1 (2%)	
Atrophy, pressure	2 (4%)	4 (8%)	4 (9%)
#Corpus callosum	(49)	(50)	(47)
Hemorrhage			1 (2%)
Malacia			1 (2%)
#Medulla oblongata	(49)	(50)	(47)
Hemorrhage			1 (2%)
SPECIAL SENSE ORGANS			
*Eye/retina	(49)	(50)	(50)
Atrophy, focal	1 (2%)	1 (2%)	3 (6%)
Atrophy, diffuse	3 (6%)		1 (2%)
*Eye/crystalline lens	(49)	(50)	(50)
Cataract	3 (6%)	2 (4%)	2 (4%)
*Harderian gland	(49)	(50)	(50)
Hyperplasia, epithelial		4 (8%)	
MUSCULOSKELETAL SYSTEM			
*Femur	(49)	(50)	(50)
Osteosclerosis	13 (27%)	20 (40%)	6 (12%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
BODY CAVITIES			
*Mediastinum	(49)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
*Epicardium	(49)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
*Mesentery	(49)	(50)	(50)
Inflammation, granulomatous focal	1 (2%)		1 (2%)
ALL OTHER SYSTEMS			
Orbital region			
Hemorrhage	1		
SPECIAL MORPHOLOGY SUMMARY			
Accidental death	1		
Auto/necropsy/histo perf			1

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE

IN THE TWO-YEAR GAVAGE STUDY OF THPS

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS

	Vehicle Control	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	2 (4%)		1 (2%)
Squamous cell carcinoma		1 (2%)	
Fibrosarcoma		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS	3 (6%)	4 (8%)	4 (8%)
Fibroma	2 (4%)	3 (6%)	2 (4%)
Fibrosarcoma	8 (16%)	3 (6%)	13 (26%)
Fibrosarcoma, invasive	1 (2%)		
Fibrosarcoma, unclear primary or metastatic	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(49)
Hepatocellular carcinoma, metastatic	3 (6%)	2 (4%)	2 (4%)
Alveolar/bronchiolar adenoma	5 (10%)	4 (8%)	6 (12%)
Alveolar/bronchiolar carcinoma	2 (4%)	6 (12%)	3 (6%)
Papillary adenocarcinoma, metastatic		1 (2%)	
Fibrosarcoma, metastatic	3 (6%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, undiffer type		1 (2%)	
Malignant lymphoma, lymphocytic type	2 (4%)		
Malignant lymphoma, histiocytic type		3 (6%)	
Malignant lymphoma, mixed type		5 (10%)	
Undifferentiated leukemia		1 (2%)	1 (2%)
#Mandibular lymph node	(36)	(47)	(45)
Papillary adenocarcinoma, metastatic		1 (2%)	
CIRCULATORY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)
#Bone marrow	(49)	(49)	(50)
Hemangiosarcoma		1 (2%)	
#Spleen	(48)	(49)	(49)
Hemangiosarcoma			1 (2%)
#Renal lymph node	(36)	(47)	(45)
Hemangiosarcoma	1 (3%)		
#Heart	(50)	(49)	(50)
Fibrosarcoma, metastatic	1 (2%)		
#Myocardium	(50)	(49)	(50)
Hemangiosarcoma	1 (2%)		
#Liver	(48)	(49)	(50)
Hemangiosarcoma	3 (6%)		1 (2%)
DIGESTIVE SYSTEM			
#Liver	(48)	(49)	(50)
Hepatocellular adenoma	9 (19%)	6 (12%)	4 (8%)
Hepatocellular carcinoma	10 (21%)	8 (16%)	13 (26%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Forestomach	(41)	(48)	(46)
Squamous cell papilloma		1 (2%)	
#Cardiac stomach	(41)	(48)	(46)
Squamous cell papilloma			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(48)	(49)
Fibrosarcoma, metastatic	1 (2%)		
#Kidney/cortex	(50)	(48)	(49)
Sarcoma, NOS, metastatic		1 (2%)	
ENDOCRINE SYSTEM			
#Adrenal	(49)	(48)	(49)
Cortical adenoma		2 (4%)	
#Adrenal/capsule	(49)	(48)	(49)
Adenoma, NOS	2 (4%)	3 (6%)	
#Adrenal medulla	(49)	(48)	(49)
Pheochromocytoma	4 (8%)	1 (2%)	7 (14%)
#Thyroid	(50)	(50)	(49)
Follicular cell adenoma	1 (2%)	2 (4%)	1 (2%)
Papillary cystadenoma, NOS	1 (2%)		
REPRODUCTIVE SYSTEM			
#Testis	(47)	(50)	(50)
Interstitial cell tumor			1 (2%)
Neurilemoma		1 (2%)	
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	1 (2%)	1 (2%)	
Papillary adenocarcinoma	1 (2%)	1 (2%)	1 (2%)
*Zymbal gland	(50)	(50)	(50)
Squamous cell carcinoma	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*Carpometacarpal joint	(50)	(50)	(50)
Giant cell tumor/tendon sheath	1 (2%)		
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)		1 (2%)
Sarcoma, NOS, metastatic		1 (2%)	

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	19	10	14
Moribund sacrifice	8	9	13
Terminal sacrifice	23	31	23
TUMOR SUMMARY			
Total animals with primary tumors**	33	38	38
Total primary tumors	62	60	62
Total animals with benign tumors	21	18	19
Total benign tumors	27	24	23
Total animals with malignant tumors	27	29	31
Total malignant tumors	33	36	39
Total animals with secondary tumors##	6	4	2
Total secondary tumors	9	6	2
Total animals with tumors uncertain-- benign or malignant	1		
Total uncertain tumors	1		
Total animals with tumors uncertain-- primary or metastatic	1		
Total uncertain tumors	1		

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS: VEHICLE CONTROL

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	105	099	089	105	037	105	105	105	023	101	090	085	105	086	066	105	074	105	102	036	105	022	090	072	088
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+
Sarcoma, NOS																			X						
Fibroma																									
Fibrosarcoma				X							X	X		X											X
Fibrosarcoma, invasive														X											
Fibrosarcoma, unclear primary or metastatic												X													
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																							X		
Alveolar/bronchiolar adenoma						X								X					X						
Alveolar/bronchiolar carcinoma				X																					
Fibrosarcoma, metastatic											X	X		X											
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	−	−	+	−	−	+	+	−	−	−	+	+	+	+	+	+	+	+	−	+	+	+	−	+
Hemangiosarcoma																									
Thymus	−	−	−	−	−	−	−	+	+	+	+	−	−	−	+	+	−	−	+	+	+	−	+	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic											X														
Hemangiosarcoma													X												
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma	X						X						X												
Hepatocellular carcinoma										X								X		X			X		
Hemangiosarcoma																									
Bile duct	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	N	+	N	+	N	+	N	N	+	N	+	N	N	+	+	+	+	+	+	N	N	N	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	−	+	−	+	+	+	+	+	+	+	+	+	−	+	−	+	+	−	+	−	+	−	+
Small intestine	+	+	+	+	−	+	+	+	+	−	+	+	+	+	−	+	−	+	−	−	+	+	+	−	+
Large intestine	+	+	−	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	−	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic												X													
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	−	−	−	+	−	−	+	+	−	+	+	−	+	+	−	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																		X							
Pheochromocytoma																		X							
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Papillary cystadenoma, NOS																									
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	N	N	N	N
Testis	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
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
Papillary adenocarcinoma																					X				
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
Squamous cell carcinoma																									
MUSCULOSKELETAL SYSTEM																									
Joint	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
Giant cell tumor/tendon sheath										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						X																			
Malignant lymphoma, lymphocytic type									X												X				

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 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: TISSUES TUMORS
WEEKS ON STUDY	062	105	105	105	030	090	105	105	105	105	054	105	045	095	083	105	105	091	105	105	102	105	103	105	091	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma		X																	X							2
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS						X								X												3
Fibroma																X	X									2
Fibrosarcoma								X										X	X							8
Fibrosarcoma, invasive																										1
Fibrosarcoma, unclear primary or meta																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																X							X		3	
Alveolar/bronchiolar adenoma				X													X									5
Alveolar/bronchiolar carcinoma									X																	2
Fibrosarcoma, metastatic																										3
Trachea	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+		48
Lymph nodes	−	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	−	+		36
Hemangiosarcoma															X											1
Thymus	+	+	−	−	−	+	−	+	+	+	+	−	−	+	+	+	+	−	+	+	+	+	−	+	+	27
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic																										1
Hemangiosarcoma																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+		48
Hepatocellular adenoma						X	X	X	X								X		X							9
Hepatocellular carcinoma								X								X		X		X			X		X	10
Hemangiosarcoma												X			X				X							3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+		48
Gallbladder & common bile duct	+	+	+	N	+	N	+	N	+	+	+	+	N	+	+	N	N	N	+	+	N	+	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	41
Small intestine	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	−	+	−	+	−	37
Large intestine	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	42
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic																										1
Urinary bladder	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	47
ENDOCRINE SYSTEM																										
Pituitary	−	+	−	+	+	+	+	−	−	+	+	+	+	−	+	+	+	−	−	+	+	+	+	+	+	35
Adrenal	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS									X																	2
Pheochromocytoma							X							X									X			4
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma									X																	1
Papillary cystadenoma, NOS												X														1
Parathyroid	+	+	+	+	−	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	−	27
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	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	47
Prostate	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	46
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	*50
Adenoma, NOS																										1
Papillary adenocarcinoma																										1
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	*50
Squamous cell carcinoma																	X									1
MUSCULOSKELETAL SYSTEM																										
Joint	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
Giant cell tumor/tendon sheath																										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
Sarcoma, NOS																										1
Malignant lymphoma, lymphocytic type																										2

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS: LOW DOSE

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025
WEEKS ON STUDY	105	001	105	078	105	105	054	105	105	105	083	105	102	105	097	105	105	103	102	105	105	105	105	105	103
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																					X				
Fibrosarcoma										X															
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS											X			X	X										
Fibroma																		X							
Fibrosarcoma								X@	X																
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																									
Alveolar/bronchiolar adenoma												X	X												
Alveolar/bronchiolar carcinoma																			X					X	
Papillary adenocarcinoma, metastatic																						X			
Trachea	+	+	+	+	−	+	−	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Hemangiosarcoma																					X				
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Papillary adenocarcinoma, metastatic																						X			
Thymus	+	−	+	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Hepatocellular adenoma			X													X								X	
Hepatocellular carcinoma					X											X		X						X	
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	N	+	+	+	N	+	+	+	+	+	+	N	N	+	N	N	+	+	+	+	+	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Squamous cell papilloma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	−
Large intestine	+	+	+	+	+	−	+	−	+	+	+	−	−	−	+	−	+	+	−	+	+	+	+	+	−
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Sarcoma, NOS, metastatic																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	−	+	−	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Adenoma, NOS																									
Cortical adenoma																		X							
Pheochromocytoma													X											•	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma						X														X					
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	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma																									
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																
Papillary adenocarcinoma																						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, undiffer type																									
Malignant lymphoma, histiocytic type							X					X													
Malignant lymphoma, mixed type				X	X													X							
Undifferentiated leukemia																									

@: Multiple occurrence of morphology

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW 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	096	105	105	105	105	105	105	068	105	083	105	081	083	077	055	105	082	105	047	105	105	074	105	105	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell carcinoma																										1
Fibrosarcoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS						X																				4
Fibroma					X		X																			3
Fibrosarcoma		X																								3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic						X			X																	2
Alveolar/bronchiolar adenoma													X								X					4
Alveolar/bronchiolar carcinoma					X			X									X							X		6
Papillary adenocarcinoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	−	+	+	+	+	+	42
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	47
Papillary adenocarcinoma, metastatic																										1
Thymus	+	+	+	+	+	−	+	+	−	+	+	+	+	−	+	−	+	−	−	+	+	+	+	+	+	38
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma												X												X	X	6
Hepatocellular carcinoma						X			X													X	X			8
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	N	N	+	+	+	N	+	N	+	+	N	N	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell papilloma	X																									1
Small intestine	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	45
Large intestine	−	+	+	+	−	+	+	+	+	+	−	−	+	−	+	+	−	+	+	+	+	+	+	−	+	35
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	48
Sarcoma, NOS, metastatic						X																				1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	42
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS	X						X	X																		3
Cortical adenoma					X																					2
Pheochromocytoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										2
Parathyroid	−	−	+	+	+	+	+	+	−	−	+	−	−	−	−	−	+	−	−	−	+	+	+	−	−	29
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	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma																									X	1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
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	*50
Adenoma, NOS																										1
Papillary adenocarcinoma																										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
Sarcoma, NOS, metastatic																										1
Malignant lymphoma, undiffer type													X													1
Malignant lymphoma, histiocytic type														X												3
Malignant lymphoma, mixed type										X							X									5
Undifferentiated leukemia											X															1

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS: 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	090	077	090	092	078	105	105	105	102	105	100	105	093	105	102	105	105	099	079	105	045	105	105	105	103
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+
Sarcoma, NOS		X																		X					
Fibroma				X																					
Fibrosarcoma	X				X				X				X			X									
Hemangiosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic				X																					
Alveolar/bronchiolar adenoma														X						X					X
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph nodes	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Thymus	+	−	−	+	+	+	+	+	+	+	+	−	−	+	−	−	+	−	−	+	−	+	−	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																								X	
Hepatocellular carcinoma			X	X					X						X			X	X						X
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	N	+	+	+	+	N	+	+	+	+	+	N	+	+	+	N	+	N	+	+	+	N
Pancreas	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Squamous cell papilloma																									
Small intestine	+	+	+	−	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	−
Large intestine	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	−	+	+	+	−	+	+	−	−	+	−	+	+	+	+	+	+	+	+	−	+	+	−	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Pheochromocytoma										X		X			X									X	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
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	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
Papillary adenocarcinoma												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																									
Undifferentiated leukemia			X																						

TABLE C2. 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	098	105	091	102	105	105	105	105	096	100	088	099	105	082	105	104	105	052	079	105	081	105	025	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	*50
Squamous cell papilloma						X																				1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	*50
Sarcoma, NOS	X		X																							4
Fibroma											X															2
Fibrosarcoma						X		X	X	X	X	X	X		X											13
Hemangiosarcoma																								X		1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	49
Hepatocellular carcinoma, metastatic																							X			2
Alveolar/bronchiolar adenoma							X						X									X				6
Alveolar/bronchiolar carcinoma									X		X													X		3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	49
Hemangiosarcoma					X																					1
Lymph nodes	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	45
Thymus	+	+	+	+	+	+	+	−	+	−	+	−	+	+	−	+	+	−	+	−	−	+	+	+	+	32
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma							X										X	X								4
Hepatocellular carcinoma		X			X											X					X	X	X			13
Hemangiosarcoma									X																	1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	N	+	N	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	N	N	N	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	46
Squamous cell papilloma																							X			1
Small intestine	+	+	−	+	+	+	+	+	−	−	+	−	+	−	+	+	+	+	+	+	−	+	−	+	+	38
Large intestine	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	44
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	49
Urinary bladder	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	−	+	+	+	40
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma				X								X												X		7
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	49
Follicular cell adenoma																		X								1
Parathyroid	+	−	−	+	+	+	+	+	+	+	−	−	+	+	+	−	+	+	−	−	−	−	+	+	−	29
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	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor							X																			1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	*50
Papillary adenocarcinoma																										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	X	N	N	N	*50
Sarcoma, NOS																										1
Undifferentiated leukemia																										1

* Animals necropsied

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS

	Vehicle Control	5 mg/kg	10 mg/kg
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	8.7%	9.3%	5.5%
Terminal Rates (c)	2/23 (9%)	2/31 (6%)	0/24 (0%)
Week of First Observation	105	103	92
Life Table Tests (d)	P=0.554N	P=0.636	P=0.643N
Incidental Tumor Tests (d)	P=0.498N	P=0.608	P=0.635N
Cochran-Armitage Trend Test (d)	P=0.594		
Fisher Exact Test		P=0.500	P=0.691
Subcutaneous Tissue: Sarcoma			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	9.9%	11.3%	12.9%
Terminal Rates (c)	0/23 (0%)	2/31 (6%)	2/24 (8%)
Week of First Observation	90	83	70
Life Table Tests (d)	P=0.485	P=0.612	P=0.570
Incidental Tumor Tests (d)	P=0.536	P=0.440	P=0.590
Cochran-Armitage Trend Test (d)	P=0.424		
Fisher Exact Test		P=0.500	P=0.500
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	8/50 (16%)	3/50 (6%)	13/50 (26%)
Adjusted Rates (b)	24.8%	9.0%	37.3%
Terminal Rates (c)	3/23 (13%)	2/31 (6%)	5/24 (21%)
Week of First Observation	85	96	78
Life Table Tests (d)	P=0.166	P=0.061N	P=0.259
Incidental Tumor Tests (d)	P=0.174	P=0.149N	P=0.227
Cochran-Armitage Trend Test (d)	P=0.110		
Fisher Exact Test		P=0.100N	P=0.163
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	10/50 (20%)	6/50 (12%)	14/50 (28%)
Adjusted Rates (b)	32.3%	17.8%	39.0%
Terminal Rates (c)	5/23 (22%)	4/31 (13%)	5/24 (21%)
Week of First Observation	85	96	78
Life Table Tests (d)	P=0.272	P=0.105N	P=0.358
Incidental Tumor Tests (d)	P=0.294	P=0.225N	P=0.317
Cochran-Armitage Trend Test (d)	P=0.191		
Fisher Exact Test		P=0.207N	P=0.241
Integumentary System: Fibrosarcoma			
Overall Rates (a)	8/50 (16%)	4/50 (8%)	13/50 (26%)
Adjusted Rates (b)	24.8%	12.1%	37.3%
Terminal Rates (c)	3/23 (13%)	3/31 (10%)	5/24 (21%)
Week of First Observation	85	96	78
Life Table Tests (d)	P=0.170	P=0.108N	P=0.259
Incidental Tumor Tests (d)	P=0.179	P=0.235N	P=0.227
Cochran-Armitage Trend Test (d)	P=0.114		
Fisher Exact Test		P=0.178N	P=0.163
Integumentary System: Fibroma or Fibrosarcoma			
Overall Rates (a)	10/50 (20%)	7/50 (14%)	14/50 (28%)
Adjusted Rates (b)	32.3%	20.9%	39.0%
Terminal Rates (c)	5/23 (22%)	5/31 (16%)	5/24 (21%)
Week of First Observation	85	96	78
Life Table Tests (d)	P=0.275	P=0.157N	P=0.358
Incidental Tumor Tests (d)	P=0.297	P=0.308N	P=0.317
Cochran-Armitage Trend Test (d)	P=0.194		
Fisher Exact Test		P=0.298N	P=0.241

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Integumentary System: Sarcoma or Fibrosarcoma			
Overall Rates (a)	11/50 (22%)	8/50 (16%)	17/50 (34%)
Adjusted Rates (b)	32.3%	22.6%	46.7%
Terminal Rates (c)	3/23 (13%)	5/31 (16%)	7/24 (29%)
Week of First Observation	85	83	77
Life Table Tests (d)	P=0.175	P=0.177N	P=0.251
Incidental Tumor Tests (d)	P=0.189	P=0.408N	P=0.214
Cochran-Armitage Trend Test (d)	P=0.099		
Fisher Exact Test (d)		P=0.306N	P=0.133
Integumentary System: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	13/50 (26%)	11/50 (22%)	18/50 (36%)
Adjusted Rates (b)	39.0%	30.8%	48.2%
Terminal Rates (c)	5/23 (22%)	7/31 (23%)	7/24 (29%)
Week of First Observation	85	83	77
Life Table Tests (d)	P=0.260	P=0.214N	P=0.335
Incidental Tumor Tests (d)	P=0.291	P=0.456N	P=0.293
Cochran-Armitage Trend Test (d)	P=0.158		
Fisher Exact Test (d)		P=0.408N	P=0.194
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	5/50 (10%)	4/50 (8%)	6/49 (12%)
Adjusted Rates (b)	18.6%	11.3%	21.8%
Terminal Rates (c)	3/23 (13%)	2/31 (6%)	4/24 (17%)
Week of First Observation	86	81	88
Life Table Tests (d)	P=0.475	P=0.356N	P=0.545
Incidental Tumor Tests (d)	P=0.514	P=0.490N	P=0.576
Cochran-Armitage Trend Test (d)	P=0.420		
Fisher Exact Test		P=0.500N	P=0.486
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	2/50 (4%)	6/50 (12%)	3/49 (6%)
Adjusted Rates (b)	8.7%	18.5%	11.0%
Terminal Rates (c)	2/23 (9%)	5/31 (16%)	2/24 (8%)
Week of First Observation	105	102	96
Life Table Tests (d)	P=0.455	P=0.247	P=0.536
Incidental Tumor Tests (d)	P=0.519	P=0.230	P=0.577
Cochran-Armitage Trend Test (d)	P=0.413		
Fisher Exact Test		P=0.134	P=0.490
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	7/50 (14%)	10/50 (20%)	9/49 (18%)
Adjusted Rates (b)	26.8%	28.7%	31.7%
Terminal Rates (c)	5/23 (22%)	7/31 (23%)	6/24 (25%)
Week of First Observation	86	81	88
Life Table Tests (d)	P=0.396	P=0.527	P=0.452
Incidental Tumor Tests (d)	P=0.470	P=0.404	P=0.501
Cochran-Armitage Trend Test (d)	P=0.329		
Fisher Exact Test		P=0.298	P=0.376
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	0.0%	7.6%	0.0%
Terminal Rates (c)	0/23 (0%)	1/31 (3%)	0/24 (0%)
Week of First Observation	--	54	--
Life Table Tests (d)	P=0.627N	P=0.149	(e)
Incidental Tumor Tests (d)	P=0.570	P=0.108	(e)
Cochran-Armitage Trend Test (d)	P=0.640		
Fisher Exact Test		P=0.121	(e)

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	0/50 (0%)	5/50 (10%)	0/50 (0%)
Adjusted Rates (b)	0.0%	14.4%	0.0%
Terminal Rates (c)	0/23 (0%)	3/31 (10%)	0/24 (0%)
Week of First Observation	--	76	--
Life Table Tests (d)	P=0.586N	P=0.064	(e)
Incidental Tumor Tests (d)	P=0.602N	P=0.057	(e)
Cochran-Armitage Trend Test (d)	P=0.610		
Fisher Exact Test		P=0.028	(e)
Hematopoietic Lymphoma: Lymphoma, All Malignant			
Overall Rates (a)	2/50 (4%)	9/50 (18%)	0/50 (0%)
Adjusted Rates (b)	6.3%	23.1%	0.0%
Terminal Rates (c)	1/23 (4%)	4/31 (13%)	0/24 (0%)
Week of First Observation	23	54	--
Life Table Tests (d)	P=0.253N	P=0.063	P=0.233N
Incidental Tumor Tests (d)	P=0.350N	P=0.023	P=0.308N
Cochran-Armitage Trend Test (d)	P=0.283N		
Fisher Exact Test		P=0.026	P=0.248N
Hematopoietic System: Lymphoma or Leukemia			
Overall Rates (a)	2/50 (4%)	10/50 (20%)	1/50 (2%)
Adjusted Rates (b)	6.3%	25.1%	2.5%
Terminal Rates (c)	1/23 (4%)	4/31 (13%)	0/24 (0%)
Week of First Observation	23	54	90
Life Table Tests (d)	P=0.390N	P=0.040	P=0.474N
Incidental Tumor Tests (d)	P=0.512N	P=0.009	P=0.585N
Cochran-Armitage Trend Test (d)	P=0.429N		
Fisher Exact Test		P=0.014	P=0.500N
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	4/50 (8%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	15.3%	3.2%	10.7%
Terminal Rates (c)	3/23 (13%)	1/31 (3%)	2/24 (8%)
Week of First Observation	83	105	91
Life Table Tests (d)	P=0.380N	P=0.115N	P=0.464N
Incidental Tumor Tests (d)	P=0.412N	P=0.146N	P=0.500N
Cochran-Armitage Trend Test (d)	P=0.412N		
Fisher Exact Test		P=0.181N	P=0.500N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	9/48 (19%)	6/49 (12%)	4/50 (8%)
Adjusted Rates (b)	38.2%	19.4%	16.0%
Terminal Rates (c)	8/22 (36%)	6/31 (19%)	3/24 (13%)
Week of First Observation	90	105	104
Life Table Tests (d)	P=0.050N	P=0.093N	P=0.078N
Incidental Tumor Tests (d)	P=0.047N	P=0.112N	P=0.070N
Cochran-Armitage Trend Test (d)	P=0.076N		
Fisher Exact Test		P=0.273N	P=0.102N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	10/48 (21%)	8/49 (16%)	13/50 (26%)
Adjusted Rates (b)	32.9%	22.2%	33.0%
Terminal Rates (c)	4/22 (18%)	5/31 (16%)	2/24 (8%)
Week of First Observation	36	68	79
Life Table Tests (d)	P=0.376	P=0.204N	P=0.450
Incidental Tumor Tests (d)	P=0.356	P=0.396N	P=0.447
Cochran-Armitage Trend Test (d)	P=0.303		
Fisher Exact Test		P=0.379N	P=0.358

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	18/48 (38%)	12/49 (24%)	17/50 (34%)
Adjusted Rates (b)	60.2%	34.2%	44.5%
Terminal Rates (c)	11/22 (50%)	9/31 (29%)	5/24 (21%)
Week of First Observation	36	68	179
Life Table Tests (d)	P=0.335N	P=0.025N	P=0.358N
Incidental Tumor Tests (d)	P=0.321N	P=0.072N	P=0.313N
Cochran-Armitage Trend Test (d)	P=0.403N		
Fisher Exact Test		P=0.122N	P=0.440N
Adrenal Capsule: Adenoma			
Overall Rates (a)	2/49 (4%)	3/48 (6%)	0/49 (0%)
Adjusted Rates (b)	8.2%	9.7%	0.0%
Terminal Rates (c)	1/22 (5%)	3/31 (10%)	0/24 (0%)
Week of First Observation	102	105	--
Life Table Tests (d)	P=0.169N	P=0.647	P=0.218N
Incidental Tumor Tests (d)	P=0.141N	P=0.607	P=0.158N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test		P=0.490	P=0.247N
Adrenal: All Adenoma			
Overall Rates (a)	2/49 (4%)	5/48 (10%)	0/49 (0%)
Adjusted Rates (b)	8.2%	15.5%	0.0%
Terminal Rates (c)	1/22 (5%)	4/31 (13%)	0/24 (0%)
Week of First Observation	102	103	--
Life Table Tests (d)	P=0.201N	P=0.367	P=0.218N
Incidental Tumor Tests (d)	P=0.147N	P=0.297	P=0.158N
Cochran-Armitage Trend Test (d)	P=0.239N		
Fisher Exact Test		P=0.209	P=0.247N
Adrenal: Pheochromocytoma			
Overall Rates (a)	4/49 (8%)	1/48 (2%)	7/49 (14%)
Adjusted Rates (b)	15.9%	2.9%	26.0%
Terminal Rates (c)	2/22 (9%)	0/31 (0%)	5/24 (21%)
Week of First Observation	95	102	100
Life Table Tests (d)	P=0.210	P=0.106N	P=0.325
Incidental Tumor Tests (d)	P=0.348	P=0.159N	P=0.452
Cochran-Armitage Trend Test (d)	P=0.179		
Fisher Exact Test		P=0.187N	P=0.262

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle 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 vehicle 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 exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the 10 mg/kg and vehicle control groups.

TABLE C4. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN MALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls		
	Lymphoma	Leukemia	Lymphoma or Leukemia
Historical Incidence in All Water Vehicle Controls			
THPS (b)	2/50	0/50	2/50
Chlorinated trisodium phosphate (c)	4/50	0/50	4/50
THPC (b)	9/50	0/50	9/50
Chlorpheniramine maleate (b)	9/50	0/50	9/50
TOTAL	24/200 (12.0%)	0/200 (0.0%)	24/200 (12.0%)
SD (d)	7.12%	0.00%	7.12%
Range (e)			
High	9/50	0/50	9/50
Low	2/50	0/50	2/50
Overall Historical Incidence in Untreated Controls			
TOTAL	217/1,791 (12.1%)	(f) 6/1,791 (0.3%)	(f) 223/1,791 (12.5%)
SD (d)	7.35%	0.76%	7.55%
Range (e)			
High	16/50	1/49	16/50
Low	1/50	0/50	1/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Battelle Columbus Laboratories
(c) EG&G Mason Research Institute
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.
(f) Excludes one mast cell leukemia

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS

	Vehicle Control	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)
Ulcer, NOS		2 (4%)	1 (2%)
Ulceration, diffuse	1 (2%)		
Inflammation, acute focal		1 (2%)	1 (2%)
Inflammation, active chronic		1 (2%)	
Inflammation, acute/chronic	1 (2%)	2 (4%)	5 (10%)
Ulcer, chronic	2 (4%)		
Inflammation, chronic focal		2 (4%)	
Inflammation, granulomatous focal		1 (2%)	
Fibrosis, focal	1 (2%)	1 (2%)	
Fibrosis, multifocal		6 (12%)	1 (2%)
Hyperplasia, focal	1 (2%)		
Hyperkeratosis		†9 (18%)	3 (6%)
Acanthosis	1 (2%)	†12 (24%)	3 (6%)
*Subcutaneous tissue	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
Inflammation, acute diffuse	1 (2%)		
Inflammation, active chronic	1 (2%)		
Inflammation, granulomatous		2 (4%)	
Inflammation, granulomatous focal	1 (2%)		
Fibrosis, multifocal	1 (2%)		
RESPIRATORY SYSTEM			
#Tracheal gland	(48)	(42)	(49)
Inflammation, acute focal		3 (7%)	1 (2%)
#Lung	(50)	(50)	(49)
Congestion, NOS		1 (2%)	
Congestion, acute	5 (10%)	11 (22%)	10 (20%)
Edema, NOS		1 (2%)	
Edema, interstitial		1 (2%)	
Hemorrhage			1 (2%)
Lymphocytic inflammatory infiltrate	1 (2%)	2 (4%)	1 (2%)
Inflammation, interstitial	1 (2%)	3 (6%)	1 (2%)
Alveolar macrophages		7 (14%)	4 (8%)
Hyperplasia, alveolar epithelium	1 (2%)	3 (6%)	1 (2%)
#Lung/alveoli	(50)	(50)	(49)
Edema, NOS		1 (2%)	
Hemorrhage	1 (2%)		
#Alveolar wall	(50)	(50)	(49)
Mineralization		1 (2%)	
HEMATOPOIETIC SYSTEM			
#Bone marrow	(49)	(49)	(50)
Atrophy, focal	1 (2%)		
Hyperplasia, granulocytic	6 (12%)	4 (8%)	9 (18%)
Aplasia, erythroid		1 (2%)	
#Spleen	(48)	(49)	(49)
Necrosis, focal		1 (2%)	
Depletion, lymphoid	2 (4%)	1 (2%)	
#Splenic follicles	(48)	(49)	(49)
Necrosis, focal	2 (4%)		
Depletion, lymphoid	2 (4%)	2 (4%)	1 (2%)
Hyperplasia, lymphoid	8 (17%)	13 (27%)	12 (24%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Splenic red pulp	(48)	(49)	(49)
Hematopoiesis	14 (29%)	10 (20%)	24 (49%)
#Mandibular lymph node	(36)	(47)	(45)
Hemorrhage			1 (2%)
Necrosis, focal		1 (2%)	
Pigmentation, NOS		1 (2%)	
Depletion, lymphoid		2 (4%)	
Histiocytosis		1 (2%)	
Hyperplasia, lymphoid	1 (3%)		3 (6%)
Hematopoiesis	1 (3%)		
#Tracheal lymph node	(36)	(47)	(45)
Hyperplasia, lymphoid		3 (6%)	1 (2%)
#Pancreatic lymph node	(36)	(47)	(45)
Hemorrhage			1 (2%)
Angiectasis	1 (3%)		2 (4%)
Hyperplasia, lymphoid		1 (2%)	
Hematopoiesis			2 (4%)
#Mesenteric lymph node	(36)	(47)	(45)
Congestion, acute		1 (2%)	
Hemorrhage		2 (4%)	2 (4%)
Inflammation, acute focal		1 (2%)	2 (4%)
Inflammation, acute/chronic		1 (2%)	
Hyperplasia, diffuse	1 (3%)		
Angiectasis	8 (22%)	4 (9%)	3 (7%)
Histiocytosis		1 (2%)	
Hyperplasia, lymphoid		4 (9%)	
Hematopoiesis			2 (4%)
#Renal lymph node	(36)	(47)	(45)
Angiectasis			1 (2%)
Hematopoiesis			1 (2%)
#Thymic lymph node	(36)	(47)	(45)
Hyperplasia, lymphoid		1 (2%)	1 (2%)
#Liver	(48)	(49)	(50)
Hematopoiesis	1 (2%)	4 (8%)	6 (12%)
#Peyer's patch	(37)	(45)	(38)
Hyperplasia, lymphoid		3 (7%)	1 (3%)
#Thymus	(27)	(38)	(32)
Ultimobranchial cyst	2 (7%)	7 (18%)	
Inflammation, chronic diffuse		1 (3%)	
Depletion, lymphoid	1 (4%)	8 (21%)	9 (28%)
Hyperplasia, reticulum cell		4 (11%)	
Hyperplasia, lymphoid		1 (3%)	
#Thymic lymphocytes	(27)	(38)	(32)
Necrosis, diffuse	4 (15%)	2 (5%)	3 (9%)
CIRCULATORY SYSTEM			
#Mesenteric lymph node	(36)	(47)	(45)
Thrombosis, NOS		1 (2%)	
#Lung	(50)	(50)	(49)
Perivasculitis		1 (2%)	
#Heart	(50)	(49)	(50)
Angiectasis		1 (2%)	
#Right atrium	(50)	(49)	(50)
Thrombus, fibrin		1 (2%)	
#Left atrium	(50)	(49)	(50)
Thrombus, fibrin			1 (2%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
CIRCULATORY SYSTEM (Continued)			
#Myocardium	(50)	(49)	(50)
Mineralization		1 (2%)	
Inflammation, acute focal	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
Degeneration, NOS	2 (4%)	8 (16%)	3 (6%)
Necrosis, focal	1 (2%)	1 (2%)	
Nuclear size alteration	1 (2%)		
#Myocardium of right atrium	(50)	(49)	(50)
Degeneration, NOS		1 (2%)	
*Aorta	(50)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
*Coronary artery	(50)	(50)	(50)
Inflammation, fibrinoid		1 (2%)	
*Pulmonary artery	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
*Renal artery	(50)	(50)	(50)
Inflammation, granulomatous focal		1 (2%)	
#Thymus	(27)	(38)	(32)
Thrombosis, NOS			1 (3%)
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
Hyperkeratosis			1 (2%)
Acanthosis			1 (2%)
#Salivary gland	(50)	(48)	(50)
Necrosis, focal	1 (2%)		
Atrophy, focal		1 (2%)	
#Liver	(48)	(49)	(50)
Cyst, NOS			1 (2%)
Congestion, acute		1 (2%)	
Hemorrhage		1 (2%)	
Inflammation, acute focal			1 (2%)
Inflammation, acute/chronic		1 (2%)	
Necrosis, focal		2 (4%)	
Necrosis, coagulative		2 (4%)	1 (2%)
Infarct, acute		2 (4%)	
Cell size alteration	1 (2%)		
Angiectasis	1 (2%)		1 (2%)
#Liver/centrilobular	(48)	(49)	(50)
Inflammation, acute/chronic	1 (2%)		
Regeneration, NOS	1 (2%)		
#Liver/periportal	(48)	(49)	(50)
Degeneration, NOS	1 (2%)		
Necrosis, focal	1 (2%)		
#Liver/hepatocytes	(48)	(49)	(50)
Inflammation, acute focal	1 (2%)		
Degeneration, cystic	1 (2%)		
Necrosis, focal	2 (4%)	1 (2%)	2 (4%)
Necrosis, coagulative	2 (4%)		
Metamorphosis, fatty	2 (4%)	1 (2%)	
Cytoplasmic vacuolization		1 (2%)	
*Gallbladder	(50)	(50)	(50)
Cyst, NOS			1 (2%)
Necrosis, focal		1 (2%)	
Hyperplasia, epithelial	1 (2%)	1 (2%)	
#Pancreas	(49)	(49)	(49)
Inflammation, acute hemorrhagic			1 (2%)
Inflammation, acute/chronic			2 (4%)
Inflammation, chronic diffuse		1 (2%)	
Atrophy, focal		1 (2%)	3 (6%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Pancreatic acinus	(49)	(49)	(49)
Necrosis, focal	1 (2%)		
Focal cellular change		1 (2%)	
Atrophy, focal		3 (6%)	
Atrophy, diffuse		1 (2%)	
Hypertrophy, focal		3 (6%)	1 (2%)
#Esophagus	(50)	(50)	(50)
Mineralization		1 (2%)	
Inflammation, acute diffuse			1 (2%)
#Gastric mucosa	(41)	(48)	(46)
Erosion	1 (2%)		
Necrosis, focal	1 (2%)		
#Gastric fundal gland	(41)	(48)	(46)
Ectopia			1 (2%)
Mineralization		1 (2%)	
Dilatation, NOS			2 (4%)
Cyst, NOS		1 (2%)	
Inflammation, acute focal		1 (2%)	
#Glandular stomach	(41)	(48)	(46)
Mineralization			1 (2%)
Dilatation, NOS	2 (5%)		
Hyperplasia, focal			1 (2%)
Metaplasia, squamous	1 (2%)		
#Forestomach	(41)	(48)	(46)
Hyperkeratosis	1 (2%)	1 (2%)	2 (4%)
Acanthosis		1 (2%)	2 (4%)
#Gastric fundus	(41)	(48)	(46)
Inflammation, acute focal			1 (2%)
Metaplasia, squamous	1 (2%)		
#Jejunum	(37)	(45)	(38)
Ulcer, NOS		1 (2%)	
Inflammation, active chronic		1 (2%)	
#Colon	(42)	(35)	(44)
Parasitism	7 (17%)	2 (6%)	5 (11%)
#Cecum	(42)	(35)	(44)
Parasitism	1 (2%)	1 (3%)	
*Rectum	(50)	(50)	(50)
Parasitism	1 (2%)		1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(48)	(49)
Hydronephrosis	1 (2%)		2 (4%)
Cyst, NOS			1 (2%)
Inflammation, interstitial			1 (2%)
Pyelonephritis, acute	2 (4%)		
Inflammation, acute focal	1 (2%)	1 (2%)	
Pyelonephritis, chronic		1 (2%)	
Nephropathy	1 (2%)	1 (2%)	5 (10%)
#Kidney/capsule	(50)	(48)	(49)
Inflammation, acute focal			1 (2%)
Fibrosis, multifocal		1 (2%)	
#Kidney/cortex	(50)	(48)	(49)
Mineralization	1 (2%)		
Inflammation, acute/chronic			1 (2%)
Fibrosis, focal		2 (4%)	
Fibrosis, multifocal		1 (2%)	
Degeneration, NOS		1 (2%)	
Deposit, NOS		1 (2%)	
#Renal cortical interstitial tissue	(50)	(48)	(49)
Lymphocytic inflammatory infiltrate	2 (4%)	7 (15%)	6 (12%)
Inflammation, acute diffuse	1 (2%)		

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM (Continued)			
#Kidney/tubule	(50)	(48)	(49)
Mineralization	3 (6%)	3 (6%)	6 (12%)
Dilatation, NOS	2 (4%)	2 (4%)	4 (8%)
Cyst, NOS		1 (2%)	
Degeneration, NOS	1 (2%)	1 (2%)	1 (2%)
Necrosis, focal	1 (2%)		1 (2%)
Cytoplasmic aggregate, NOS		2 (4%)	
Atrophy, focal			1 (2%)
Regeneration, NOS	20 (40%)	31 (65%)	17 (35%)
#Kidney/pelvis	(50)	(48)	(49)
Mineralization		1 (2%)	
Dilatation, NOS	1 (2%)		
Inflammation, acute focal	2 (4%)		
Necrosis, focal	1 (2%)		
#Urinary bladder	(47)	(48)	(47)
Inflammation, acute focal	1 (2%)		
Inflammation, acute/chronic	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, epithelial	1 (2%)	1 (2%)	
#Urinary bladder/mucosa	(47)	(48)	(47)
Inflammation, multifocal			1 (2%)
Necrosis, focal	1 (2%)		
#Urinary bladder/submucosa	(47)	(48)	(47)
Inflammation, acute/chronic		1 (2%)	
#Urinary bladder/serosa	(47)	(48)	(47)
Inflammation, chronic focal	1 (2%)		
ENDOCRINE SYSTEM			
#Anterior pituitary	(35)	(42)	(40)
Embryonal duct cyst		1 (2%)	
Cyst, NOS		1 (2%)	
Hyperplasia, focal	1 (3%)		
#Adrenal/capsule	(49)	(48)	(49)
Hyperplasia, focal	18 (37%)	26 (54%)	26 (53%)
#Adrenal cortex	(49)	(48)	(49)
Cyst, NOS			1 (2%)
Degeneration, NOS	2 (4%)		2 (4%)
Degeneration, lipoid	1 (2%)	4 (8%)	
Focal cellular change	5 (10%)	5 (10%)	4 (8%)
Hypertrophy, focal	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, focal	2 (4%)	5 (10%)	5 (10%)
#Adrenal medulla	(49)	(48)	(49)
Inflammation, acute focal	1 (2%)		
Basophilic cyto change		3 (6%)	
Hyperplasia, focal	3 (6%)	5 (10%)	10 (20%)
#Periadrenal tissue	(49)	(48)	(49)
Inflammation, acute/chronic			1 (2%)
#Thyroid	(50)	(50)	(49)
Follicular cyst, NOS	5 (10%)	6 (12%)	8 (16%)
Hyperplasia, follicular cell	7 (14%)	7 (14%)	9 (18%)
#Thyroid follicle	(50)	(50)	(49)
Multiple cysts			1 (2%)
#Parathyroid	(27)	(29)	(29)
Inflammation, acute/chronic		1 (3%)	
REPRODUCTIVE SYSTEM			
*Penis	(50)	(50)	(50)
Inflammation, chronic diffuse			1 (2%)
*Prepuce	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
*Preputial gland	(50)	(50)	(50)
Dilatation/ducts		4 (8%)	1 (2%)
Multiple cysts	2 (4%)		1 (2%)
Abscess, NOS			1 (2%)
Inflammation, acute/chronic	2 (4%)		1 (2%)
Inflammation, granulomatous focal	1 (2%)		
Metaplasia, squamous		1 (2%)	
#Prostate	(46)	(48)	(49)
Steatitis		1 (2%)	
Inflammation, acute focal	4 (9%)		2 (4%)
Inflammation, acute diffuse	1 (2%)		1 (2%)
Inflammation, acute/chronic	2 (4%)	2 (4%)	2 (4%)
Inflammation, chronic focal			1 (2%)
*Seminal vesicle	(50)	(50)	(50)
Dilatation, NOS	1 (2%)		
Inflammation, acute diffuse	1 (2%)		1 (2%)
Inflammation, acute/chronic			1 (2%)
#Testis	(47)	(50)	(50)
Mineralization	1 (2%)		
Granuloma, spermatic		1 (2%)	1 (2%)
#Spermatogenic epithelium	(47)	(50)	(50)
Mineralization	3 (6%)	7 (14%)	5 (10%)
Degeneration, NOS	6 (13%)	1 (2%)	2 (4%)
Atrophy, NOS		1 (2%)	
Atrophy, focal		6 (12%)	9 (18%)
Atrophy, diffuse	1 (2%)	1 (2%)	1 (2%)
Hypospermatogenesis	1 (2%)		
*Epididymis	(50)	(50)	(50)
Mineralization			1 (2%)
Inflammation, acute/chronic		1 (2%)	2 (4%)
Inflammation, granulomatous focal	1 (2%)		
Granuloma, spermatic	3 (6%)		1 (2%)
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(49)
Perivascular cuffing		1 (2%)	
#Brain/thalamus	(50)	(50)	(49)
Mineralization	23 (46%)	27 (54%)	23 (47%)
*Accessory nerve	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate			1 (2%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Degeneration, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
*Skeletal muscle	(50)	(50)	(50)
Inflammation, necrotizing granulomatous		1 (2%)	
Necrosis, focal		1 (2%)	
*Muscle of leg	(50)	(50)	(50)
Inflammation, acute focal			1 (2%)
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Inflammation, acute diffuse			1 (2%)
*Abdominal cavity	(50)	(50)	(50)
Hemorrhage			1 (2%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
BODY CAVITIES (Continued)			
*Pleura	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	1 (2%)
Fibrosis, focal		2 (4%)	
*Mesentery	(50)	(50)	(50)
Hemorrhage		1 (2%)	
Inflammation, acute/chronic		1 (2%)	
Inflammation, granulomatous focal		1 (2%)	
Necrosis, focal			1 (2%)
Necrosis, fat	1 (2%)	1 (2%)	2 (4%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Mineralization		1 (2%)	
Lymphocytic inflammatory infiltrate		1 (2%)	
SPECIAL MORPHOLOGY SUMMARY			
None			

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
† Multiple occurrence of morphology in the same organ; tissue is counted once only.

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE

IN THE TWO-YEAR GAVAGE STUDY OF THPS

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS

	Vehicle Control	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)
Squamous cell papilloma		1 (2%)	
Fibrosarcoma			1 (2%)
*Subcutaneous tissue	(50)	(50)	(49)
Sarcoma, NOS	1 (2%)		
Fibrosarcoma	1 (2%)		1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(49)
Adenocarcinoma, NOS, metastatic		1 (2%)	
Alveolar/bronchiolar adenoma	1 (2%)	2 (4%)	1 (2%)
Alveolar/bronchiolar carcinoma	1 (2%)	1 (2%)	2 (4%)
Papillary adenocarcinoma, metastatic			1 (2%)
Acinar cell carcinoma, metastatic			1 (2%)
Sarcoma, NOS, metastatic	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(49)
Malignant lymphoma, NOS	9 (18%)	1 (2%)	
Malignant lymphoma, undiffer type	1 (2%)	1 (2%)	
Malignant lymphoma, lymphocytic type	4 (8%)	1 (2%)	5 (10%)
Malignant lymphoma, histiocytic type	1 (2%)	5 (10%)	2 (4%)
Malignant lymphoma, mixed type	1 (2%)	8 (16%)	9 (18%)
Leukemia, NOS	1 (2%)		
Lymphocytic leukemia	1 (2%)		
#Liver	(50)	(50)	(49)
Malignant lymphoma, lymphocytic type		1 (2%)	
#Jejunum	(49)	(45)	(46)
Malignant lymphoma, NOS			1 (2%)
#Uterus	(50)	(50)	(49)
Malignant lymphoma, NOS			1 (2%)
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(49)
Hemangiosarcoma		2 (4%)	
#Spleen	(50)	(50)	(49)
Hemangiosarcoma			1 (2%)
#Splenic red pulp	(50)	(50)	(49)
Hemangioma	1 (2%)		
#Uterus	(50)	(50)	(49)
Hemangioma			1 (2%)
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(49)
Squamous cell carcinoma			1 (2%)
#Liver	(50)	(50)	(49)
Hepatocellular adenoma	5 (10%)	3 (6%)	2 (4%)
Hepatocellular carcinoma	3 (6%)		1 (2%)
#Forestomach	(50)	(47)	(48)
Squamous cell papilloma		1 (2%)	

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Cecum	(49)	(44)	(45)
Leiomyoma	1 (2%)		
URINARY SYSTEM			
#Kidney/cortex	(50)	(50)	(49)
Adenocarcinoma, NOS, metastatic		1 (2%)	
ENDOCRINE SYSTEM			
#Anterior pituitary	(43)	(46)	(45)
Adenoma, NOS	8 (19%)	8 (17%)	8 (18%)
#Adrenal	(50)	(50)	(49)
Alveolar/bronchiolar carcinoma, metastatic	1 (2%)		
Cortical adenoma	1 (2%)	2 (4%)	
#Adrenal/capsule	(50)	(50)	(49)
Adenoma, NOS		1 (2%)	
#Adrenal medulla	(50)	(50)	(49)
Pheochromocytoma		3 (6%)	2 (4%)
#Thyroid	(49)	(49)	(48)
Follicular cell adenoma	1 (2%)		
Follicular cell carcinoma		1 (2%)	
#Pancreatic islets	(48)	(48)	(49)
Islet cell adenoma	1 (2%)	1 (2%)	
Islet cell carcinoma			1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(49)
Squamous cell carcinoma		1 (2%)	
Adenocarcinoma, NOS		1 (2%)	
Acinar cell carcinoma			1 (2%)
#Uterus	(50)	(50)	(49)
Adenocarcinoma, NOS		1 (2%)	
Leiomyosarcoma	1 (2%)		
Endometrial stromal polyp	2 (4%)	2 (4%)	6 (12%)
#Ovary	(50)	(50)	(48)
Papillary cystadenoma, NOS		1 (2%)	
Teratoma, NOS			1 (2%)
#Ovary/cortex	(50)	(50)	(48)
Granulosa cell tumor		1 (2%)	
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(49)
Papillary adenocarcinoma	2 (4%)	1 (2%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(49)
Fibrosarcoma, metastatic	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	7	8	6
Moribund sacrifice	13	12	10
Terminal sacrifice	28	30	33
Dosing accident	1		
Accidentally killed, NOS	1		
Animal missing			1
TUMOR SUMMARY			
Total animals with primary tumors**	32	35	35
Total primary tumors	48	51	49
Total animals with benign tumors	17	19	17
Total benign tumors	21	25	20
Total animals with malignant tumors	25	20	23
Total malignant tumors	27	25	28
Total animals with secondary tumors##	3	1	2
Total secondary tumors	3	2	2
Total animals with tumors uncertain-- benign or malignant		1	1
Total uncertain tumors		1	1

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS: VEHICLE CONTROL

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025
WEEKS ON STUDY	1105	1105	1105	1105	0821	0997	0800	0997	0821	1105	1105	1105	1105	0996	1105	0965	1105	1105	1205	1105	0775	0860	1105	1105	1105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS														X											
Fibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																					X				
Sarcoma, NOS, metastatic														X											
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma					X																				
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+
Thymus	+	+	+	+	+	−	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma										X														X	
Hepatocellular carcinoma	X																								
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Leiomyoma		X																							
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	−	+	+	+
Adenoma, NOS					X					X	X				X			X						X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic																					X				
Cortical adenoma																		X							
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma	X																								
Parathyroid	−	+	−	−	−	+	−	+	+	+	−	+	+	−	+	+	+	−	+	+	+	+	+	−	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Islet cell adenoma							X																		
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	N	+	N	N	N	N	N	N	N	+	+	N	N	+	+	N	N	+	N	N	N	N
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																	X								
Endometrial stromal polyp																						X			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Papillary adenocarcinoma											X			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
Fibrosarcoma, metastatic																									
Malignant lymphoma, NOS		X				X		X				X													
Malignant lymphoma, undiffer type																									
Malignant lymphoma, lymphocytic type															X		X			X					
Malignant lymphoma, histiocytic type									X																
Malignant lymphoma, mixed type																									
Leukemia, NOS																									
Lymphocytic leukemia																									

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 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	080	001	001	088	060	075	101	105	105	059	098	014	105	105	105	105	100	105	105	105	105	033	105	101	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibrosarcoma																		X								1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma															X											1
Alveolar/bronchiolar carcinoma																										1
Sarcoma, NOS, metastatic																										1
Trachea	+	−	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	46
Thymus	+	+	+	+	+	+	−	+	+	+	−	+	−	+	−	+	+	−	+	+	+	+	+	+	−	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma							X			X													X			5
Hepatocellular carcinoma																							X	X		3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	N	+	+	+	N	+	+	+	+	N	N	+	+	+	N	+	+	+	+	+	+	N	N	+	*50
Pancreas	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	−	+	+	−	+	−	+	+	+	+	+	−	+	+	+	+	+	43
Adenoma, NOS																	X									8
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, meta																										1
Cortical adenoma																										1
Thyroid	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma																										1
Parathyroid	+	−	+	+	−	−	−	+	−	+	+	−	−	+	+	−	+	+	+	−	+	−	−	−	−	28
Pancreatic islets	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	+	+	+	N	+	N	+	N	N	N	N	+	N	+	N	N	N	+	N	+	+	N	N	*50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Endometrial stromal polyp																				X						2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	*50
Papillary adenocarcinoma																										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	*50
Fibrosarcoma, metastatic																		X								1
Malignant lymphoma, NOS								X		X					X	X	X									9
Malignant lymphoma, undiffer type		X																								1
Malignant lymphoma, lymphocytic type						X																				4
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type							X																			1
Leukemia, NOS												X														1
Lymphocytic leukemia																										1

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS: 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	075	105	072	066	067	104	093	105	105	105	105	105	102	104	105	104	105	105	105	105	091	105	090	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+
Squamous cell papilloma						X																			
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic																									
Alveolar/bronchiolar adenoma																								X	
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–
Thymus	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																	X	X							
Malignant lymphoma, lymphocytic type																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	+	N	+	N	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	N
Pancreas	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic																									
Urinary bladder	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS									X						X		X					X			X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Cortical adenoma																	X								
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma											X														
Parathyroid	+	–	+	+	+	–	–	+	+	–	–	+	–	+	+	+	+	–	+	–	+	–	–	–	+
Pancreatic islets	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																				X					
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	+	+	+	N	N	N	N	+	N	N	+	+	+	+	N	N	+	N	+	N	N	N
Squamous cell carcinoma																X									
Adenocarcinoma, NOS											X														
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Endometrial stromal polyp																								X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary cystadenoma, NOS																									
Granulosa cell tumor														X											X
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
Papillary adenocarcinoma																		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
Hemangiosarcoma											X		X												
Malignant lymphoma, NOS																					X				
Malignant lymphoma, undiffer type																									
Malignant lymphoma, lymphocytic type																			X						
Malignant lymphoma, histiocytic type				X	X																				
Malignant lymphoma, mixed type								X			X	X		X		X									

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	0026	0027	0028	0029	0030	0031	0032	0033	0034	0035	0036	0037	0038	0039	0040	0041	0042	0043	0044	0045	0046	0047	0048	0049	0050	TOTAL:
WEEKS ON STUDY	1005	1005	1004	1005	1005	1005	1005	1005	1005	1005	0771	0773	0773	0777	0781	0666	1005	1005	1005	1005	1005	0773	0992	1005	1005	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic				X																						1
Alveolar/bronchiolar adenoma						X																				2
Alveolar/bronchiolar carcinoma								X																		1
Trachea	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	46
Thymus	+	+	+	+	+	+	–	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	44
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma		X																								3
Malignant lymphoma, lymphocytic type								X																		1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	N	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	–	+	+	47
Squamous cell papilloma								X																		1
Small intestine	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	–	+	+	45
Large intestine	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	44
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic				X																						1
Urinary bladder	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	–	46
Adenoma, NOS					X			X												X						8
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS				X																						1
Cortical adenoma																		X								2
Pheochromocytoma												X							X	X						3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell carcinoma																										1
Parathyroid	+	+	+	+	+	+	–	–	+	–	–	–	–	–	+	+	+	+	+	+	–	–	+	+	+	30
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	48
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	N	N	+	N	N	N	+	+	N	N	+	N	N	N	+	+	+	N	N	+	+	N	*50
Squamous cell carcinoma																										1
Adenocarcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS				X																						1
Endometrial stromal polyp																		X								2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papillary cystadenoma, NOS																										1
Granulosa cell tumor																										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	*50
Papillary adenocarcinoma																										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
Hemangiosarcoma																										2
Malignant lymphoma, NOS																										1
Malignant lymphoma, undiffer type														X												1
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, histiocytic type			X			X																	X			5
Malignant lymphoma, mixed type	X																							X	X	8

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS: HIGH DOSE

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025
WEEKS ON STUDY	105	003	105	105	105	086	075	075	075	075	105	105	105	097	105	105	105	105	105	105	105	072	105	010	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Papillary adenocarcinoma, metastatic																									
Acinar cell carcinoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph nodes	+	−	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+
Thymus	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	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
Squamous cell carcinoma																						X			
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma															X										
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS																									
Large intestine	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	−	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+
Adenoma, NOS											X					X			X						
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma						X																			
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	+	−	+	+	−	+	+	+	+	−	+	−	−	−	+	−	+	−	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	+	N	N	N	N	+	+	+	N	N	+	N	+	+	N	+	+	N	+	+
Acinar cell carcinoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																			X	X					X
Hemangioma												X													
Malignant lymphoma, NOS																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Teratoma, NOS																								X	
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
Papillary adenocarcinoma																									
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
Malignant lymphoma, lymphocytic type			X											X			X				X				
Malignant lymphoma, histiocytic type																X									
Malignant lymphoma, mixed type											X	X	X		X								X		

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE 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:
WEEKS ON STUDY	105	105	105	105	105	105	091	105	105	105	096	105	105	095	105	083	093	105	096	101	105	105	087	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	*49
Fibrosarcoma												X														1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	*49
Fibrosarcoma							X																			1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Alveolar/bronchiolar adenoma						X																				1
Alveolar/bronchiolar carcinoma											X													X		2
Papillary adenocarcinoma, metastatic		X																								1
Acinar cell carcinoma, metastatic											X															1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Hemangiosarcoma												X														1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	M	+	+	44
Thymus	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	–	+	+	–	+	+	+	M	+	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
DIGESTIVE SYSTEM																										
Oral cavity	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	*49
Squamous cell carcinoma															X											1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Hepatocellular adenoma																			X							2
Hepatocellular carcinoma																								X		1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	M	N	+	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	M	+	+	46
Malignant lymphoma, NOS															X											1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	M	+	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	M	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	45
Adenoma, NOS				X	X								X	X										X		8
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Pheochromocytoma													X													2
Thyroid	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
Parathyroid	+	+	+	–	+	+	+	–	–	–	+	+	–	–	–	+	+	+	+	–	+	–	M	+	+	32
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Islet cell carcinoma																						X				1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	+	N	N	N	N	N	N	+	+	N	N	N	N	N	N	N	N	N	N	+	M	N	N	*49
Acinar cell carcinoma											X															1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Endometrial stromal polyp								X										X							X	6
Hemangioma																										1
Malignant lymphoma, NOS																								X		1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	M	+	+	48
Teratoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	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	M	N	N	*49
Papillary adenocarcinoma		X																								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	M	N	N	*49
Malignant lymphoma, lymphocytic type																						X				5
Malignant lymphoma, histiocytic type																			X							2
Malignant lymphoma, mixed type	X			X						X										X						9

* Animals necropsied

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS

	Vehicle Control	5 mg/kg	10 mg/kg
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	3/49 (6%)
Adjusted Rates (b)	5.9%	10.0%	8.6%
Terminal Rates (c)	1/28 (4%)	3/30 (10%)	2/33 (6%)
Week of First Observation	75	105	96
Life Table Tests (d)	P=0.480	P=0.529	P=0.559
Incidental Tumor Tests (d)	P=0.452	P=0.571	P=0.514
Cochran-Armitage Trend Test (d)	P=0.402		
Fisher Exact Test		P=0.500	P=0.490
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	5/49 (10%)
Adjusted Rates (b)	12.7%	6.7%	14.6%
Terminal Rates (c)	3/28 (11%)	2/30 (7%)	4/33 (12%)
Week of First Observation	60	105	97
Life Table Tests (d)	P=0.504	P=0.303N	P=0.585
Incidental Tumor Tests (d)	P=0.484	P=0.274N	P=0.556
Cochran-Armitage Trend Test (d)	P=0.413		
Fisher Exact Test		P=0.339N	P=0.487
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	1/50 (2%)	5/50 (10%)	2/49 (4%)
Adjusted Rates (b)	2.6%	12.4%	5.9%
Terminal Rates (c)	0/28 (0%)	1/30 (3%)	1/33 (3%)
Week of First Observation	82	66	101
Life Table Tests (d)	P=0.477	P=0.137	P=0.547
Incidental Tumor Tests (d)	P=0.336	P=0.119	P=0.443
Cochran-Armitage Trend Test (d)	P=0.402		
Fisher Exact Test		P=0.102	P=0.492
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	1/50 (2%)	8/50 (16%)	9/49 (18%)
Adjusted Rates (b)	2.4%	24.7%	27.3%
Terminal Rates (c)	0/28 (0%)	6/30 (20%)	9/33 (27%)
Week of First Observation	75	104	105
Life Table Tests (d)	P=0.021	P=0.027	P=0.018
Incidental Tumor Tests (d)	P=0.017	P=0.024	P=0.016
Cochran-Armitage Trend Test (d)	P=0.009		
Fisher Exact Test		P=0.015	P=0.007
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	16/50 (32%)	17/50 (34%)	18/49 (37%)
Adjusted Rates (b)	44.1%	43.3%	51.4%
Terminal Rates (c)	9/28 (32%)	9/30 (30%)	16/33 (48%)
Week of First Observation	60	66	97
Life Table Tests (d)	P=0.504N	P=0.548N	P=0.549N
Incidental Tumor Tests (d)	P=0.418	P=0.581	P=0.499
Cochran-Armitage Trend Test (d)	P=0.348		
Fisher Exact Test		P=0.500	P=0.388
Hematopoietic System: Lymphoma or Leukemia			
Overall Rates (a)	18/50 (36%)	17/50 (34%)	18/49 (37%)
Adjusted Rates (b)	47.0%	43.3%	51.4%
Terminal Rates (c)	9/28 (32%)	9/30 (30%)	16/33 (48%)
Week of First Observation	60	66	97
Life Table Tests (d)	P=0.350N	P=0.394N	P=0.386N
Incidental Tumor Tests (d)	P=0.505N	P=0.405N	P=0.516N
Cochran-Armitage Trend Test (d)	P=0.512		
Fisher Exact Test		P=0.500N	P=0.553

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	5 mg/kg	10 mg/kg
Liver: Hepatocellular Adenoma			
Overall Rates (a)	5/50 (10%)	3/50 (6%)	2/49 (4%)
Adjusted Rates (b)	16.3%	10.0%	5.9%
Terminal Rates (c)	4/28 (14%)	3/30 (10%)	1/33 (3%)
Week of First Observation	75	105	101
Life Table Tests (d)	P=0.113N	P=0.319N	P=0.163N
Incidental Tumor Tests (d)	P=0.126N	P=0.289N	P=0.192N
Cochran-Armitage Trend Test (d)	P=0.164N		
Fisher Exact Test		P=0.357N	P=0.226N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	1/49 (2%)
Adjusted Rates (b)	10.7%	0.0%	3.0%
Terminal Rates (c)	3/28 (11%)	0/30 (0%)	1/33 (3%)
Week of First Observation	105	--	105
Life Table Tests (d)	P=0.142N	P=0.108N	P=0.247N
Incidental Tumor Tests (d)	P=0.142N	P=0.108N	P=0.247N
Cochran-Armitage Trend Test (d)	P=0.180N		
Fisher Exact Test		P=0.121N	P=0.316N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	7/50 (14%)	3/50 (6%)	3/49 (6%)
Adjusted Rates (b)	23.3%	10.0%	8.8%
Terminal Rates (c)	6/28 (21%)	3/30 (10%)	2/33 (6%)
Week of First Observation	75	105	101
Life Table Tests (d)	P=0.068N	P=0.130N	P=0.104N
Incidental Tumor Tests (d)	P=0.075N	P=0.113N	P=0.123N
Cochran-Armitage Trend Test (d)	P=0.112N		
Fisher Exact Test		P=0.159N	P=0.167N
Pituitary: Adenoma			
Overall Rates (a)	8/43 (19%)	8/46 (17%)	8/45 (18%)
Adjusted Rates (b)	31.0%	28.6%	23.9%
Terminal Rates (c)	7/24 (29%)	8/28 (29%)	7/32 (22%)
Week of First Observation	82	105	95
Life Table Tests (d)	P=0.317N	P=0.481N	P=0.377N
Incidental Tumor Tests (d)	P=0.334N	P=0.495N	P=0.406N
Cochran-Armitage Trend Test (d)	P=0.516N		
Fisher Exact Test		P=0.550N	P=0.569N
Adrenal: Pheochromocytoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	2/49 (4%)
Adjusted Rates (b)	0.0%	8.7%	5.3%
Terminal Rates (c)	0/28 (0%)	2/30 (7%)	1/33 (3%)
Week of First Observation	--	73	86
Life Table Tests (d)	P=0.246	P=0.137	P=0.275
Incidental Tumor Tests (d)	P=0.190	P=0.162	P=0.200
Cochran-Armitage Trend Test (d)	P=0.196		
Fisher Exact Test		P=0.121	P=0.242
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	2/50 (4%)	2/50 (4%)	6/49 (12%)
Adjusted Rates (b)	5.7%	6.7%	18.2%
Terminal Rates (c)	1/28 (4%)	2/30 (7%)	6/33 (18%)
Week of First Observation	60	105	105
Life Table Tests (d)	P=0.114	P=0.666N	P=0.187
Incidental Tumor Tests (d)	P=0.106	P=0.629N	P=0.175
Cochran-Armitage Trend Test (d)	P=0.076		
Fisher Exact Test		P=0.691	P=0.128

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle 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 vehicle 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 exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS

	Vehicle Control	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)
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic		1 (2%)	
Inflammation, chronic focal			1 (2%)
*Subcutaneous tissue	(50)	(50)	(49)
Inflammation, acute focal	1 (2%)		
RESPIRATORY SYSTEM			
#Tracheal gland	(47)	(48)	(49)
Dilatation, NOS		1 (2%)	
Hyperplasia, focal			1 (2%)
Hyperplasia, diffuse			1 (2%)
#Lung	(50)	(50)	(49)
Congestion, acute	2 (4%)	7 (14%)	9 (18%)
Hemorrhage	1 (2%)	1 (2%)	1 (2%)
Lymphocytic inflammatory infiltrate	4 (8%)	3 (6%)	
Inflammation, interstitial		1 (2%)	1 (2%)
Inflammation, acute necrotizing		1 (2%)	
Inflammation, active chronic	1 (2%)		
Inflammation, chronic suppurative		1 (2%)	
Abscess, chronic	1 (2%)		
Alveolar macrophages	1 (2%)	7 (14%)	
Hyperplasia, alveolar epithelium			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(49)
Hyperplasia, lymphoid		2 (4%)	1 (2%)
#Bone marrow	(50)	(49)	(49)
Necrosis, focal		1 (2%)	
Myelofibrosis	7 (14%)	13 (27%)	10 (20%)
Hyperplasia, granulocytic		6 (12%)	6 (12%)
#Spleen	(50)	(50)	(49)
Inflammation, acute/chronic	1 (2%)		
Necrosis, focal		1 (2%)	2 (4%)
Hyperplasia, lymphoid			1 (2%)
#Splenic follicles	(50)	(50)	(49)
Necrosis, focal			2 (4%)
Depletion, lymphoid	2 (4%)		
Hyperplasia, lymphoid	16 (32%)	21 (42%)	16 (33%)
#Splenic red pulp	(50)	(50)	(49)
Necrosis, focal		1 (2%)	
Hematopoiesis	5 (10%)	6 (12%)	9 (18%)
#Lymph node	(46)	(46)	(44)
Inflammation, granulomatous	1 (2%)		
#Mandibular lymph node	(46)	(46)	(44)
Hemorrhage			1 (2%)
Pigmentation, NOS		1 (2%)	
Histiocytosis	2 (4%)	3 (7%)	
Hyperplasia, lymphoid	14 (30%)	20 (43%)	19 (43%)
#Bronchial lymph node	(46)	(46)	(44)
Necrosis, focal			1 (2%)

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Tracheal lymph node	(46)	(46)	(44)
Hyperplasia, lymphoid		1 (2%)	1 (2%)
#Mediastinal lymph node	(46)	(46)	(44)
Plasmacytosis	1 (2%)		
#Abdominal lymph node	(46)	(46)	(44)
Hyperplasia, lymphoid			1 (2%)
#Pancreatic lymph node	(46)	(46)	(44)
Abscess, NOS			1 (2%)
Hyperplasia, lymphoid			1 (2%)
#Lumbar lymph node	(46)	(46)	(44)
Angiectasis		1 (2%)	
#Mesenteric lymph node	(46)	(46)	(44)
Hemorrhage			1 (2%)
Inflammation, acute focal		1 (2%)	
Necrosis, focal			1 (2%)
Angiectasis			2 (5%)
Hyperplasia, lymphoid		2 (4%)	1 (2%)
#Ileocolic lymph node	(46)	(46)	(44)
Hemorrhage		1 (2%)	
#Renal lymph node	(46)	(46)	(44)
Hemorrhage			1 (2%)
Inflammation, chronic focal			1 (2%)
Plasmacytosis			1 (2%)
Hyperplasia, lymphoid		1 (2%)	1 (2%)
Hematopoiesis		1 (2%)	
#Thymic lymph node	(46)	(46)	(44)
Hyperplasia, lymphoid		1 (2%)	2 (5%)
#Salivary gland	(50)	(50)	(48)
Hyperplasia, lymphoid	1 (2%)		
#Liver	(50)	(50)	(49)
Hematopoiesis	2 (4%)	5 (10%)	6 (12%)
#Peyer's patch	(49)	(45)	(46)
Hyperplasia, lymphoid		2 (4%)	
#Urinary bladder/submucosa	(48)	(47)	(47)
Hyperplasia, lymphoid			1 (2%)
#Adrenal	(50)	(50)	(49)
Hematopoiesis			1 (2%)
#Adrenal cortex	(50)	(50)	(49)
Hematopoiesis		1 (2%)	
#Thymus	(41)	(44)	(41)
Ultimobranchial cyst	1 (2%)	3 (7%)	
Steatitis		1 (2%)	
Inflammation, acute focal		1 (2%)	
Depletion, lymphoid	2 (5%)	3 (7%)	2 (5%)
Hyperplasia, lymphoid	1 (2%)	2 (5%)	2 (5%)
#Thymic cortex	(41)	(44)	(41)
Depletion, lymphoid	3 (7%)		
#Thymic lymphocytes	(41)	(44)	(41)
Necrosis, focal		1 (2%)	1 (2%)
Necrosis, diffuse	2 (5%)		4 (10%)
Hyperplasia, diffuse	1 (2%)		
CIRCULATORY SYSTEM			
#Heart	(50)	(50)	(49)
Myxomatosis, cardiac valve	1 (2%)		
Inflammation, chronic focal		1 (2%)	
#Base of heart	(50)	(50)	(49)
Inflammation, acute/chronic	1 (2%)		
#Heart/atrium	(50)	(50)	(49)
Inflammation, acute/chronic	1 (2%)		

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
CIRCULATORY SYSTEM (Continued)			
#Left ventricle	(50)	(50)	(49)
Inflammation, granulomatous			1 (2%)
#Outflow tract, left ventricle	(50)	(50)	(49)
Inflammation, suppurative	1 (2%)		
#Myocardium	(50)	(50)	(49)
Mineralization		1 (2%)	
Inflammation, acute focal		2 (4%)	
Inflammation, acute/chronic			1 (2%)
Inflammation, chronic focal		1 (2%)	
Degeneration, NOS	1 (2%)	3 (6%)	
*Aorta	(50)	(50)	(49)
Thrombosis, NOS	1 (2%)		
Inflammation, acute diffuse	1 (2%)		
Inflammation, granulomatous focal			1 (2%)
*Pulmonary artery	(50)	(50)	(49)
Mineralization	1 (2%)		
Thrombus, organized			1 (2%)
Embolism, NOS		1 (2%)	
Inflammation, acute/chronic	1 (2%)		
Inflammation, granulomatous focal			1 (2%)
Necrosis, fibrinoid	1 (2%)		
*Mediastinal artery	(50)	(50)	(49)
Inflammation, granulomatous	1 (2%)		
*Renal artery	(50)	(50)	(49)
Inflammation, acute/chronic	1 (2%)	1 (2%)	
Inflammation, granulomatous			1 (2%)
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(50)	(48)
Lymphocytic inflammatory infiltrate		4 (8%)	
#Liver	(50)	(50)	(49)
Congestion, acute		1 (2%)	
Hemorrhage		1 (2%)	
Inflammation, multifocal	1 (2%)		
Inflammation, suppurative		1 (2%)	
Inflammation, acute	1 (2%)		
Inflammation, acute focal	2 (4%)	7 (14%)	2 (4%)
Inflammation, acute diffuse			1 (2%)
Inflammation, acute/chronic	1 (2%)	1 (2%)	2 (4%)
Abscess, chronic		1 (2%)	
Inflammation, granulomatous focal		3 (6%)	
Necrosis, focal		3 (6%)	
Necrosis, diffuse			1 (2%)
Necrosis, coagulative	1 (2%)		1 (2%)
Pigmentation, NOS		1 (2%)	
Focal cellular change			2 (4%)
#Liver/centrilobular	(50)	(50)	(49)
Necrosis, focal	1 (2%)		
Nuclear enlargement	1 (2%)		
#Liver/hepatocytes	(50)	(50)	(49)
Necrosis, focal		2 (4%)	
Cytoplasmic vacuolization	6 (12%)	13 (26%)	7 (14%)
Hypertrophy, focal		1 (2%)	
*Gallbladder	(50)	(50)	(49)
Inflammation, acute diffuse		2 (4%)	
Inflammation, acute/chronic		2 (4%)	

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Pancreas	(48)	(48)	(49)
Dilatation/ducts		2 (4%)	
Lymphocytic inflammatory infiltrate		3 (6%)	
Inflammation, acute/chronic		3 (6%)	1 (2%)
Abscess, chronic		1 (2%)	
Necrosis, focal	1 (2%)		
#Pancreatic acinus	(48)	(48)	(49)
Basophilic cyto change		1 (2%)	
Atrophy, focal		8 (17%)	
Atrophy, diffuse		2 (4%)	1 (2%)
#Esophagus	(49)	(50)	(49)
Inflammation, acute focal			1 (2%)
#Gastric fundal gland	(50)	(47)	(48)
Dilatation, NOS	1 (2%)		
#Glandular stomach	(50)	(47)	(48)
Hemorrhage		1 (2%)	
Inflammation, acute focal			1 (2%)
Degeneration, NOS		1 (2%)	
Hyperplasia, focal		1 (2%)	
#Gastric fundus	(50)	(47)	(48)
Ulcer, acute	1 (2%)		
Necrosis, focal			1 (2%)
#Jejunum	(49)	(45)	(46)
Hemorrhage		1 (2%)	
Inflammation, acute focal		1 (2%)	
#Colon	(49)	(44)	(45)
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic focal		1 (2%)	
Inflammation, granulomatous		1 (2%)	
Parasitism	3 (6%)	4 (9%)	4 (9%)
#Colonic submucosa	(49)	(44)	(45)
Inflammation, chronic focal		1 (2%)	
#Cecum	(49)	(44)	(45)
Inflammation, acute/chronic			1 (2%)
Parasitism			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(49)
Hydronephrosis		1 (2%)	
Pyelonephritis, acute		1 (2%)	
Glomerulonephritis, subacute			1 (2%)
Glomerulonephritis, chronic		1 (2%)	
Nephropathy	2 (4%)		
#Kidney/capsule	(50)	(50)	(49)
Lymphocytic inflammatory infiltrate		1 (2%)	
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic diffuse		1 (2%)	
#Kidney/cortex	(50)	(50)	(49)
Inflammation, acute focal	1 (2%)	1 (2%)	
Fibrosis, focal		1 (2%)	
Nephropathy			2 (4%)
Degeneration, NOS	1 (2%)		1 (2%)
Metaplasia, osseous	1 (2%)	2 (4%)	
#Renal cortical interstitial tissue	(50)	(50)	(49)
Lymphocytic inflammatory infiltrate	6 (12%)	5 (10%)	2 (4%)
#Kidney/glomerulus	(50)	(50)	(49)
Amyloidosis			1 (2%)

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM (Continued)			
#Kidney/tubule	(50)	(50)	(49)
Mineralization	1 (2%)		
Dilatation, NOS	1 (2%)	3 (6%)	1 (2%)
Degeneration, NOS	1 (2%)		
Regeneration, NOS	8 (16%)	7 (14%)	10 (20%)
#Kidney/pelvis	(50)	(50)	(49)
Mineralization			1 (2%)
#Urinary bladder	(48)	(47)	(47)
Hemorrhage		1 (2%)	
Lymphocytic inflammatory infiltrate		1 (2%)	
#Urinary bladder/submucosa	(48)	(47)	(47)
Lymphocytic inflammatory infiltrate		1 (2%)	
ENDOCRINE SYSTEM			
#Anterior pituitary	(43)	(46)	(45)
Cyst, NOS		1 (2%)	
Multiple cysts	1 (2%)		
Hemorrhage	1 (2%)	1 (2%)	
Hypertrophy, focal		1 (2%)	
Hyperplasia, focal	2 (5%)	5 (11%)	4 (9%)
#Pituitary posterior	(43)	(46)	(45)
Necrosis, focal		1 (2%)	
#Adrenal/capsule	(50)	(50)	(49)
Hyperplasia, focal	29 (58%)	43 (86%)	44 (90%)
#Adrenal cortex	(50)	(50)	(49)
Cyst, NOS	1 (2%)		
Inflammation, acute focal		2 (4%)	
Degeneration, NOS	1 (2%)		3 (6%)
Degeneration, lipoid	4 (8%)	17 (34%)	9 (18%)
Necrosis, focal		1 (2%)	
Focal cellular change	2 (4%)	2 (4%)	2 (4%)
#Zona reticularis	(50)	(50)	(49)
Inflammation, granulomatous focal	1 (2%)		
#Adrenal medulla	(50)	(50)	(49)
Hyperplasia, focal	2 (4%)		2 (4%)
#Periadrenal tissue	(50)	(50)	(49)
Inflammation, acute diffuse			1 (2%)
#Thyroid	(49)	(49)	(48)
Cyst, NOS			1 (2%)
Follicular cyst, NOS	2 (4%)	5 (10%)	3 (6%)
Inflammation, acute/chronic	1 (2%)		
Inflammation, granulomatous focal		1 (2%)	
Hyperplasia, follicular cell	6 (12%)	3 (6%)	9 (19%)
#Thyroid follicle	(49)	(49)	(48)
Multiple cysts	1 (2%)		
#Parathyroid	(28)	(30)	(32)
Lymphocytic inflammatory infiltrate			1 (3%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(49)
Dilatation/ducts	1 (2%)	1 (2%)	
#Uterus	(50)	(50)	(49)
Dilatation, NOS	2 (4%)	6 (12%)	7 (14%)
Inflammation, suppurative		1 (2%)	1 (2%)
Inflammation, acute focal	2 (4%)	3 (6%)	4 (8%)
Inflammation, acute diffuse			1 (2%)
Abscess, NOS		1 (2%)	
Infarct, focal	1 (2%)		

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
#Endometrial gland	(50)	(50)	(49)
Dilatation, NOS	4 (8%)	2 (4%)	1 (2%)
Multiple cysts	2 (4%)		2 (4%)
Inflammation, acute focal			2 (4%)
Necrosis, focal			1 (2%)
Hyperplasia, focal	1 (2%)		
Hyperplasia, cystic	34 (68%)	37 (74%)	34 (69%)
Metaplasia, squamous	5 (10%)	7 (14%)	6 (12%)
#Ovary/parovarian region	(50)	(50)	(48)
Inflammation, acute		1 (2%)	
Abscess, NOS		1 (2%)	
Inflammation, granulomatous focal		1 (2%)	
Inflammation, pyogranulomatous		1 (2%)	
Necrosis, fat		1 (2%)	
#Ovary	(50)	(50)	(48)
Mineralization	2 (4%)		
Cyst, NOS	7 (14%)	8 (16%)	4 (8%)
Follicular cyst, NOS	1 (2%)		
Multiple cysts			1 (2%)
Congestion, acute			1 (2%)
Hematocele	1 (2%)		
Inflammation, suppurative			1 (2%)
Inflammation, acute diffuse			1 (2%)
Abscess, NOS			3 (6%)
Inflammation, chronic focal	1 (2%)		
Necrosis, focal			1 (2%)
Infarct, NOS	1 (2%)		
Foreign material, NOS			1 (2%)
Atrophy, NOS	19 (38%)	10 (20%)	10 (21%)
#Ovary/cortex	(50)	(50)	(48)
Cyst, NOS	3 (6%)	9 (18%)	8 (17%)
Hemorrhage	1 (2%)		
Hemorrhagic cyst	1 (2%)	10 (20%)	3 (6%)
#Mesovarium	(50)	(50)	(48)
Steatitis		1 (2%)	
NERVOUS SYSTEM			
*Brain/neuropil	(50)	(50)	(49)
Atrophy, pressure			1 (2%)
#Brain/meninges	(50)	(49)	(49)
Perivascular cuffing			2 (4%)
#Brain	(50)	(49)	(49)
Hydrocephalus, NOS		1 (2%)	
Hemorrhage	2 (4%)		
Lymphocytic inflammatory infiltrate	1 (2%)		
#Brain stem	(50)	(49)	(49)
Inflammation, acute focal		1 (2%)	
#Corpus callosum	(50)	(49)	(49)
Malacia	1 (2%)		
#Brain/thalamus	(50)	(49)	(49)
Mineralization	21 (42%)	23 (47%)	24 (49%)
Hemorrhage	1 (2%)		
*Cauda equina	(50)	(50)	(49)
Demyelinization		1 (2%)	

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(49)
Degeneration, NOS	1 (2%)		
*Harderian gland	(50)	(50)	(49)
Inflammation, granulomatous focal	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*Abdominal muscle	(50)	(50)	(49)
Inflammation, pyogranulomatous		1 (2%)	
BODY CAVITIES			
*Mediastinum	(50)	(50)	(49)
Inflammation, acute	2 (4%)		
Inflammation, acute fibrinous			1 (2%)
Foreign material, NOS	2 (4%)		
*Peritoneal mesothelium	(50)	(50)	(49)
Hypertrophy, diffuse			1 (2%)
*Parietal peritoneum	(50)	(50)	(49)
Inflammation, acute diffuse			1 (2%)
*Inguinal region	(50)	(50)	(49)
Necrosis, fat		1 (2%)	
*Pleura	(50)	(50)	(49)
Lymphocytic inflammatory infiltrate	2 (4%)	6 (12%)	
Inflammation, acute diffuse			1 (2%)
Inflammation, acute/chronic		1 (2%)	2 (4%)
Inflammation, chronic focal			1 (2%)
Fibrosis, focal			1 (2%)
Fibrosis, multifocal		2 (4%)	
*Pleural mesothelium	(50)	(50)	(49)
Hypertrophy, diffuse			1 (2%)
*Pericardium	(50)	(50)	(49)
Inflammation, acute fibrinous			1 (2%)
Inflammation, acute/chronic	1 (2%)		
*Epicardium	(50)	(50)	(49)
Inflammation, acute focal		1 (2%)	
Inflammation, acute diffuse	2 (4%)		
*Mesentery	(50)	(50)	(49)
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, suppurative			1 (2%)
Inflammation, acute/chronic		1 (2%)	
Necrosis, fat		3 (6%)	3 (6%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(49)
Mineralization	1 (2%)		
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, acute focal		1 (2%)	3 (6%)
Inflammation, acute diffuse			1 (2%)
Inflammation, active chronic			1 (2%)
Inflammation, acute/chronic		4 (8%)	3 (6%)
Inflammation, granulomatous focal		1 (2%)	
Bacterial septicemia		1 (2%)	
Adipose tissue			
Inflammation, acute/chronic	1		

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPS (Continued)

	Vehicle Control	Low Dose	High Dose
SPECIAL MORPHOLOGY SUMMARY			
Animal missing/no necropsy			1

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX E

SUMMARY OF LESIONS IN MALE RATS

IN THE TWO-YEAR GAVAGE STUDY OF THPC

TABLE E1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC

	Vehicle Control	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)
Papilloma, NOS	1 (2%)		
Basal cell tumor		1 (2%)	
Trichoepithelioma		1 (2%)	1 (2%)
Sebaceous adenoma		1 (2%)	
Keratoacanthoma	1 (2%)	3 (6%)	
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)		
Fibroma		3 (6%)	3 (6%)
Fibrosarcoma	1 (2%)	1 (2%)	
Fibrous histiocytoma, malignant		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Transitional cell carcinoma, metastatic	1 (2%)		
C-cell carcinoma, metastatic	1 (2%)		1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	19 (38%)	25 (50%)	16 (32%)
#Cervical lymph node	(47)	(48)	(47)
C-cell carcinoma, metastatic	1 (2%)		
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(49)
Neoplastic nodule	1 (2%)	4 (8%)	2 (4%)
#Pancreas	(49)	(50)	(49)
Acinar cell adenoma	2 (4%)		
#Jejunum	(48)	(49)	(47)
Fibrosarcoma			1 (2%)
#Colon	(48)	(50)	(48)
Fibrosarcoma		1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(49)
Sarcoma, NOS	1 (2%)		1 (2%)
#Kidney/pelvis	(50)	(50)	(49)
Transitional cell carcinoma	1 (2%)		
ENDOCRINE SYSTEM			
#Pituitary intermedia	(50)	(49)	(49)
Adenoma, NOS		1 (2%)	
#Anterior pituitary	(50)	(49)	(49)
Carcinoma, NOS	1 (2%)		
Adenoma, NOS	17 (34%)	11 (22%)	11 (22%)

TABLE E1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Adrenal medulla	(50)	(50)	(49)
Pheochromocytoma	19 (38%)	21 (42%)	16 (33%)
#Thyroid	(47)	(50)	(49)
Follicular cell adenoma		1 (2%)	
Follicular cell carcinoma			1 (2%)
C-cell adenoma	5 (11%)	4 (8%)	2 (4%)
C-cell carcinoma	1 (2%)	1 (2%)	2 (4%)
#Parathyroid	(41)	(44)	(43)
Adenoma, NOS		1 (2%)	
#Pancreatic islets	(49)	(50)	(49)
Islet cell adenoma	2 (4%)	1 (2%)	1 (2%)
Islet cell carcinoma		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS			1 (2%)
Adenocarcinoma, NOS			1 (2%)
Fibroadenoma	2 (4%)	1 (2%)	
*Preputial gland	(50)	(50)	(50)
Adenoma, NOS		1 (2%)	1 (2%)
Adenocarcinoma, NOS		1 (2%)	1 (2%)
#Testis	(50)	(50)	(50)
Interstitial cell tumor	44 (88%)	34 (68%)	38 (76%)
NERVOUS SYSTEM			
#Fourth ventricle	(50)	(50)	(50)
Ependymoma			1 (2%)
#Brain	(50)	(50)	(50)
Astrocytoma	1 (2%)		
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
*Cranial and facial bones	(50)	(50)	(50)
Osteoma	1 (2%)		
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Fibrosarcoma, metastatic		1 (2%)	
*Tunica vaginalis	(50)	(50)	(50)
Mesothelioma, NOS		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Fibrous histiocytoma, metastatic		1 (2%)	
Mesothelioma, malignant	1 (2%)		
Diaphragm			
Fibrosarcoma, metastatic		1	

TABLE E1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	4	7	16
Moribund sacrifice	19	25	16
Terminal sacrifice	26	17	18
Dosing accident	1	1	
TUMOR SUMMARY			
Total animals with primary tumors**	49	44	44
Total primary tumors	123	121	101
Total animals with benign tumors	49	43	43
Total benign tumors	94	85	74
Total animals with malignant tumors	27	27	21
Total malignant tumors	28	31	25
Total animals with secondary tumors##	2	2	1
Total secondary tumors	3	3	1
Total animals with tumors uncertain--benign or malignant	1	5	2
Total uncertain tumors	1	5	2

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE E2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC: VEHICLE CONTROL

ANIMAL NUMBER	029	010	011	040	018	003	001	022	028	047	015	031	034	035	038	006	017	025	045	042	013	009	012	026	002
WEEKS ON STUDY	049	064	065	069	072	073	075	081	084	087	088	089	090	094	098	100	100	100	100	101	102	103	103	103	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS														X											
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS			X																						
Fibrosarcoma		X																							
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma, metastatic													X												
C-cell carcinoma, metastatic																									
Trachea	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	−	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell carcinoma, metastatic																									
Thymus	+	+	+	+	−	−	+	+	+	+	−	+	−	+	+	+	+	+	+	−	−	+	−	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma													X												
Urinary bladder	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS			X						X		X	X			X		X				X		X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma								X		X	X		X					X		X	X		X		X
Thyroid	−	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																									
C-cell carcinoma																									
Parathyroid	+	+	−	+	+	+	−	+	+	+	−	−	+	+	−	−	+	+	+	+	+	+	+	+	−
Pancreatic islets	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma		X														X									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	N	N	N	N	+	+	N	N	N	N	N	+	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	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma																									
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
Carcinoma, NOS							X																		
MUSCULOSKELETAL SYSTEM																									
Bone	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
Osteoma					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
Mesothelioma, malignant																							X		
Leukemia, mononuclear cell						X			X	X	X	X		X	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 missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE E2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0004	0005	0007	0008	0014	0016	0019	0020	0021	0023	0024	0027	0030	0032	0033	0036	0037	0039	0041	0043	0044	0046	0048	0049	0050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50	
Papilloma, NOS																									1	
Keratoacanthoma																					X				1	
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50	
Sarcoma, NOS																									1	
Fibrosarcoma																									1	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Transitional cell carcinoma, metastatic																									1	
C-cell carcinoma, metastatic											X														1	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
C-cell carcinoma, metastatic											X														1	
Thymus	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	–	+	40	
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Neoplastic nodule						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	*50	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Acinar cell adenoma			X	X																					2	
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	48	
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	48	
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	48	
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Sarcoma, NOS			X																						1	
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Transitional cell carcinoma																									1	
Urinary bladder	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Carcinoma, NOS																		X							1	
Adenoma, NOS						X					X	X		X	X					X		X		X	17	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Pheochromocytoma	X	X	X					X		X		X									X	X	X		X	19	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
C-cell adenoma		X										X			X		X						X		5	
C-cell carcinoma											X														1	
Parathyroid	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	41	
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Islet cell adenoma																									2	
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	+	+	+	+	N	+	N	N	N	N	N	N	+	+	+	+	+	N	+	N	+	N	*50
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	X	X	44	
Prostate	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Astrocytoma																	X								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	*50	
Carcinoma, NOS																									1	
MUSCULOSKELETAL SYSTEM																										
Bone	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	
Osteoma																									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	*50	
Mesothelioma, malignant																									1	
Leukemia, mononuclear cell		X	X					X		X				X										X	19	

* Animals necropsied

TABLE E2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC: LOW DOSE

ANIMAL NUMBER	021	032	045	041	018	036	011	005	027	046	047	015	030	034	010	026	013	097	022	006	019	037	001	043	016
WEEKS ON STUDY	019	022	030	037	060	065	077	078	080	084	086	087	091	092	094	094	095	096	096	097	097	097	098	099	100
INTEGUMENTARY SYSTEM																									
Skin																									
Basal cell tumor																									
Trichoepithelioma																									
Sebaceous adenoma																									
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																X									
Fibrosarcoma					X																				
Fibrous histiocytoma, malignant																					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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS							X	X				X			X			X		X	X	X		X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma										X			X		X	X			X		X	X	X		X
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
C-cell adenoma																						X	X		
C-cell carcinoma																									
Parathyroid	+	−	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−
Adenoma, NOS																									
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
Islet cell carcinoma																		X							
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	N	+	N	+	+	N	+	+	N	N	+	N	+	+	N	N	+	+	+	+	N	N
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor									X	X		X	X	X			X		X	X			X		X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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																									
Adenocarcinoma, NOS													X												
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																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, 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
Fibrous histiocytoma, metastatic																					X				
Leukemia, mononuclear cell									X			X	X	X	X	X	X	X	X	X	X	X	X		X
Diaphragm, NOS																									
Fibrosarcoma, metastatic																									

TABLE E2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	017	014	048	033	040	042	035	044	002	003	004	008	009	012	020	023	024	025	028	029	031	038	039	049	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	100	101	101	102	102	102	103	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Basal cell tumor													X													1
Trichoepithelioma																								X		1
Sebaceous adenoma				X																						1
Keratoacanthoma										X											X			X		3
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma		X												X												3
Fibrosarcoma																										1
Fibrous histiocytoma, malignant																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	−	+	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																		X	X		X		X			4
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma								X																		1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS				X	X									X												12
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma		X	X			X			X	X	X		X				X	X	X			X			X	21
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma				X																						1
C-cell adenoma										X													X			4
C-cell carcinoma									X																	1
Parathyroid	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenoma, NOS																			X							1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																						X				1
Islet cell carcinoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	N	N	N	+	N	+	+	+	N	+	N	+	+	+	+	N	N	+	+	+	+	+	+	*50
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	34
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	49
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	*50
Adenoma, NOS																X										1
Adenocarcinoma, NOS																										1
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	*50
Fibrosarcoma, metastatic								X																		1
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
Fibrous histiocytoma, metastatic																										1
Leukemia, mononuclear cell	X	X			X				X		X	X		X	X		X		X			X				25
Diaphragm, NOS																										
Fibrosarcoma, metastatic								X																		1

* Animals necropsied

TABLE E2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC: HIGH DOSE

ANIMAL NUMBER	018	035	007	031	030	028	042	015	034	013	022	024	020	032	047	049	010	046	029	038	019	043	004	026	039
WEEKS ON STUDY	003	003	005	028	045	064	065	080	080	084	084	087	088	088	091	091	092	093	094	094	095	097	098	100	100
INTEGUMENTARY SYSTEM																									
Skin	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trichoepithelioma																				X					
Subcutaneous tissue	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																				X					
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell carcinoma, metastatic																									X
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	
Thymus	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
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	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Large intestine	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Urinary bladder	+	–	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS										X		X					X		X				X	X	X
Adrenal	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma											X	X	X		X		X					X		X	
Thyroid	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																							X		
C-cell adenoma																									
C-cell carcinoma																									X
Parathyroid	+	–	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	N	+	N	N	+	N	+	N	N	N	N	+	N	+	N	N	N	N	N	+	+	+	N
Adenoma, NOS																									
Adenocarcinoma, NOS																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor								X	X			X	X	X	X	X	X	X		X	X	X		X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
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																									
Adenocarcinoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ependymoma																									
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
Carcinoma, 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
Leukemia, mononuclear cell									X						X	X				X		X	X		

TABLE E2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	023	008	012	016	005	036	045	001	002	003	006	009	011	014	017	021	025	027	033	037	040	041	044	048	050	TOTAL:
WEEKS ON STUDY	101	102	102	102	103	103	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Trichoepithelioma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																X		X								3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell carcinoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	47
Thymus	−	+	+	−	+	+	−	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	42
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule												X			X											2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Fibrosarcoma		X																								1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, NOS	X																									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS			X			X														X				X		11
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma			X	X			X			X			X			X							X	X	X	16
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell carcinoma																										1
C-cell adenoma															X					X						2
C-cell carcinoma																						X				2
Parathyroid	+	−	−	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma																	X									1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	+	N	+	+	N	N	+	N	+	+	+	+	+	+	+	+	N	N	+	+	N	N	+	*50
Adenoma, NOS																					X					1
Adenocarcinoma, NOS													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	38
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	*50
Adenoma, NOS									X																	1
Adenocarcinoma, NOS																							X			1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ependymoma													X													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
Carcinoma, 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	X					X		X	X		X								X	X	X	16

* Animals necropsied

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC

	Vehicle Control	3.75 mg/kg	7.5 mg/kg
Skin: Keratoacanthoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	3.8%	17.6%	0.0%
Terminal Rates (c)	1/26 (4%)	3/17 (18%)	0/18 (0%)
Week of First Observation	104	104	
Life Table Tests (d)	P=0.506N	P=0.165	P=0.573N
Incidental Tumor Tests (d)	P=0.506N	P=0.165	P=0.573N
Cochran-Armitage Trend Test (d)	P=0.378N		
Fisher Exact Test (d)		P=0.309	P=0.500N
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	0.0%	12.3%	13.9%
Terminal Rates (c)	0/26 (0%)	1/17 (6%)	2/18 (11%)
Week of First Observation		94	94
Life Table Tests (d)	P=0.064	P=0.085	P=0.076
Incidental Tumor Tests (d)	P=0.085	P=0.156	P=0.096
Cochran-Armitage Trend Test (d)	P=0.101		
Fisher Exact Test (d)		P=0.121	P=0.121
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	2.0%	14.2%	13.9%
Terminal Rates (c)	0/26 (0%)	1/17 (6%)	2/18 (11%)
Week of First Observation	64	60	94
Life Table Tests (d)	P=0.180	P=0.138	P=0.226
Incidental Tumor Tests (d)	P=0.145	P=0.163	P=0.184
Cochran-Armitage Trend Test (d)	P=0.252		
Fisher Exact Test (d)		P=0.181	P=0.309
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	4.1%	14.2%	13.9%
Terminal Rates (c)	0/26 (0%)	1/17 (6%)	2/18 (11%)
Week of First Observation	64	60	94
Life Table Tests (d)	P=0.320	P=0.275	P=0.407
Incidental Tumor Tests (d)	P=0.234	P=0.284	P=0.276
Cochran-Armitage Trend Test (d)	P=0.417		
Fisher Exact Test (d)		P=0.339	P=0.500
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	19/50 (38%)	25/50 (50%)	16/50 (32%)
Adjusted Rates (b)	47.0%	69.8%	55.6%
Terminal Rates (c)	6/26 (23%)	8/17 (47%)	7/18 (39%)
Week of First Observation	73	80	80
Life Table Tests (d)	P=0.398	P=0.049	P=0.484
Incidental Tumor Tests (d)	P=0.201N	P=0.282	P=0.250N
Cochran-Armitage Trend Test (d)	P=0.305N		
Fisher Exact Test (d)		P=0.157	P=0.338N
Liver: Neoplastic Nodule			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	2/49 (4%)
Adjusted Rates (b)	3.8%	23.5%	11.1%
Terminal Rates (c)	1/26 (4%)	4/17 (24%)	2/18 (11%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.250	P=0.071	P=0.371
Incidental Tumor Tests (d)	P=0.250	P=0.071	P=0.371
Cochran-Armitage Trend Test (d)	P=0.398		
Fisher Exact Test (d)		P=0.181	P=0.492

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	3.75 mg/kg	7.5 mg/kg
Pituitary Gland: Adenoma			
Overall Rates (a)	17/50 (34%)	11/49 (22%)	11/49 (22%)
Adjusted Rates (b)	47.7%	32.4%	35.3%
Terminal Rates (c)	9/26 (35%)	1/17 (6%)	2/18 (11%)
Week of First Observation	65	77	84
Life Table Tests (d)	P=0.318N	P=0.380N	P=0.379N
Incidental Tumor Tests (d)	P=0.097N	P=0.133N	P=0.114N
Cochran-Armitage Trend Test (d)	P=0.116N		
Fisher Exact Test (d)		P=0.146N	P=0.146N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	18/50 (36%)	11/49 (22%)	11/49 (22%)
Adjusted Rates (b)	50.7%	32.4%	35.3%
Terminal Rates (c)	10/26 (38%)	1/17 (6%)	2/18 (11%)
Week of First Observation	65	77	84
Life Table Tests (d)	P=0.260N	P=0.323N	P=0.320N
Incidental Tumor Tests (d)	P=0.069N	P=0.101N	P=0.084N
Cochran-Armitage Trend Test (d)	P=0.079N		
Fisher Exact Test (d)		P=0.104N	P=0.104N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	19/50 (38%)	21/50 (42%)	16/49 (33%)
Adjusted Rates (b)	54.2%	68.9%	52.7%
Terminal Rates (c)	11/26 (42%)	9/17 (53%)	6/18 (33%)
Week of First Observation	81	84	84
Life Table Tests (d)	P=0.387	P=0.107	P=0.467
Incidental Tumor Tests (d)	P=0.272N	P=0.375	P=0.286N
Cochran-Armitage Trend Test (d)	P=0.330N		
Fisher Exact Test (d)		P=0.419	P=0.365N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	5/47 (11%)	4/50 (8%)	2/49 (4%)
Adjusted Rates (b)	19.2%	17.7%	11.1%
Terminal Rates (c)	5/26 (19%)	2/17 (12%)	2/18 (11%)
Week of First Observation	104	97	104
Life Table Tests (d)	P=0.329N	P=0.548	P=0.382N
Incidental Tumor Tests (d)	P=0.280N	P=0.633N	P=0.382N
Cochran-Armitage Trend Test (d)	P=0.153N		
Fisher Exact Test (d)		P=0.460N	P=0.201N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	6/47 (13%)	5/50 (10%)	4/49 (8%)
Adjusted Rates (b)	23.1%	23.1%	19.8%
Terminal Rates (c)	6/26 (23%)	3/17 (18%)	3/18 (17%)
Week of First Observation	104	97	100
Life Table Tests (d)	P=0.543N	P=0.489	P=0.606N
Incidental Tumor Tests (d)	P=0.474N	P=0.587	P=0.567N
Cochran-Armitage Trend Test (d)	P=0.283N		
Fisher Exact Test (d)		P=0.456N	P=0.344N
Testis: Interstitial Cell Tumor			
Overall Rates (a)	44/50 (88%)	34/50 (68%)	38/50 (76%)
Adjusted Rates (b)	97.7%	100.0%	100.0%
Terminal Rates (c)	25/26 (96%)	17/17 (100%)	18/18 (100%)
Week of First Observation	65	80	80
Life Table Tests (d)	P=0.226	P=0.431	P=0.265
Incidental Tumor Tests (d)	P=0.257N	P=0.069N	P=0.361N
Cochran-Armitage Trend Test (d)	P=0.094N		
Fisher Exact Test (d)		P=0.015N	P=0.097N

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC (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 vehicle 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 vehicle 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 exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE E4. HISTORICAL INCIDENCE OF LEUKEMIA IN MALE F344/N RATS (a)

Study	Incidence in Controls
Historical Incidence in All Water Controls	
THPS (b)	30/50
THPC (b)	19/50
Chlorpheniramine maleate (b)	25/50
TOTAL	74/150 (49.3%)
SD	11.02%
Overall Historical Incidence in Untreated Controls	
TOTAL	458/1,727 (26.5%)
SD (c)	8.83%
Range (d)	
High	23/50
Low	5/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Battelle Columbus Laboratories
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE E5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC

	Vehicle Control	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%)	1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Hemorrhagic cyst			1 (2%)
Inflammation, suppurative			1 (2%)
Inflammation, chronic focal	1 (2%)	1 (2%)	
RESPIRATORY SYSTEM			
#Trachea	(49)	(50)	(50)
Inflammation, acute diffuse	2 (4%)		
#Peritracheal tissue	(49)	(50)	(50)
Inflammation, acute		1 (2%)	
Inflammation, acute/chronic	1 (2%)		
#Lung	(50)	(50)	(50)
Aspiration, foreign body	3 (6%)	1 (2%)	
Congestion, acute		1 (2%)	9 (18%)
Edema, NOS	1 (2%)	1 (2%)	6 (12%)
Hemorrhage		1 (2%)	
Inflammation, active chronic			1 (2%)
Pneumonia, interstitial chronic	9 (18%)	4 (8%)	10 (20%)
Inflammation, granulomatous focal	2 (4%)	4 (8%)	3 (6%)
Fibrosis, diffuse			1 (2%)
Alveolar macrophages			1 (2%)
Hyperplasia, alveolar epithelium	1 (2%)	1 (2%)	5 (10%)
#Lung/alveoli	(50)	(50)	(50)
Mineralization		1 (2%)	
Hemorrhage		2 (4%)	3 (6%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(48)	(50)	(49)
Hyperplasia, granulocytic			2 (4%)
Hypoplasia, hematopoietic			1 (2%)
#Spleen	(50)	(50)	(49)
Adhesion, NOS		1 (2%)	
Depletion, lymphoid		1 (2%)	
#Splenic red pulp	(50)	(50)	(49)
Congestion, NOS			1 (2%)
Fibrosis, focal	1 (2%)	3 (6%)	4 (8%)
Fibrosis, multifocal	1 (2%)	3 (6%)	
Hemosiderosis	1 (2%)		
Hematopoiesis	1 (2%)	5 (10%)	3 (6%)
#Lymph node	(47)	(48)	(47)
Hemorrhage	1 (2%)		
#Mandibular lymph node	(47)	(48)	(47)
Plasmacytosis	2 (4%)	2 (4%)	5 (11%)
Hyperplasia, lymphoid	1 (2%)		
#Mediastinal lymph node	(47)	(48)	(47)
Edema, NOS	1 (2%)		
Inflammation, granulomatous	1 (2%)		
Angiectasis	1 (2%)		
#Pancreatic lymph node	(47)	(48)	(47)
Granuloma, NOS			1 (2%)

TABLE E5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Mesenteric lymph node	(47)	(48)	(47)
Hemorrhage	1 (2%)		1 (2%)
Inflammation, chronic focal			2 (4%)
Granuloma, NOS	2 (4%)		
Depletion, lymphoid			1 (2%)
Plasmacytosis		1 (2%)	
#Renal lymph node	(47)	(48)	(47)
Hemorrhage			1 (2%)
Inflammation, granulomatous focal		1 (2%)	
#Axillary lymph node	(47)	(48)	(47)
Inflammation, acute focal	1 (2%)		
#Thymic lymph node	(47)	(48)	(47)
Hemorrhage			2 (4%)
#Liver	(50)	(50)	(49)
Hematopoiesis		1 (2%)	
#Adrenal cortex	(50)	(50)	(49)
Hematopoiesis			1 (2%)
#Thymus	(40)	(41)	(42)
Embryonal duct cyst			1 (2%)
Hemorrhage		1 (2%)	1 (2%)
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, granulomatous focal			1 (2%)
Depletion, lymphoid	23 (58%)	23 (56%)	20 (48%)
CIRCULATORY SYSTEM			
#Mandibular lymph node	(47)	(48)	(47)
Lymphangiectasis		2 (4%)	3 (6%)
#Mesenteric lymph node	(47)	(48)	(47)
Lymphangiectasis	1 (2%)	3 (6%)	
#Renal lymph node	(47)	(48)	(47)
Lymphangiectasis		1 (2%)	1 (2%)
#Thymic lymph node	(47)	(48)	(47)
Lymphangiectasis		1 (2%)	1 (2%)
#Heart/atrium	(50)	(50)	(50)
Dilatation, NOS			1 (2%)
Thrombus, mural	6 (12%)	4 (8%)	4 (8%)
#Myocardium	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic focal			1 (2%)
Degeneration, NOS	43 (86%)	42 (84%)	42 (84%)
*Sup. pancreaticoduodenal artery	(50)	(50)	(50)
Hyperplasia, focal			1 (2%)
*Hepatic vein	(50)	(50)	(50)
Thrombus, mural	1 (2%)		
*Central veins/liver	(50)	(50)	(50)
Thrombus, mural			1 (2%)
#Pancreas	(49)	(50)	(49)
Periarteritis		1 (2%)	
*Mesentery	(50)	(50)	(50)
Periarteritis		2 (4%)	
#Testis	(50)	(50)	(50)
Periarteritis	1 (2%)	1 (2%)	
#Adrenal cortex	(50)	(50)	(49)
Thrombosis, NOS	1 (2%)		
#Thymus	(40)	(41)	(42)
Periarteritis	1 (3%)		

TABLE E5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM			
#Salivary gland	(48)	(49)	(50)
Atrophy, focal		1 (2%)	
#Salivary seromucous gland	(48)	(49)	(50)
Necrosis, focal			1 (2%)
#Liver	(50)	(50)	(49)
Inflammation, acute focal	1 (2%)		
Inflammation, chronic focal	1 (2%)		
Basophilic cyto change	20 (40%)	18 (36%)	13 (27%)
Eosinophilic cyto change		2 (4%)	2 (4%)
Clear cell change	3 (6%)	6 (12%)	
Angiectasis	16 (32%)	17 (34%)	13 (27%)
#Liver/centrilobular	(50)	(50)	(49)
Necrosis, focal	1 (2%)	1 (2%)	2 (4%)
Cytoplasmic vacuolization		1 (2%)	
#Liver/periportal	(50)	(50)	(49)
Cytoplasmic vacuolization		8 (16%)	23 (47%)
#Liver/hepatocytes	(50)	(50)	(49)
Degeneration, cystic	12 (24%)	26 (52%)	23 (47%)
#Bile duct	(50)	(50)	(49)
Hyperplasia, focal	27 (54%)	37 (74%)	34 (69%)
#Pancreas	(49)	(50)	(49)
Dilatation/ducts	1 (2%)		1 (2%)
Hemorrhage			1 (2%)
Inflammation, chronic focal		1 (2%)	
Focal cellular change	1 (2%)		
#Pancreatic acinus	(49)	(50)	(49)
Atrophy, focal	14 (29%)	13 (26%)	18 (37%)
Atrophy, diffuse	1 (2%)		
Hyperplasia, NOS	1 (2%)		
#Periesophageal tissue	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
#Glandular stomach	(48)	(50)	(49)
Mineralization	1 (2%)	5 (10%)	1 (2%)
Ulcer, acute		2 (4%)	1 (2%)
Inflammation, active chronic		1 (2%)	1 (2%)
Necrosis, focal	1 (2%)		
#Gastric submucosa	(48)	(50)	(49)
Inflammation, active chronic		1 (2%)	
#Forestomach	(48)	(50)	(49)
Ulcer, acute	1 (2%)	1 (2%)	
Inflammation, acute focal		1 (2%)	
Inflammation, acute diffuse	1 (2%)		
Inflammation, active chronic		1 (2%)	2 (4%)
Hyperplasia, epithelial	1 (2%)	1 (2%)	1 (2%)
#Jejunum	(48)	(49)	(47)
Ulcer, chronic	1 (2%)		
#Colon	(48)	(50)	(48)
Ulcer, NOS		1 (2%)	
Parasitism	1 (2%)		1 (2%)
#Cecum	(48)	(50)	(48)
Inflammation, acute diffuse	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(50)	(49)
Nephropathy	47 (94%)	47 (94%)	46 (94%)
Infarct, acute	1 (2%)		
Infarct, healed		1 (2%)	

TABLE E5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM (Continued)			
#Kidney/cortex	(50)	(50)	(49)
Cyst, NOS	1 (2%)	2 (4%)	2 (4%)
Multiple cysts		2 (4%)	
Necrosis, focal	2 (4%)		
#Renal papilla	(50)	(50)	(49)
Necrosis, NOS		1 (2%)	
#Kidney/tubule	(50)	(50)	(49)
Mineralization		1 (2%)	
Pigmentation, NOS		2 (4%)	
#Kidney/pelvis	(50)	(50)	(49)
Hemorrhage			1 (2%)
Inflammation, acute diffuse	1 (2%)		
#Renal pelvis/mucosa	(50)	(50)	(49)
Hyperplasia, epithelial	9 (18%)	9 (18%)	6 (12%)
#Urinary bladder	(48)	(50)	(47)
Retention fluid		1 (2%)	
Hemorrhage			1 (2%)
Ulcer, acute		2 (4%)	
Inflammation, acute focal	1 (2%)	1 (2%)	
Inflammation, acute diffuse	1 (2%)	1 (2%)	1 (2%)
Inflammation, active chronic		2 (4%)	
Hyperplasia, epithelial		3 (6%)	2 (4%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(49)	(49)
Cyst, NOS		6 (12%)	4 (8%)
Hemorrhagic cyst			1 (2%)
Necrosis, hemorrhagic	1 (2%)		
Focal cellular change		1 (2%)	
Hyperplasia, focal	5 (10%)	6 (12%)	10 (20%)
#Adrenal/capsule	(50)	(50)	(49)
Hyperplasia, focal		1 (2%)	
#Adrenal cortex	(50)	(50)	(49)
Hemorrhage			3 (6%)
Necrosis, focal			1 (2%)
Metamorphosis, fatty	8 (16%)	14 (28%)	9 (18%)
Cytoplasmic vacuolization			3 (6%)
Focal cellular change	1 (2%)	3 (6%)	
Hyperplasia, focal	6 (12%)	4 (8%)	4 (8%)
#Adrenal medulla	(50)	(50)	(49)
Hemorrhagic cyst	1 (2%)		
Hyperplasia, focal	14 (28%)	16 (32%)	10 (20%)
#Thyroid	(47)	(50)	(49)
Embryonal duct cyst			1 (2%)
Follicular cyst, NOS	2 (4%)	4 (8%)	3 (6%)
Hyperplasia, C-cell	29 (62%)	16 (32%)	19 (39%)
Hyperplasia, follicular cell		1 (2%)	
#Parathyroid	(41)	(44)	(43)
Hyperplasia, NOS	10 (24%)	13 (30%)	8 (19%)
#Pancreatic islets	(49)	(50)	(49)
Atrophy, focal		1 (2%)	
Hyperplasia, focal	1 (2%)		1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Hyperplasia, cystic	24 (48%)	25 (50%)	20 (40%)
*Prepuce	(50)	(50)	(50)
Inflammation chronic suppurative			2 (4%)

TABLE E5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
*Preputial gland	(50)	(50)	(50)
Dilatation/ducts			1 (2%)
Retention fluid			1 (2%)
Cyst, NOS			1 (2%)
Abscess, NOS		1 (2%)	1 (2%)
Inflammation, active chronic			4 (8%)
#Prostate	(48)	(49)	(49)
Hemorrhage		1 (2%)	
Inflammation, acute focal	2 (4%)	1 (2%)	3 (6%)
Inflammation, active chronic	11 (23%)	10 (20%)	13 (27%)
Inflammation, chronic focal	3 (6%)	4 (8%)	2 (4%)
Hyperplasia, epithelial	1 (2%)		2 (4%)
*Seminal vesicle	(50)	(50)	(50)
Retention fluid			1 (2%)
Hemorrhage		1 (2%)	
Inflammation, acute focal			1 (2%)
Inflammation, acute diffuse		1 (2%)	
Hyperplasia, epithelial		1 (2%)	
#Testis	(50)	(50)	(50)
Degeneration, NOS	1 (2%)		
Hyperplasia, interstitial cell	12 (24%)	22 (44%)	22 (44%)
#Tunica albuginea	(50)	(50)	(50)
Inflammation, chronic diffuse	1 (2%)		
#Testis/tubule	(50)	(50)	(50)
Mineralization		3 (6%)	
Degeneration, NOS	2 (4%)	11 (22%)	8 (16%)
Necrosis, focal	1 (2%)		
Atrophy, focal		1 (2%)	1 (2%)
Atrophy, diffuse			1 (2%)
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Inflammation, acute focal		1 (2%)	
#Cerebral ventricle	(50)	(50)	(50)
Hydrocephalus, NOS		2 (4%)	1 (2%)
Hemorrhage		1 (2%)	
#Cerebrum	(50)	(50)	(50)
Hemorrhage	2 (4%)	4 (8%)	
Necrosis, focal		1 (2%)	
Atrophy, pressure	3 (6%)	3 (6%)	4 (8%)
#Cerebellum	(50)	(50)	(50)
Hemorrhage		1 (2%)	
SPECIAL SENSE ORGANS			
*Eye/cornea	(50)	(50)	(50)
Inflammation, chronic diffuse	1 (2%)		
*Eye/retina	(50)	(50)	(50)
Atrophy, focal		1 (2%)	3 (6%)
Atrophy, diffuse	3 (6%)		1 (2%)
*Eye/crystalline lens	(50)	(50)	(50)
Cataract	3 (6%)	1 (2%)	3 (6%)
*Harderian gland	(50)	(50)	(50)
Inflammation, acute focal	1 (2%)		
Hyperplasia, epithelial			1 (2%)

TABLE E5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	Low Dose	High Dose
MUSCULOSKELETAL SYSTEM			
*Femur	(50)	(50)	(50)
Fibrous osteodystrophy	4 (8%)	7 (14%)	1 (2%)
*Skeletal muscle	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Inflammation, acute focal	1 (2%)		
Reaction, foreign body		1 (2%)	
*Epicardium	(50)	(50)	(50)
Inflammation, acute focal	1 (2%)		
*Mesentery	(50)	(50)	(50)
Inflammation, acute diffuse	1 (2%)		
Inflammation, active chronic		2 (4%)	
Inflammation, granulomatous focal			2 (4%)
Necrosis, fat		1 (2%)	
*Tunica vaginalis	(50)	(50)	(50)
Hyperplasia, mesothelial		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Mineralization	1 (2%)	2 (4%)	
Hyperplasia, focal		3 (6%)	
SPECIAL MORPHOLOGY SUMMARY			
None			

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site.

APPENDIX F

SUMMARY OF LESIONS IN FEMALE RATS

IN THE TWO-YEAR GAVAGE STUDY OF THPC

TABLE F1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC

	Vehicle Control	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 carcinoma			1 (2%)
Basal cell carcinoma			1 (2%)
Keratoacanthoma	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)		
Fibroma	1 (2%)	1 (2%)	
Fibrosarcoma		1 (2%)	1 (2%)
Fibrous histiocytoma, malignant			1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Squamous cell carcinoma		1 (2%)	
Squamous cell carcinoma, unclear prim/meta			1 (2%)
Alveolar/bronchiolar adenoma		1 (2%)	
C-cell carcinoma, metastatic			1 (2%)
Pheochromocytoma, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	4 (8%)	8 (16%)	7 (14%)
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)		1 (2%)
#Liver	(50)	(50)	(50)
Neoplastic nodule		1 (2%)	
#Pylorus	(50)	(50)	(50)
Adenocarcinoma, NOS		1 (2%)	
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(50)	(50)
Carcinoma, NOS		1 (2%)	
Adenoma, NOS	24 (49%)	28 (56%)	20 (40%)
#Adrenal	(50)	(50)	(50)
Cortical adenoma	1 (2%)		
#Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma	2 (4%)	3 (6%)	
Pheochromocytoma, malignant		1 (2%)	
#Thyroid	(50)	(50)	(50)
Follicular cell adenoma	3 (6%)		1 (2%)
C-cell adenoma	6 (12%)	11 (22%)	4 (8%)
C-cell carcinoma	1 (2%)	1 (2%)	1 (2%)

TABLE F1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Pancreatic islets	(50)	(50)	(50)
Islet cell adenoma		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS	2 (4%)	1 (2%)	
Adenocarcinoma, NOS	1 (2%)	2 (4%)	1 (2%)
Fibroadenoma	11 (22%)	7 (14%)	6 (12%)
*Clitoral gland	(50)	(50)	(50)
Adenoma, NOS		1 (2%)	
Adenocarcinoma, NOS	3 (6%)	1 (2%)	1 (2%)
#Uterus	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)		
Adenoma, NOS			1 (2%)
Endometrial stromal polyp	10 (20%)	13 (26%)	9 (18%)
#Cervix uteri	(50)	(50)	(50)
Sarcoma, NOS		1 (2%)	
#Endometrial gland	(50)	(50)	(50)
Adenomatous polyp, NOS	1 (2%)		
#Ovary	(50)	(50)	(50)
Granulosa cell tumor	1 (2%)	1 (2%)	
NERVOUS SYSTEM			
#Cerebrum	(50)	(50)	(50)
Carcinoma, NOS, invasive		1 (2%)	
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Thorax	(50)	(50)	(50)
Lipoma		1 (2%)	
*Parietal pleura	(50)	(50)	(50)
Squamous cell carcinoma, invasive		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Sarcoma, NOS, unclear primary or metastatic			1 (2%)
Fibrous histiocytoma, metastatic			1 (2%)
Broad ligament			
Leiomyosarcoma	1		

TABLE F1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	5	4	18
Moribund sacrifice	8	13	9
Terminal sacrifice	36	33	21
Dosing accident	1		2
TUMOR SUMMARY			
Total animals with primary tumors**	40	45	36
Total primary tumors	77	88	58
Total animals with benign tumors	37	40	31
Total benign tumors	63	68	42
Total animals with malignant tumors	12	17	14
Total malignant tumors	13	18	14
Total animals with secondary tumors##		3	2
Total secondary tumors		3	2
Total animals with tumors uncertain-- benign or malignant	1	2	
Total uncertain tumors	1	2	
Total animals with tumors uncertain-- primary or metastatic			2
Total uncertain tumors			2

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE F2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC: VEHICLE CONTROL

ANIMAL NUMBER	0027	0002	0039	0008	0021	0047	0046	0007	0009	0013	0019	0042	0048	0001	0003	0004	0005	0006	0010	0011	0012	0014	0015	0016	0017
WEEKS ON STUDY	074	076	077	078	085	087	092	098	098	098	101	101	102	104	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma								X																	
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS										X															
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Thymus	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	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
Squamous cell papilloma			X																						
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS		X	X	X			X	X		X		X	X					X	X				X	X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma								X																	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																	X				X				
C-cell adenoma											X								X						
C-cell carcinoma																									
Parathyroid	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	−	+	+	+	+	−	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	N	+	N	+	N	+	N	+	+	+
Adenoma, NOS																									
Adenocarcinoma, NOS																							X		
Fibroadenoma		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
Adenocarcinoma, NOS				X																					
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenomatous polyp, NOS																									
Leiomyosarcoma																				X					
Endometrial stromal polyp					X								X				X		X				X	X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Carcinoma, 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
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 missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE F2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	018	020	022	023	024	025	026	028	029	030	031	032	033	034	035	036	037	038	040	041	043	044	045	049	050	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Keratoacanthoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibroma										X																1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	46
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	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
Squamous cell papilloma																										1
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	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	49
Adenoma, NOS	X	X		X	X		X		X					X	X	X			X	X	X					24
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																								X		1
Pheochromocytoma								X																		2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma								X																		3
C-cell adenoma	X	X										X			X											6
C-cell carcinoma																				X						1
Parathyroid	+	+	–	+	+	+	–	+	+	–	–	+	+	+	–	+	+	+	+	+	+	+	–	+	+	40
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	+	*50
Adenoma, NOS										X									X							2
Adenocarcinoma, NOS																										1
Fibroadenoma				X			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	*50
Adenocarcinoma, NOS		X								X																3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS	X																									1
Adenomatous polyp, NOS															X											1
Leiomyosarcoma																										1
Endometrial stromal polyp			X					X						X									X			10
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor	X																									1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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
Carcinoma, 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									4

* Animals necropsied

TABLE F2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC: LOW DOSE

ANIMAL NUMBER	00006	00028	00044	00033	00008	00036	00037	00025	00026	00016	00021	00047	00002	00032	00111	00043	00001	00003	00004	00005	00007	00009	00110	00112	00113
WEEKS ON STUDY	03039	06021	07077	07788	08000	08585	08585	09303	09933	09966	09966	09966	09988	09909	10011	10021	10044	10044	10044	10044	10044	10044	10044	10044	10044
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma										X															
Fibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma											X														
Alveolar/bronchiolar adenoma																									
Pheochromocytoma, metastatic									X																
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	–	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS		X																							
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS							X	X		X				X	X	X	X		X	X	X	X	X	X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma									X						X					X					
Pheochromocytoma, malignant									X																
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma								X				X	X										X		
C-cell carcinoma																X									
Parathyroid	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																		X							
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	N	+	+	N	N	+	+	+	N	+	+	+	N	N	N	+	+	+	+	+	+
Adenoma, NOS															X										
Adenocarcinoma, NOS																								X	
Fibroadenoma							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																							X		
Adenocarcinoma, NOS															X										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS												X													
Endometrial stromal polyp																		X		X					X
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																									
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
Squamous cell carcinoma, invasive											X														
Lipoma																									
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, mononuclear cell					X	X		X				X	X												

TABLE F2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	0 1 4	0 1 5	0 1 7	0 1 8	0 1 9	0 2 0	0 2 2	0 2 3	0 2 4	0 2 7	0 2 9	0 3 0	0 3 1	0 3 4	0 3 5	0 3 8	0 3 9	0 4 0	0 4 1	0 4 2	0 4 5	0 4 6	0 4 8	0 4 9	0 5 0	TOTAL:
WEEKS ON STUDY	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 4	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 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50	
Fibroma																									1	
Fibrosarcoma									X																1	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Squamous cell carcinoma																									1	
Alveolar/bronchiolar adenoma												X													1	
Pheochromocytoma, metastatic																									1	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	46	
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Neoplastic nodule												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	*50	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Adenocarcinoma, NOS																									1	
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Carcinoma, NOS							X																		1	
Adenoma, NOS			X	X					X	X		X		X	X	X	X	X		X	X	X		X	28	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Pheochromocytoma																									3	
Pheochromocytoma, malignant																									1	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
C-cell adenoma				X		X		X			X	X				X		X							11	
C-cell carcinoma																									1	
Parathyroid	+	+	+	−	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	−	+	+	−	42	
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Islet cell adenoma																									1	
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	N	+	N	+	*50
Adenoma, NOS																										1
Adenocarcinoma, NOS															X											2
Fibroadenoma				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	*50
Adenoma, NOS																										1
Adenocarcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Sarcoma, NOS																										1
Endometrial stromal polyp	X	X	X		X	X	X								X	X				X			X			13
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor																							X			1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Carcinoma, NOS, invasive							X																		1	
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	*50	
Squamous cell carcinoma, invasive																									1	
Lipoma																							X		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	*50	
Leukemia, mononuclear cell						X							X	X											8	

* Animals necropsied

TABLE F2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC: HIGH DOSE

ANIMAL NUMBER	0006	0032	0036	0042	0020	0007	0010	0016	0021	0029	0045	0048	0050	0003	0002	0019	0026	0033	0004	0017	0011	0035	0055	0034	0038
WEEKS ON STUDY	007	053	055	065	068	069	070	071	071	071	071	071	071	072	074	078	078	082	088	088	090	093	094	094	095
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Basal cell carcinoma																							X		
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																X									
Fibrous histiocytoma, malignant																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, unclear primary/metastatic																X									
C-cell carcinoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	–	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	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
Squamous cell papilloma								X																	
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS			X					X		X						X		X		X			X	X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
C-cell adenoma																				X					
C-cell carcinoma																									
Parathyroid	+	+	+	+	+	–	+	–	+	–	–	–	+	+	–	+	+	+	+	+	+	+	+	–	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Fibroadenoma																									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
Adenocarcinoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																							X		
Endometrial stromal polyp							X							X										X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Sarcoma, NOS, unclear primary or metastatic		X																							
Fibrous histiocytoma, metastatic																									
Leukemia, mononuclear cell																		X		X	X	X			X

TABLE F2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	025	001	022	039	008	009	012	013	014	015	018	023	024	027	028	030	031	037	040	041	043	044	046	047	049	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	097	099	101	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell carcinoma																X										1
Basal cell carcinoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										1
Fibrous histiocytoma, malignant			X																							1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcin, unclear prim/meta																										1
C-cell carcinoma, metastatic																			X							1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	46
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	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
Squamous cell papilloma																										1
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	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS				X		X		X			X	X			X					X	X	X	X	X	X	20
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma												X														1
C-cell adenoma				X					X			X														4
C-cell carcinoma																			X							1
Parathyroid	+	+	–	+	+	–	+	+	+	+	+	+	+	–	–	+	–	+	+	–	+	+	–	–	–	34
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	*50
Adenocarcinoma, NOS											X															1
Fibroadenoma									X			X	X					X	X							6
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	*50
Adenocarcinoma, NOS																			X							1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																										1
Endometrial stromal polyp	X						X		X	X								X		X						9
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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
Sarcoma, NOS, unclear prim or meta																										1
Fibrous histiocytoma, metastatic			X																							1
Leukemia, mononuclear cell	X																						X			7

* Animals necropsied

TABLE F3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC

	Vehicle Control	3.75 mg/kg	7.5 mg/kg
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	4/50 (8%)	8/50 (16%)	7/50 (14%)
Adjusted Rates (b)	9.7%	19.1%	22.9%
Terminal Rates (c)	2/37 (5%)	3/34 (9%)	1/21 (5%)
Week of First Observation	87	80	82
Life Table Tests (d)	P=0.058	P=0.160	P=0.081
Incidental Tumor Tests (d)	P=0.209	P=0.217	P=0.271
Cochran-Armitage Trend Test (d)	P=0.226		
Fisher Exact Test (d)		P=0.178	P=0.262
Pituitary Gland: Adenoma			
Overall Rates (a)	24/49 (49%)	28/50 (56%)	20/50 (40%)
Adjusted Rates (b)	53.9%	69.8%	64.0%
Terminal Rates (c)	16/36 (44%)	22/34 (65%)	11/21 (52%)
Week of First Observation	76	85	55
Life Table Tests (d)	P=0.111	P=0.211	P=0.170
Incidental Tumor Tests (d)	P=0.456N	P=0.293	P=0.373N
Cochran-Armitage Trend Test (d)	P=0.212N		
Fisher Exact Test (d)		P=0.309	P=0.243N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	24/49 (49%)	29/50 (58%)	20/50 (40%)
Adjusted Rates (b)	53.9%	72.3%	64.0%
Terminal Rates (c)	16/36 (44%)	23/34 (68%)	11/21 (52%)
Week of First Observation	76	85	55
Life Table Tests (d)	P=0.105	P=0.162	P=0.170
Incidental Tumor Tests (d)	P=0.470N	P=0.226	P=0.373N
Cochran-Armitage Trend Test (d)	P=0.211N		
Fisher Exact Test (d)		P=0.243	P=0.243N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	2/50 (4%)	(e) 3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	5.0%	7.8%	0.0%
Terminal Rates (c)	1/37 (3%)	1/34 (3%)	0/21 (0%)
Week of First Observation	98	93	
Life Table Tests (d)	P=0.348N	P=0.464	P=0.373N
Incidental Tumor Tests (d)	P=0.200N	P=0.597	P=0.265N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test (d)		P=0.500	P=0.247N
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted Rates (b)	8.1%	0.0%	4.8%
Terminal Rates (c)	3/37 (8%)	0/34 (0%)	1/21 (5%)
Week of First Observation	104		104
Life Table Tests (d)	P=0.299N	P=0.136N	P=0.522N
Incidental Tumor Tests (d)	P=0.299N	P=0.136N	P=0.522N
Cochran-Armitage Trend Test (d)	P=0.176N		
Fisher Exact Test (d)		P=0.121N	P=0.309N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	6/50 (12%)	11/50 (22%)	4/50 (8%)
Adjusted Rates (b)	15.7%	29.0%	16.3%
Terminal Rates (c)	5/37 (14%)	8/34 (24%)	2/21 (10%)
Week of First Observation	101	93	88
Life Table Tests (d)	P=0.382	P=0.110	P=0.552
Incidental Tumor Tests (d)	P=0.552	P=0.156	P=0.568N
Cochran-Armitage Trend Test (d)	P=0.333N		
Fisher Exact Test (d)		P=0.143	P=0.370N

TABLE F3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	3.75 mg/kg	7.5 mg/kg
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	7/50 (14%)	12/50 (24%)	5/50 (10%)
Adjusted Rates (b)	18.3%	31.1%	20.7%
Terminal Rates (c)	6/37 (16%)	8/34 (24%)	3/21 (14%)
Week of First Observation	101	93	88
Life Table Tests (d)	P=0.334	P=0.118	P=0.479
Incidental Tumor Tests (d)	P=0.519	P=0.175	P=0.618
Cochran-Armitage Trend Test (d)	P=0.341N		
Fisher Exact Test (d)		P=0.154	P=0.380N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	11/50 (22%)	7/50 (14%)	6/50 (12%)
Adjusted Rates (b)	27.1%	18.2%	26.7%
Terminal Rates (c)	8/37 (22%)	4/34 (12%)	5/21 (24%)
Week of First Observation	76	85	95
Life Table Tests (d)	P=0.445N	P=0.283N	P=0.559N
Incidental Tumor Tests (d)	P=0.228N	P=0.209N	P=0.342N
Cochran-Armitage Trend Test (d)	P=0.110N		
Fisher Exact Test (d)		P=0.218N	P=0.143N
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (a)	11/50 (22%)	8/50 (16%)	6/50 (12%)
Adjusted Rates (b)	27.1%	20.5%	26.7%
Terminal Rates (c)	8/37 (22%)	4/34 (12%)	5/21 (24%)
Week of First Observation	76	85	95
Life Table Tests (d)	P=0.465N	P=0.381N	P=0.559N
Incidental Tumor Tests (d)	P=0.223N	P=0.275N	P=0.342N
Cochran-Armitage Trend Test (d)	P=0.114N		
Fisher Exact Test (d)		P=0.306N	P=0.143N
Mammary Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	8.1%	8.5%	4.8%
Terminal Rates (c)	3/37 (8%)	2/34 (6%)	1/21 (5%)
Week of First Observation	104	100	104
Life Table Tests (d)	P=0.443N	P=0.621	P=0.522N
Incidental Tumor Tests (d)	P=0.393N	P=0.661	P=0.522N
Cochran-Armitage Trend Test (d)	P=0.238N		
Fisher Exact Test (d)		P=0.661	P=0.309N
Mammary Gland: Adenoma, Fibroadenoma, or Adenocarcinoma			
Overall Rates (a)	11/50 (22%)	10/50 (20%)	7/50 (14%)
Adjusted Rates (b)	27.1%	25.8%	31.3%
Terminal Rates (c)	8/37 (22%)	6/34 (18%)	6/21 (29%)
Week of First Observation	76	85	95
Life Table Tests (d)	P=0.479	P=0.578N	P=0.520
Incidental Tumor Tests (d)	P=0.376N	P=0.474N	P=0.482N
Cochran-Armitage Trend Test (d)	P=0.185N		
Fisher Exact Test (d)		P=0.500N	P=0.218N
Clitoral Gland: Adenocarcinoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	7.4%	2.8%	4.8%
Terminal Rates (c)	2/37 (5%)	0/34 (0%)	1/21 (5%)
Week of First Observation	78	100	104
Life Table Tests (d)	P=0.340N	P=0.332N	P=0.495N
Incidental Tumor Tests (d)	P=0.178N	P=0.311N	P=0.336N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test (d)		P=0.309N	P=0.309N

TABLE F3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	3.75 mg/kg	7.5 mg/kg
Clitoral Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	7.4%	5.6%	4.8%
Terminal Rates (c)	2/37 (5%)	1/34 (3%)	1/21 (5%)
Week of First Observation	78	100	104
Life Table Tests (d)	P=0.387N	P=0.532N	P=0.495N
Incidental Tumor Tests (d)	P=0.226N	P=0.513N	P=0.336N
Cochran-Armitage Trend Test (d)	P=0.222N		
Fisher Exact Test (d)		P=0.500N	P=0.309N
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	10/50 (20%)	13/50 (26%)	9/50 (18%)
Adjusted Rates (b)	26.0%	38.2%	32.9%
Terminal Rates (c)	9/37 (24%)	13/34 (38%)	5/21 (24%)
Week of First Observation	85	104	70
Life Table Tests (d)	P=0.164	P=0.234	P=0.239
Incidental Tumor Tests (d)	P=0.311	P=0.235	P=0.475
Cochran-Armitage Trend Test (d)	P=0.451N		
Fisher Exact Test (d)		P=0.317	P=0.500N

(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 vehicle 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 vehicle 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 exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) A malignant pheochromocytoma was also present in one of these animals.

TABLE F4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
None			
RESPIRATORY SYSTEM			
#Trachea	(49)	(50)	(50)
Inflammation, acute focal		1 (2%)	1 (2%)
#Lung	(50)	(50)	(50)
Aspiration, foreign body	1 (2%)		1 (2%)
Congestion, acute	3 (6%)	2 (4%)	12 (24%)
Edema, NOS		2 (4%)	11 (22%)
Hemorrhage		1 (2%)	1 (2%)
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, interstitial	3 (6%)	3 (6%)	6 (12%)
Abscess, NOS	1 (2%)		
Inflammation, active chronic			2 (4%)
Inflammation, granulomatous focal	8 (16%)	2 (4%)	1 (2%)
Necrosis, focal			1 (2%)
Alveolar macrophages	4 (8%)	1 (2%)	2 (4%)
Hyperplasia, alveolar epithelium	3 (6%)	3 (6%)	2 (4%)
Metaplasia, squamous			1 (2%)
HEMATOPOIETIC SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Hematopoiesis	1 (2%)		
#Bone marrow	(50)	(50)	(48)
Hyperplasia, granulocytic		1 (2%)	
Hyperplasia, reticulum cell	2 (4%)		
#Spleen	(50)	(50)	(50)
Depletion, lymphoid	1 (2%)		
Hyperplasia, lymphoid			1 (2%)
#Splenic red pulp	(50)	(50)	(50)
Inflammation, granulomatous focal			1 (2%)
Fibrosis, multifocal		1 (2%)	1 (2%)
Pigmentation, NOS		1 (2%)	
Hemosiderosis	1 (2%)	1 (2%)	4 (8%)
Hematopoiesis	3 (6%)	9 (18%)	15 (30%)
#Mandibular lymph node	(49)	(49)	(49)
Hemorrhage	3 (6%)	3 (6%)	
Inflammation, chronic focal	1 (2%)		
Angiectasis	3 (6%)		
Plasmacytosis	15 (31%)	12 (24%)	8 (16%)
Hyperplasia, lymphoid			2 (4%)
#Mesenteric lymph node	(49)	(49)	(49)
Inflammation, granulomatous focal			1 (2%)
Plasmacytosis	1 (2%)		
#Thymic lymph node	(49)	(49)	(49)
Hemorrhage			1 (2%)
Inflammation, chronic focal		2 (4%)	
Inflammation, granulomatous focal	2 (4%)	1 (2%)	
Hemosiderosis			1 (2%)
Plasmacytosis	1 (2%)		
#Liver	(50)	(50)	(50)
Hematopoiesis	1 (2%)	1 (2%)	3 (6%)
#Hepatic sinusoid	(50)	(50)	(50)
Leukocytosis, NOS			1 (2%)

TABLE F4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Jejunum	(50)	(50)	(48)
Hyperplasia, lymphoid		2 (4%)	
#Colon	(50)	(50)	(50)
Hyperplasia, lymphoid		1 (2%)	
#Thymus	(46)	(46)	(46)
Dilatation/ducts		2 (4%)	
Inflammation, acute/chronic			1 (2%)
Depletion, lymphoid	30 (65%)	37 (80%)	21 (46%)
CIRCULATORY SYSTEM			
#Mandibular lymph node	(49)	(49)	(49)
Lymphangiectasis		2 (4%)	2 (4%)
#Pancreatic lymph node	(49)	(49)	(49)
Lymphangiectasis	1 (2%)		
#Heart	(50)	(50)	(50)
Periarteritis		1 (2%)	
#Heart/atrium	(50)	(50)	(50)
Thrombus, mural	1 (2%)	1 (2%)	
#Left atrium	(50)	(50)	(50)
Inflammation, chronic focal		1 (2%)	
#Myocardium	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, acute/chronic	1 (2%)	2 (4%)	
Degeneration, NOS	41 (82%)	34 (68%)	34 (68%)
#Mitral valve	(50)	(50)	(50)
Endocarditis, bacterial		1 (2%)	
*Aortic tunica adventitia	(50)	(50)	(50)
Hemorrhage		1 (2%)	
*Pulmonary artery	(50)	(50)	(50)
Foreign body, NOS		1 (2%)	
Mineralization		1 (2%)	
Inflammation, acute focal			1 (2%)
*Ovarian vein	(50)	(50)	(50)
Dilatation, NOS	1 (2%)		
*Splenic vein	(50)	(50)	(50)
Thrombus, mural			1 (2%)
#Pancreas	(50)	(50)	(50)
Periarteritis		1 (2%)	
DIGESTIVE SYSTEM			
#Submaxillary gland	(50)	(50)	(50)
Necrosis, focal			1 (2%)
#Liver	(50)	(50)	(50)
Inflammation, granulomatous	1 (2%)		
Inflammation, granulomatous focal	26 (52%)	18 (36%)	12 (24%)
Basophilic cyto change	41 (82%)	31 (62%)	24 (48%)
Eosinophilic cyto change	1 (2%)		
Clear cell change	4 (8%)	1 (2%)	
Hyperplasia, nodular	2 (4%)		1 (2%)
Angiectasis		1 (2%)	
#Liver/centrilobular	(50)	(50)	(50)
Necrosis, focal	2 (4%)	4 (8%)	6 (12%)
#Liver/periportal	(50)	(50)	(50)
Necrosis, focal			2 (4%)
Cytoplasmic vacuolization	3 (6%)	11 (22%)	25 (50%)
#Bile duct	(50)	(50)	(50)
Hyperplasia, focal	25 (50%)	21 (42%)	27 (54%)

TABLE F4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Pancreas	(50)	(50)	(50)
Ectopia			1 (2%)
Dilatation/ducts	3 (6%)	1 (2%)	1 (2%)
Inflammation, active chronic		1 (2%)	
Inflammation, chronic focal		4 (8%)	
Focal cellular change	1 (2%)		
#Pancreatic acinus	(50)	(50)	(50)
Atrophy, focal	14 (28%)	20 (40%)	9 (18%)
#Esophagus	(50)	(50)	(50)
Inflammation, acute necrotizing		1 (2%)	
Inflammation, active chronic			1 (2%)
Necrosis, focal	1 (2%)		
#Esophagus/muscularis	(50)	(50)	(50)
Hemorrhage		1 (2%)	
#Glandular stomach	(50)	(50)	(50)
Inflammation, active chronic	1 (2%)		
Necrosis, focal	1 (2%)		
#Forestomach	(50)	(50)	(50)
Edema, NOS	1 (2%)		
Ulcer, acute		1 (2%)	1 (2%)
Inflammation, acute/chronic	1 (2%)	1 (2%)	2 (4%)
Ulcer, chronic		1 (2%)	1 (2%)
Hyperplasia, epithelial		2 (4%)	
#Colon	(50)	(50)	(50)
Parasitism	2 (4%)	1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Pyelonephritis, acute			2 (4%)
Nephropathy	39 (78%)	42 (84%)	33 (66%)
#Kidney/cortex	(50)	(50)	(50)
Cyst, NOS	1 (2%)	2 (4%)	
Metamorphosis, fatty			1 (2%)
#Kidney/medulla	(50)	(50)	(50)
Mineralization	1 (2%)		
Granuloma, NOS			1 (2%)
#Kidney/tubule	(50)	(50)	(50)
Degeneration, NOS	1 (2%)	2 (4%)	
Necrosis, focal	2 (4%)		
#Kidney/pelvis	(50)	(50)	(50)
Mineralization			2 (4%)
#Renal pelvis/mucosa	(50)	(50)	(50)
Hyperplasia, epithelial		1 (2%)	
#Urinary bladder	(49)	(50)	(50)
Calculus, gross observation only			1 (2%)
Inflammation, acute focal		1 (2%)	
Inflammation, active chronic	1 (2%)	1 (2%)	
Hyperplasia, epithelial	4 (8%)		3 (6%)
Metaplasia, squamous			1 (2%)
ENDOCRINE SYSTEM			
#Pituitary intermedia	(49)	(50)	(50)
Hyperplasia, epithelial		1 (2%)	
#Anterior pituitary	(49)	(50)	(50)
Cyst, NOS	3 (6%)	3 (6%)	3 (6%)
Multiple cysts	17 (35%)	14 (28%)	12 (24%)
Hemorrhage	1 (2%)	1 (2%)	
Hemorrhagic cyst		3 (6%)	4 (8%)
Hyperplasia, focal	14 (29%)	15 (30%)	8 (16%)

TABLE F4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Adrenal/capsule	(50)	(50)	(50)
Hyperplasia, focal	1 (2%)		
#Adrenal cortex	(50)	(50)	(50)
Hemorrhage		1 (2%)	2 (4%)
Hemorrhagic cyst		1 (2%)	
Degeneration, NOS	1 (2%)		
Necrosis, focal	1 (2%)	1 (2%)	3 (6%)
Metamorphosis, fatty	5 (10%)	15 (30%)	6 (12%)
Focal cellular change	5 (10%)	3 (6%)	4 (8%)
Hypertrophy, NOS		1 (2%)	
Hyperplasia, focal	9 (18%)	7 (14%)	6 (12%)
Angiectasis	1 (2%)	2 (4%)	2 (4%)
#Adrenal medulla	(50)	(50)	(50)
Hyperplasia, focal	5 (10%)	5 (10%)	4 (8%)
#Thyroid	(50)	(50)	(50)
Embryonal duct cyst		1 (2%)	
Follicular cyst, NOS	1 (2%)		
Hyperplasia, C-cell	23 (46%)	22 (44%)	16 (32%)
#Parathyroid	(40)	(42)	(34)
Inflammation, active chronic			1 (3%)
Hyperplasia, focal	1 (3%)		
#Pancreatic islets	(50)	(50)	(50)
Hyperplasia, focal		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Galactocele	1 (2%)		
Hyperplasia, cystic	19 (38%)	22 (44%)	20 (40%)
*Clitoral gland	(50)	(50)	(50)
Inflammation, active chronic			1 (2%)
Inflammation, chronic focal	1 (2%)		
Abscess, chronic	1 (2%)		
#Uterus	(50)	(50)	(50)
Dilatation, NOS	4 (8%)	8 (16%)	1 (2%)
Hemorrhage, chronic	1 (2%)	2 (4%)	
Inflammation, acute focal			1 (2%)
Inflammation, chronic focal	1 (2%)		1 (2%)
Fibrosis, multifocal			1 (2%)
#Cervix uteri	(50)	(50)	(50)
Dilatation, NOS	1 (2%)		
Diverticulum		1 (2%)	
Inflammation, active chronic	1 (2%)		
Hyperkeratosis	1 (2%)		
Acanthosis	1 (2%)		
#Endometrial gland	(50)	(50)	(50)
Hyperplasia, cystic	11 (22%)	6 (12%)	12 (24%)
#Ovary	(50)	(50)	(50)
Follicular cyst, NOS	1 (2%)	3 (6%)	4 (8%)
Parovarian cyst	2 (4%)	5 (10%)	4 (8%)
Congestion, NOS	1 (2%)		
Fibrosis, multifocal			1 (2%)
Atrophy, NOS		3 (6%)	
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Hemorrhage	2 (4%)		
Inflammation, acute focal	2 (4%)		

TABLE F4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	Low Dose	High Dose
NERVOUS SYSTEM (Continued)			
#Cerebral ventricle	(50)	(50)	(50)
Hydrocephalus, NOS	2 (4%)	2 (4%)	1 (2%)
#Cerebrum	(50)	(50)	(50)
Inflammation, acute necrotizing	1 (2%)		
Necrosis, hemorrhagic	1 (2%)		
Atrophy, pressure	6 (12%)	11 (22%)	9 (18%)
#Cerebellum	(50)	(50)	(50)
Hemorrhage		1 (2%)	
#Medulla oblongata	(50)	(50)	(50)
Hemorrhage	1 (2%)		
SPECIAL SENSE ORGANS			
*Eye/cornea	(50)	(50)	(50)
Ulcer, NOS			1 (2%)
Inflammation, acute focal		1 (2%)	
Inflammation, active chronic			1 (2%)
Inflammation, chronic focal	1 (2%)		
*Eye/iris	(50)	(50)	(50)
Inflammation, acute focal		1 (2%)	
*Eye/retina	(50)	(50)	(50)
Atrophy, focal	1 (2%)	3 (6%)	4 (8%)
*Eye/crystalline lens	(50)	(50)	(50)
Cataract	1 (2%)	3 (6%)	2 (4%)
*Eye/lacrimal gland	(50)	(50)	(50)
Atrophy, focal		1 (2%)	
Hyperplasia, focal		1 (2%)	
*Harderian gland	(50)	(50)	(50)
Inflammation, chronic focal	2 (4%)		1 (2%)
Hyperplasia, epithelial			1 (2%)
MUSCULOSKELETAL SYSTEM			
*Cortex of bone	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
*Femur	(50)	(50)	(50)
Osteosclerosis	11 (22%)	9 (18%)	7 (14%)
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Hemorrhage		1 (2%)	
Inflammation, acute focal		1 (2%)	
Inflammation, acute fibrinous		1 (2%)	1 (2%)
Inflammation, chronic focal		1 (2%)	
Inflammation chronic suppurative	2 (4%)		
Inflammation, granulomatous focal	1 (2%)		
*Pleura	(50)	(50)	(50)
Inflammation, acute fibrinous			1 (2%)
Inflammation, acute necrotizing	1 (2%)		
Inflammation, acute/chronic	1 (2%)	1 (2%)	
Fibrosis, multifocal		1 (2%)	
*Epicardium	(50)	(50)	(50)
Inflammation, acute fibrinous			1 (2%)
Inflammation, acute/chronic		1 (2%)	
Inflammation chronic suppurative	2 (4%)		
*Mesentery	(50)	(50)	(50)
Inflammation, granulomatous focal		2 (4%)	

TABLE F4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	Low Dose	High Dose
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Hyperplasia, focal			1 (2%)
SPECIAL MORPHOLOGY SUMMARY			
None			

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX G

SUMMARY OF LESIONS IN MALE MICE

IN THE TWO-YEAR GAVAGE STUDY OF THPC

TABLE G1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPC

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(49)	(50)
Squamous cell papilloma			1 (2%)
*Subcutaneous tissue	(50)	(49)	(50)
Sarcoma, NOS	4 (8%)	1 (2%)	1 (2%)
Fibrosarcoma	3 (6%)	8 (16%)	2 (4%)
Lipoma			1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(49)	(50)
Carcinoma, NOS, metastatic			1 (2%)
Adenocarcinoma, NOS, metastatic			1 (2%)
Hepatocellular carcinoma, metastatic	6 (12%)	2 (4%)	1 (2%)
Alveolar/bronchiolar adenoma	1 (2%)	3 (6%)	4 (8%)
Alveolar/bronchiolar carcinoma	3 (6%)	3 (6%)	4 (8%)
Sarcoma, NOS, metastatic	1 (2%)	1 (2%)	
Fibrosarcoma, metastatic	1 (2%)		1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(49)	(50)
Malignant lymphoma, lymphocytic type	1 (2%)	2 (4%)	2 (4%)
Malignant lymphoma, histiocytic type	1 (2%)		
Malignant lymphoma, mixed type	4 (8%)	2 (4%)	4 (8%)
#Spleen	(48)	(49)	(48)
Malignant lymphoma, lymphocytic type	2 (4%)		
Malignant lymphoma, mixed type	1 (2%)		2 (4%)
#Axillary lymph node	(46)	(46)	(47)
Sarcoma, NOS, metastatic	1 (2%)		
CIRCULATORY SYSTEM			
*Subcutaneous tissue	(50)	(49)	(50)
Hemangiosarcoma		1 (2%)	
#Liver	(49)	(49)	(50)
Hemangiosarcoma			1 (2%)
#Jejunum	(45)	(44)	(47)
Hemangiosarcoma			1 (2%)
DIGESTIVE SYSTEM			
*Tongue	(50)	(49)	(50)
Squamous cell carcinoma	1 (2%)		
#Liver	(49)	(49)	(50)
Hepatocellular adenoma	8 (16%)	10 (20%)	6 (12%)
Hepatocellular carcinoma	10 (20%)	6 (12%)	8 (16%)
#Forestomach	(47)	(47)	(47)
Squamous cell papilloma		1 (2%)	
Squamous cell carcinoma	1 (2%)		
URINARY SYSTEM			
#Kidney	(49)	(49)	(50)
Tubular cell adenoma	1 (2%)		
#Perirenal tissue	(49)	(49)	(50)
Paraganglioma, NOS	1 (2%)		

TABLE G1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Anterior pituitary	(45)	(43)	(45)
Adenoma, NOS	1 (2%)		
#Adrenal/capsule	(50)	(48)	(50)
Adenoma, NOS	2 (4%)	2 (4%)	4 (8%)
#Adrenal medulla	(50)	(48)	(50)
Pheochromocytoma	1 (2%)	1 (2%)	3 (6%)
#Thyroid	(48)	(49)	(50)
Follicular cell adenoma	2 (4%)	1 (2%)	3 (6%)
REPRODUCTIVE SYSTEM			
*Preputial gland	(50)	(49)	(50)
Carcinoma, NOS	1 (2%)		
#Testis	(49)	(49)	(50)
Interstitial cell tumor		1 (2%)	
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Nasolacrimal duct	(50)	(49)	(50)
Carcinoma, NOS			1 (2%)
*Harderian gland	(50)	(49)	(50)
Adenoma, NOS	1 (2%)	1 (2%)	3 (6%)
Adenocarcinoma, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mediastinum	(50)	(49)	(50)
Hepatocellular carcinoma, metastatic		1 (2%)	
Alveolar/bronchiolar carcinoma, metastatic			1 (2%)
*Mesentery	(50)	(49)	(50)
Squamous cell carcinoma, metastatic	1 (2%)		
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(49)	(50)
Sarcoma, NOS, metastatic	2 (4%)		

TABLE G1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	14	8	15
Moribund sacrifice	11	10	1
Terminal sacrifice	23	30	34
Dosing accident	2	1	
Animal missexed		1	
TUMOR SUMMARY			
Total animals with primary tumors**	33	31	33
Total primary tumors	50	43	52
Total animals with benign tumors	15	16	20
Total benign tumors	17	20	25
Total animals with malignant tumors	25	21	22
Total malignant tumors	32	23	27
Total animals with secondary tumors##	11	3	4
Total secondary tumors	12	4	5
Total animals with tumors uncertain-- benign or malignant	1		
Total uncertain tumors	1		

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE G2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPC: VEHICLE CONTROL

ANIMAL NUMBER	0119	0444	0224	0227	0445	0117	0334	0223	0115	0226	0441	0116	0221	0337	0331	0449	0111	0009	0220	0228	0114	0440	0448	0001	0229
WEEKS ON STUDY	0664	0665	0700	0700	0711	0722	0744	0753	0799	0799	0799	0800	0800	0800	0866	0866	0911	0922	0933	0933	0944	0977	0999	1011	1011
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																					X	X			X
Fibrosarcoma										X									X						
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic												X	X	X		X									
Alveolar/bronchiolar adenoma		X																							
Alveolar/bronchiolar carcinoma																		X							
Sarcoma, NOS, metastatic																									
Fibrosarcoma, metastatic																									
Trachea	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, lymphocytic type																									
Malignant lymphoma, mixed type																									
Lymph nodes	−	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Sarcoma, NOS, metastatic																									
Thymus	−	−	+	+	+	−	−	−	+	+	−	−	−	−	+	−	−	−	+	−	−	+	−	−	−
CIRCULATORY SYSTEM																									
Heart	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
	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
							X																		
	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
				X			X					X													X
											X	X	X	X		X	X								
Bile duct	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	+	N	+	+	N	N	+	+	+	+	+	N	N	N	N	N	+	+	+	+	+	+	+
Pancreas	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	−	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma							X																		
Small intestine	−	−	+	−	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	−	+	+	−	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Paraganglioma, NOS																X									
Urinary bladder	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																							X		
Pheochromocytoma																									
Thyroid	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
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	N	N	N	N
Testis	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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																									
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
Squamous cell carcinoma, 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
Sarcoma, NOS, metastatic																					X				X
Malignant lymphoma, lymphocytic type																						X			
Malignant lymphoma, histiocytic type																									
Malignant lymphoma, mixed type																							X		

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
.: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE G2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	008	047	002	003	004	005	006	007	010	012	013	018	022	025	030	032	033	035	036	038	039	042	043	046	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	103	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS		X																								4
Fibrosarcoma																									X	3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic													X				X									6
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																	X	X								3
Sarcoma, NOS, metastatic		X																								1
Fibrosarcoma, metastatic																									X	1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Malignant lymphoma, lymphocytic type				X													X									2
Malignant lymphoma, mixed type						X																				1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Sarcoma, NOS, metastatic		X																								1
Thymus	–	+	+	–	+	–	+	+	+	+	+	–	–	–	+	+	+	+	+	+	+	+	+	–	–	24
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Oral cavity	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
Squamous cell carcinoma																										1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma			X							X				X		X										8
Hepatocellular carcinoma	X			X									X				X									10
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell carcinoma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tubular cell adenoma															X											1
Paraganglioma, NOS																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	–	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma, NOS				X																						1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS															X											2
Pheochromocytoma	X																									1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma				X																	X					2
Parathyroid	+	–	+	+	+	–	–	+	+	–	–	+	–	+	+	+	+	+	+	–	–	+	+	–	–	31
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	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	*50
Carcinoma, NOS																										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	*50
Adenoma, NOS																			X							1
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	*50
Squamous cell carcinoma, metastatic																										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
Sarcoma, NOS, metastatic																										2
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, histiocytic type	X																									1
Malignant lymphoma, mixed type							X									X							X			4

* Animals necropsied

TABLE G2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPC: LOW DOSE

ANIMAL NUMBER	0007	0008	0006	0488	0299	0333	0122	0288	0355	0422	0114	0266	0155	0277	0233	0499	0399	0455	0113	0101	0002	0003	0004	0005	0009
WEEKS ON STUDY	0000	0011	0115	0445	0664	0666	0700	0711	0711	0721	0744	0800	0866	0887	0991	0991	0994	0997	1100	1004	1044	1044	1044	1044	1044
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Fibrosarcoma								X	X			X					X		X	X					
Hemangiosarcoma													X												
RESPIRATORY SYSTEM																									
Lungs and bronchi	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic														X										X	
Alveolar/bronchiolar adenoma																									X
Alveolar/bronchiolar carcinoma																			X		X				
Sarcoma, NOS, metastatic																									
Trachea	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	S	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	S	+	+	+	+	−	−	−	+	−	−	−	+	−	+	+	−	−	−	−	+	+	−	−	+
CIRCULATORY SYSTEM																									
Heart	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma							X													X					
Hepatocellular carcinoma														X		X		X				X		X	
Bile duct	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	S	N	+	N	+	N	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	S	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	S	+	+	−	+	−	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	S	+	+	+	+	−	+	+	−	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	S	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	S	−	−	+	+	−	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Adrenal	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									X
Pheochromocytoma																									
Thyroid	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	S	−	+	+	−	−	+	−	+	+	+	+	+	−	+	+	+	+	+	−	−	+	+	−	+
REPRODUCTIVE SYSTEM																									
Mammary gland	S	N	N	N	N	N	+	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor																				X					
Prostate	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	S	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																									
BODY CAVITIES																									
Mediastinum	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hepatocellular carcinoma, metastatic														X											
ALL OTHER SYSTEMS																									
Multiple organs, NOS	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, lymphocytic type																									
Malignant lymphoma, mixed type													X												

TABLE G2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	0110	0111	0116	0117	0118	0119	0120	0121	0122	0124	0125	0130	0131	0132	0134	0136	0137	0138	0140	0141	0143	0144	0146	0147	0150	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	*49
Sarcoma, NOS																					X					1
Fibrosarcoma			X																					X		8
Hemangiosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic																										2
Alveolar/bronchiolar adenoma			X																					X		3
Alveolar/bronchiolar carcinoma														X												3
Sarcoma, NOS, metastatic																					X					1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	46
Thymus	+	+	−	+	+	−	+	+	+	−	+	−	+	−	+	+	+	+	+	+	−	+	−	+	+	29
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma		X							X							X		X	X					X	X	10
Hepatocellular carcinoma												X													X	6
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell papilloma					X																					1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	44
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	43
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	48
Adenoma, NOS															X											2
Pheochromocytoma																									X	1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma										X																1
Parathyroid	+	+	+	+	+	−	+	+	−	−	+	+	−	−	+	−	+	+	+	+	+	−	+	−	+	33
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	N	*49
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	*49
Adenoma, NOS													X													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	*49
Hepatocellular carcinoma, metastatic																										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	*49
Malignant lymphoma, lymphocytic type						X										X										2
Malignant lymphoma, mixed type															X											2

* Animals necropsied

TABLE G2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPC: HIGH DOSE

ANIMAL NUMBER	0171	0451	0191	0051	0161	0333	0422	0336	0371	0411	0338	0301	0181	0123	0223	0011	0022	0033	0044	0066	0077	0088	0091	0101	0111
WEEKS ON STUDY	0510	0604	0684	0688	0688	0690	0700	0744	0833	0866	0900	0944	0955	0977	1000	1044	1044	1044	1044	1044	1044	1048	1044	1044	1044
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																			X						
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Fibrosarcoma																						X			
Lipoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic																									
Adenocarcinoma, NOS, metastatic																									
Hepatocellular carcinoma, metastatic																	X								
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma						X											X		X						
Fibrosarcoma, metastatic																									
Trachea	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Thymus	−	−	+	+	−	−	+	+	−	−	−	+	+	−	+	+	−	+	+	+	−	−	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma														X								X	X		X
Hepatocellular carcinoma					X							X	X	X			X								
Hemangiosarcoma										X															
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	+	+	+	+	+	N	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+
Pancreas	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	−	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																X									
Large intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	−	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Pheochromocytoma														X			X								
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma													X								X				
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	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Lacrimal 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																									
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								X							
Adenocarcinoma, NOS																									
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
Alveolar/bronchiolar carcinoma, 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
Malignant lymphoma, lymphocytic type															X						X				
Malignant lymphoma, mixed type																			X						

TABLE G2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (*Continued*)

ANIMAL NUMBER	0 1 3	0 1 4	0 1 5	0 2 0	0 2 1	0 2 2	0 2 4	0 2 5	0 2 6	0 2 7	0 2 8	0 2 9	0 3 1	0 3 2	0 3 4	0 3 5	0 3 9	0 4 0	0 4 3	0 4 4	0 4 6	0 4 7	0 4 8	0 4 9	0 5 0	TOTAL:
WEEKS ON STUDY	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 4	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 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS									X																	1
Fibrosarcoma																						X				2
Lipoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, metastatic																								X		1
Adenocarcinoma, NOS, metastatic																						X				1
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma						X		X					X						X							4
Alveolar/bronchiolar carcinoma															X											4
Fibrosarcoma, metastatic																						X				1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Malignant lymphoma, mixed type											X					X										2
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymus	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	−	+	+	+	36
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma											X		X													6
Hepatocellular carcinoma															X	X				X						8
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	45
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS	X	X		X												X										4
Pheochromocytoma		X																								3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma					X																					3
Parathyroid	−	+	−	+	+	+	−	−	+	−	−	+	−	+	+	−	+	+	−	+	+	+	+	−	+	30
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	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPECIAL SENSE ORGANS																										
Lacrimal 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
Carcinoma, NOS																								X		1
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	*50
Adenoma, NOS					X																					3
Adenocarcinoma, NOS																						X				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	*50
Alveolar/bronchiolar carcinoma, meta																										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
Malignant lymphoma, lymphocytic type							X			X								X								2
Malignant lymphoma, mixed type																										4

* Animals necropsied

TABLE G3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPC

	Vehicle Control	7.5 mg/kg	15 mg/kg
Subcutaneous Tissue: Sarcoma			
Overall Rates (a)	4/50 (8%)	1/49 (2%)	1/50 (2%)
Adjusted Rates (b)	13.7%	3.2%	2.9%
Terminal Rates (c)	0/23 (0%)	1/31 (3%)	1/35 (3%)
Week of First Observation	94	104	104
Life Table Tests (d)	P=0.056N	P=0.135N	P=0.106N
Incidental Tumor Tests (d)	P=0.210N	P=0.467N	P=0.361N
Cochran-Armitage Trend Test (d)	P=0.102N		
Fisher Exact Test (d)		P=0.187N	P=0.181N
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	8/49 (16%)	2/50 (4%)
Adjusted Rates (b)	9.5%	21.1%	5.7%
Terminal Rates (c)	1/23 (4%)	3/31 (10%)	2/35 (6%)
Week of First Observation	79	71	104
Life Table Tests (d)	P=0.296N	P=0.153	P=0.371N
Incidental Tumor Tests (d)	P=0.571N	P=0.029	P=0.558N
Cochran-Armitage Trend Test (d)	P=0.430N		
Fisher Exact Test (d)		P=0.094	P=0.500N
Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Overall Rates (a)	7/50 (14%)	9/49 (18%)	3/50 (6%)
Adjusted Rates (b)	22.0%	23.9%	8.6%
Terminal Rates (c)	1/23 (4%)	4/31 (13%)	3/35 (9%)
Week of First Observation	79	71	104
Life Table Tests (d)	P=0.067N	P=0.512	P=0.074N
Incidental Tumor Tests (d)	P=0.315N	P=0.079	P=0.305N
Cochran-Armitage Trend Test (d)	P=0.147N		
Fisher Exact Test (d)		P=0.376	P=0.159N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	1/50 (2%)	3/49 (6%)	4/50 (8%)
Adjusted Rates (b)	2.0%	9.7%	11.4%
Terminal Rates (c)	0/23 (0%)	3/31 (10%)	4/35 (11%)
Week of First Observation	65	104	104
Life Table Tests (d)	P=0.237	P=0.380	P=0.290
Incidental Tumor Tests (d)	P=0.233	P=0.375	P=0.282
Cochran-Armitage Trend Test (d)	P=0.134		
Fisher Exact Test (d)		P=0.301	P=0.181
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	3/50 (6%)	3/49 (6%)	4/50 (8%)
Adjusted Rates (b)	11.5%	9.4%	10.6%
Terminal Rates (c)	2/23 (9%)	2/31 (6%)	3/35 (9%)
Week of First Observation	92	100	69
Life Table Tests (d)	P=0.568N	P=0.551N	P=0.641N
Incidental Tumor Tests (d)	P=0.451	P=0.629	P=0.569
Cochran-Armitage Trend Test (d)	P=0.421		
Fisher Exact Test (d)		P=0.651	P=0.500
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	6/49 (12%)	8/50 (16%)
Adjusted Rates (b)	13.3%	18.8%	21.8%
Terminal Rates (c)	2/23 (9%)	5/31 (16%)	7/35 (20%)
Week of First Observation	65	100	69
Life Table Tests (d)	P=0.320	P=0.512	P=0.366
Incidental Tumor Tests (d)	P=0.225	P=0.385	P=0.283
Cochran-Armitage Trend Test (d)	P=0.141		
Fisher Exact Test (d)		P=0.357	P=0.178

TABLE G3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	7.5 mg/kg	15 mg/kg
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	3/50 (6%)	2/49 (4%)	2/50 (4%)
Adjusted Rates (b)	11.8%	6.5%	5.6%
Terminal Rates (c)	2/23 (9%)	2/31 (6%)	1/35 (3%)
Week of First Observation	97	104	100
Life Table Tests (d)	P=0.258N	P=0.381N	P=0.342N
Incidental Tumor Tests (d)	P=0.396N	P=0.482N	P=0.528N
Cochran-Armitage Trend Test (d)	P=0.407N		
Fisher Exact Test (d)		P=0.510N	P=0.500N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	5/50 (10%)	2/49 (4%)	6/50 (12%)
Adjusted Rates (b)	20.3%	5.8%	17.1%
Terminal Rates (c)	4/23 (17%)	1/31 (3%)	6/35 (17%)
Week of First Observation	99	86	104
Life Table Tests (d)	P=0.484N	P=0.133N	P=0.474N
Incidental Tumor Tests (d)	P=0.541	P=0.221N	P=0.542N
Cochran-Armitage Trend Test (d)	P=0.430		
Fisher Exact Test (d)		P=0.227N	P=0.500
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	9/50 (18%)	4/49 (8%)	8/50 (16%)
Adjusted Rates (b)	33.9%	12.1%	22.2%
Terminal Rates (c)	6/23 (26%)	3/31 (10%)	7/35 (20%)
Week of First Observation	97	86	100
Life Table Tests (d)	P=0.185N	P=0.049N	P=0.191N
Incidental Tumor Tests (d)	P=0.381N	P=0.137N	P=0.372N
Cochran-Armitage Trend Test (d)	P=0.443N		
Fisher Exact Test (d)		P=0.125N	P=0.500N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	8/49 (16%)	10/49 (20%)	6/50 (12%)
Adjusted Rates (b)	25.8%	29.5%	16.6%
Terminal Rates (c)	4/23 (17%)	8/31 (26%)	5/35 (14%)
Week of First Observation	70	70	97
Life Table Tests (d)	P=0.140N	P=0.575	P=0.189N
Incidental Tumor Tests (d)	P=0.254N	P=0.459	P=0.324N
Cochran-Armitage Trend Test (d)	P=0.325N		
Fisher Exact Test (d)		P=0.397	P=0.371N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	10/49 (20%)	6/49 (12%)	8/50 (16%)
Adjusted Rates (b)	29.0%	17.8%	20.0%
Terminal Rates (c)	3/23 (13%)	4/31 (13%)	4/35 (11%)
Week of First Observation	79	87	68
Life Table Tests (d)	P=0.172N	P=0.135N	P=0.215N
Incidental Tumor Tests (d)	P=0.465	P=0.416N	P=0.463
Cochran-Armitage Trend Test (d)	P=0.325N		
Fisher Exact Test (d)		P=0.207N	P=0.380N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	17/49 (35%)	15/49 (31%)	13/50 (26%)
Adjusted Rates (b)	47.7%	42.2%	32.9%
Terminal Rates (c)	7/23 (30%)	11/31 (35%)	9/35 (26%)
Week of First Observation	70	70	68
Life Table Tests (d)	P=0.054N	P=0.224N	P=0.076N
Incidental Tumor Tests (d)	P=0.314N	P=0.545N	P=0.396N
Cochran-Armitage Trend Test (d)	P=0.203N		
Fisher Exact Test (d)		P=0.415N	P=0.235N

TABLE G3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	7.5 mg/kg	15 mg/kg
Adrenal Gland Capsule: Adenoma			
Overall Rates (a)	2/50 (4%)	2/48 (4%)	4/50 (8%)
Adjusted Rates (b)	7.8%	6.7%	11.4%
Terminal Rates (c)	1/23 (4%)	2/30 (7%)	4/35 (11%)
Week of First Observation	99	104	104
Life Table Tests (d)	P=0.417	P=0.608N	P=0.527
Incidental Tumor Tests (d)	P=0.349	P=0.682	P=0.440
Cochran-Armitage Trend Test (d)	P=0.254		
Fisher Exact Test (d)		P=0.676	P=0.339
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	1/50 (2%)	1/48 (2%)	3/50 (6%)
Adjusted Rates (b)	4.0%	3.3%	8.3%
Terminal Rates (c)	0/23 (0%)	1/30 (3%)	2/35 (6%)
Week of First Observation	103	104	97
Life Table Tests (d)	P=0.307	P=0.706N	P=0.439
Incidental Tumor Tests (d)	P=0.169	P=0.684	P=0.233
Cochran-Armitage Trend Test (d)	P=0.203		
Fisher Exact Test (d)		P=0.742	P=0.309
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	2/48 (4%)	1/49 (2%)	3/50 (6%)
Adjusted Rates (b)	8.7%	3.2%	8.2%
Terminal Rates (c)	2/23 (9%)	1/31 (3%)	2/35 (6%)
Week of First Observation	104	104	95
Life Table Tests (d)	P=0.555	P=0.396N	P=0.673
Incidental Tumor Tests (d)	P=0.471	P=0.396N	P=0.583
Cochran-Armitage Trend Test (d)	P=0.415		
Fisher Exact Test (d)		P=0.492N	P=0.520
Harderian Gland: Adenoma			
Overall Rates (a)	1/50 (2%)	1/49 (2%)	3/50 (6%)
Adjusted Rates (b)	4.3%	3.2%	8.0%
Terminal Rates (c)	1/23 (4%)	1/31 (3%)	2/35 (6%)
Week of First Observation	104	104	86
Life Table Tests (d)	P=0.302	P=0.694N	P=0.436
Incidental Tumor Tests (d)	P=0.219	P=0.694N	P=0.311
Cochran-Armitage Trend Test (d)	P=0.202		
Fisher Exact Test (d)		P=0.747	P=0.309
Harderian Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	1/50 (2%)	1/49 (2%)	4/50 (8%)
Adjusted Rates (b)	4.3%	3.2%	10.8%
Terminal Rates (c)	1/23 (4%)	1/31 (3%)	3/35 (9%)
Week of First Observation	104	104	86
Life Table Tests (d)	P=0.177	P=0.694N	P=0.303
Incidental Tumor Tests (d)	P=0.121	P=0.694N	P=0.206
Cochran-Armitage Trend Test (d)	P=0.102		
Fisher Exact Test (d)		P=0.747	P=0.181

(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 vehicle 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 vehicle 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 exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE G4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPC

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(49)	(50)
Epidermal inclusion cyst	1 (2%)		
Inflammation, acute/chronic	4 (8%)	2 (4%)	1 (2%)
*Subcutaneous tissue	(50)	(49)	(50)
Inflammation, acute		1 (2%)	
Inflammation, chronic		1 (2%)	1 (2%)
Infection, fungal		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(50)	(49)	(50)
Vegetable foreign body	1 (2%)		
Hemorrhage	1 (2%)		2 (4%)
Inflammation, acute	4 (8%)		2 (4%)
Inflammation, chronic		1 (2%)	2 (4%)
Hemosiderosis			1 (2%)
Alveolar macrophages	2 (4%)	6 (12%)	5 (10%)
Hyperplasia, alveolar epithelium	3 (6%)	5 (10%)	5 (10%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(49)	(49)	(49)
Inflammation, pyogranulomatous	1 (2%)		
Hyperplasia, granulocytic	8 (16%)	8 (16%)	5 (10%)
#Spleen	(48)	(49)	(48)
Necrosis, diffuse	2 (4%)	1 (2%)	1 (2%)
Depletion, lymphoid		1 (2%)	1 (2%)
Hyperplasia, lymphoid			1 (2%)
Hematopoiesis	13 (27%)	7 (14%)	12 (25%)
#Mandibular lymph node	(46)	(46)	(47)
Angiectasis	1 (2%)		
#Pancreatic lymph node	(46)	(46)	(47)
Angiectasis	2 (4%)	1 (2%)	
#Lumbar lymph node	(46)	(46)	(47)
Angiectasis			1 (2%)
#Mesenteric lymph node	(46)	(46)	(47)
Angiectasis	7 (15%)	7 (15%)	3 (6%)
#Inguinal lymph node	(46)	(46)	(47)
Inflammation, acute	1 (2%)		
#Lung	(50)	(49)	(50)
Leukocytosis, NOS	3 (6%)	1 (2%)	1 (2%)
#Liver	(49)	(49)	(50)
Hematopoiesis	2 (4%)	1 (2%)	1 (2%)
#Thymus	(24)	(29)	(36)
Necrosis, diffuse	2 (8%)	2 (7%)	2 (6%)
CIRCULATORY SYSTEM			
#Pancreatic lymph node	(46)	(46)	(47)
Thrombosis, NOS		1 (2%)	
#Heart	(49)	(49)	(50)
Necrosis, focal	3 (6%)	1 (2%)	
#Heart/atrium	(49)	(49)	(50)
Thrombosis, NOS		1 (2%)	1 (2%)
#Liver	(49)	(49)	(50)
Thrombus, organized		1 (2%)	

TABLE G4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM			
#Salivary gland	(49)	(49)	(50)
Inflammation, chronic			1 (2%)
Atrophy, NOS		1 (2%)	1 (2%)
#Liver	(49)	(49)	(50)
Cyst, NOS		2 (4%)	1 (2%)
Inflammation, chronic	2 (4%)		1 (2%)
Necrosis, focal	8 (16%)		2 (4%)
Cytoplasmic vacuolization		39 (80%)	44 (88%)
Atrophy, focal		1 (2%)	
Angiectasis		1 (2%)	
Nodular regeneration			1 (2%)
#Pancreas	(48)	(49)	(48)
Inflammation, acute		1 (2%)	1 (2%)
Inflammation, chronic	1 (2%)	1 (2%)	
Atrophy, focal	4 (8%)	5 (10%)	2 (4%)
#Pancreatic acinus	(48)	(49)	(48)
Focal cellular change			1 (2%)
#Esophagus	(50)	(49)	(50)
Inflammation, acute/chronic	1 (2%)	1 (2%)	
#Glandular stomach	(47)	(47)	(47)
Mineralization	1 (2%)		
Inflammation, acute		1 (2%)	
#Forestomach	(47)	(47)	(47)
Inflammation, acute		1 (2%)	
Hyperplasia, epithelial		1 (2%)	
#Duodenum	(45)	(44)	(47)
Hemorrhage			1 (2%)
#Jejunum	(45)	(44)	(47)
Hemorrhage			1 (2%)
#Colon	(46)	(45)	(49)
Parasitism	2 (4%)		2 (4%)
URINARY SYSTEM			
#Kidney	(49)	(49)	(50)
Mineralization	4 (8%)	2 (4%)	2 (4%)
Multiple cysts			2 (4%)
Pyelonephritis, acute	4 (8%)	3 (6%)	2 (4%)
Glomerulonephritis, chronic	8 (16%)	6 (12%)	10 (20%)
Pyelonephritis, chronic		1 (2%)	1 (2%)
Infection, bacterial		1 (2%)	2 (4%)
Infarct, NOS	4 (8%)	3 (6%)	2 (4%)
Hyperplasia, tubular cell	1 (2%)		1 (2%)
Metaplasia, osseous		1 (2%)	3 (6%)
#Kidney/tubule	(49)	(49)	(50)
Dilatation, NOS	1 (2%)	1 (2%)	
#Urinary bladder	(48)	(46)	(48)
Inflammation, acute/chronic	3 (6%)	6 (13%)	1 (2%)
*Urethra	(50)	(49)	(50)
Dilatation, NOS			1 (2%)
Inflammation, acute necrotizing		3 (6%)	2 (4%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(45)	(43)	(45)
Hyperplasia, focal	1 (2%)	1 (2%)	
#Adrenal cortex	(50)	(48)	(50)
Hypertrophy, NOS			1 (2%)
Hypertrophy, focal	12 (24%)	10 (21%)	11 (22%)
Hyperplasia, focal	8 (16%)	10 (21%)	3 (6%)

TABLE G4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Adrenal medulla	(50)	(48)	(50)
Hyperplasia, focal	4 (8%)	1 (2%)	4 (8%)
#Thyroid	(48)	(49)	(50)
Follicular cyst, NOS		1 (2%)	
Inflammation, acute		1 (2%)	
Inflammation, chronic		1 (2%)	
Hyperplasia, follicular cell	6 (13%)	2 (4%)	10 (20%)
REPRODUCTIVE SYSTEM			
*Penis	(50)	(49)	(50)
Inflammation, acute	1 (2%)		1 (2%)
*Prepuce	(50)	(49)	(50)
Dilatation, NOS			1 (2%)
Inflammation, acute necrotizing			1 (2%)
*Preputial gland	(50)	(49)	(50)
Dilatation/ducts	1 (2%)	1 (2%)	1 (2%)
Inflammation, acute/chronic	5 (10%)	3 (6%)	2 (4%)
#Prostate	(50)	(49)	(50)
Inflammation, acute	4 (8%)	1 (2%)	3 (6%)
Inflammation, acute/chronic	4 (8%)	1 (2%)	1 (2%)
*Seminal vesicle	(50)	(49)	(50)
Dilatation, NOS	5 (10%)	3 (6%)	4 (8%)
Inflammation, acute/chronic	2 (4%)	2 (4%)	1 (2%)
#Testis	(49)	(49)	(50)
Inflammation, chronic			1 (2%)
Degeneration, NOS	6 (12%)	2 (4%)	4 (8%)
*Epididymis	(50)	(49)	(50)
Inflammation, chronic	5 (10%)	1 (2%)	2 (4%)
Granuloma, spermatic	1 (2%)		2 (4%)
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Eye/cornea	(50)	(49)	(50)
Inflammation, chronic			2 (4%)
*Eye/crystalline lens	(50)	(49)	(50)
Cataract			2 (4%)
MUSCULOSKELETAL SYSTEM			
*Tarsal joint	(50)	(49)	(50)
Hyperostosis	17 (34%)	18 (37%)	17 (34%)
Metaplasia, osseous	17 (34%)	18 (37%)	17 (34%)
*Skeletal muscle	(50)	(49)	(50)
Mineralization	1 (2%)		
BODY CAVITIES			
*Peritoneum	(50)	(49)	(50)
Inflammation, acute/chronic	1 (2%)		
Reaction, foreign body			1 (2%)
Necrosis, fat		1 (2%)	
*Pleura	(50)	(49)	(50)
Inflammation, acute necrotizing	1 (2%)	1 (2%)	1 (2%)
Inflammation, acute/chronic	1 (2%)		2 (4%)

TABLE G4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	Low Dose	High Dose
ALL OTHER SYSTEMS			
None			
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported	1		
Animal missexed/no necropsy		1	

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX H

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPC

TABLE H1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPC

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)	1 (2%)	
Fibrosarcoma		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Hepatocellular carcinoma, metastatic	1 (2%)		1 (2%)
Alveolar/bronchiolar adenoma	3 (6%)	2 (4%)	1 (2%)
Alveolar/bronchiolar carcinoma		1 (2%)	1 (2%)
Sarcoma, NOS, metastatic		1 (2%)	
Carcinosarcoma, metastatic			1 (2%)
Osteosarcoma, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS		2 (4%)	
Malignant lymphoma, undiffer type	1 (2%)		
Malignant lymphoma, lymphocytic type	8 (16%)	1 (2%)	6 (12%)
Malignant lymphoma, histiocytic type	2 (4%)	4 (8%)	2 (4%)
Malignant lymphoma, mixed type	9 (18%)	6 (12%)	8 (16%)
#Spleen	(49)	(50)	(50)
Malignant lymphoma, mixed type	1 (2%)		1 (2%)
#Jejunum	(47)	(48)	(50)
Malignant lymphoma, mixed type			1 (2%)
#Ileum	(47)	(48)	(50)
Malignant lymphoma, mixed type		1 (2%)	
#Thymus	(42)	(45)	(40)
Malignant lymphoma, mixed type			1 (3%)
CIRCULATORY SYSTEM			
#Mesenteric lymph node	(49)	(47)	(47)
Hemangiosarcoma			1 (2%)
DIGESTIVE SYSTEM			
#Liver	(49)	(50)	(50)
Hepatocellular adenoma	3 (6%)	2 (4%)	6 (12%)
Hepatocellular carcinoma	1 (2%)	2 (4%)	1 (2%)
#Pancreas	(48)	(50)	(50)
Acinar cell adenoma		1 (2%)	
#Forestomach	(49)	(50)	(50)
Squamous cell papilloma	2 (4%)		1 (2%)
*Perirectal tissue	(50)	(50)	(50)
Osteosarcoma		1 (2%)	
URINARY SYSTEM			
None			

TABLE H1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Pituitary intermedia	(50)	(49)	(50)
Adenoma, NOS			1 (2%)
#Anterior pituitary	(50)	(49)	(50)
Carcinoma, NOS			1 (2%)
Adenoma, NOS	11 (22%)	12 (24%)	7 (14%)
#Adrenal/capsule	(50)	(50)	(48)
Adenoma, NOS	1 (2%)		
#Adrenal medulla	(50)	(50)	(48)
Pheochromocytoma			1 (2%)
#Thyroid	(48)	(50)	(49)
Follicular cell adenoma	1 (2%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS		1 (2%)	
Carcinosarcoma			1 (2%)
#Uterus	(50)	(50)	(50)
Carcinoma in situ, NOS			1 (2%)
Carcinoma, NOS	1 (2%)		
Leiomyoma		1 (2%)	
Endometrial stromal polyp	2 (4%)		1 (2%)
#Ovary	(50)	(48)	(48)
Papillary adenoma	1 (2%)		1 (2%)
Luteoma	1 (2%)		1 (2%)
Granulosa cell tumor		1 (2%)	
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS		2 (4%)	
Adenocarcinoma, NOS			2 (4%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			

TABLE H1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	Low Dose	High Dose
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Adenocarcinoma, NOS, metastatic			1 (2%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	9	8	5
Moribund sacrifice	3	2	6
Terminal sacrifice	37	40	38
Dosing accident	1		1
TUMOR SUMMARY			
Total animals with primary tumors**	35	32	36
Total primary tumors	49	43	47
Total animals with benign tumors	20	17	18
Total benign tumors	25	21	20
Total animals with malignant tumors	24	20	25
Total malignant tumors	24	21	27
Total animals with secondary tumors##	1	2	3
Total secondary tumors	1	2	3
Total animals with tumors uncertain-- benign or malignant		1	
Total uncertain tumors		1	

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE H2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPC: VEHICLE CONTROL

ANIMAL NUMBER	04461	00011	03131	03391	01121	02241	00041	03301	00051	04771	00031	04441	02261	00021	00061	00071	00081	00091	01101	01121	01131	01141	01151	01161	01171
WEEKS ON STUDY	05515	06633	06891	07766	08202	08687	09292	09302	09985	09991	10101	10111	10303	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									X
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																									
Alveolar/bronchiolar adenoma	X							X			X														
Trachea	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																	X								
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	+	+	+	+	+	+	−	+	+	−	−	−	+	+	+	+	+	−	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Liver	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma														X			X					X			
Hepatocellular carcinoma																									
Bile duct	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																	X								
Small intestine	−	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	−	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																			X			X			
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	+	+	+	+	+	−	+	+	+	+	−	+	−	+	+	−	+	−	−	−	+	+	+	−	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	N	+	+	N	N	+	N	+	N	N	N	+	+	+	N	N	N	+	N	+	+	N
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Endometrial stromal polyp																							X		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary adenoma																							X		
Luteoma																									
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
Malignant lymphoma, undiffer type						X																			
Malignant lymphoma, lymphocytic type				X							X								X	X					
Malignant lymphoma, histiocytic type									X				X												
Malignant lymphoma, mixed type					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 missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE H2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0 1 8	0 1 9	0 2 0	0 2 1	0 2 2	0 2 3	0 2 5	0 2 7	0 2 8	0 2 9	0 3 2	0 3 3	0 3 4	0 3 5	0 3 6	0 3 7	0 3 8	0 4 0	0 4 1	0 4 2	0 4 3	0 4 5	0 4 8	0 4 9	0 5 0	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	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 4	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 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																					X					1
Alveolar/bronchiolar adenoma																										3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, mixed type																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	42
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma																										3
Hepatocellular carcinoma																					X					1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																						X				2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS					X		X					X	X				X		X		X	X	X			11
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																X										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma																							X			1
Parathyroid	–	+	+	+	+	+	+	–	+	–	–	+	–	–	+	+	+	+	+	+	–	–	+	+	+	34
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	N	+	N	N	N	+	N	+	N	+	N	N	+	+	+	+	N	+	+	+	+	+	+	*50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																						X				1
Endometrial stromal polyp								X																		2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papillary adenoma																										1
Luteoma																X										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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
Malignant lymphoma, undiffer type																										1
Malignant lymphoma, lymphocytic type	X										X		X			X										8
Malignant lymphoma, histiocytic type																										2
Malignant lymphoma, mixed type				X										X												9

* Animals necropsied

TABLE H2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPC: LOW DOSE

ANIMAL NUMBER	026	042	044	029	050	021	046	007	047	002	001	003	004	005	006	008	009	010	011	012	013	014	015	016	017
WEEKS ON STUDY	068	069	074	077	084	094	099	101	102	103	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Fibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X														
Alveolar/bronchiolar carcinoma																									
Sarcoma, NOS, metastatic																									
Osteosarcoma, metastatic								X																	
Trachea	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	−	+	+	+	−	+	+	~	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma	X																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rectum	N	+	N	+	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma								X																	
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS		X														X				X		X			X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																						X			
Parathyroid	−	−	+	−	−	+	+	−	+	+	+	+	+	−	+	−	+	−	+	+	+	+	−	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	N	N	+	+	N	N	+	+	+	+	N	+	+	+	N	N	+	+	+	+	+	+
Adenocarcinoma, NOS																						X			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma											X														
Ovary	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor												X													
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							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
Malignant lymphoma, NOS						X	X																		
Malignant lymphoma, lymphocytic type																				X					
Malignant lymphoma, histiocytic type	X		X	X																					
Malignant lymphoma, mixed type													X								X				

TABLE H2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	0 1 8	0 1 9	0 2 0	0 2 2	0 2 3	0 2 4	0 2 5	0 2 7	0 2 8	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 3	0 4 5	0 4 8	0 4 9	TOTAL:
WEEKS ON STUDY	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS										X																1
Fibrosarcoma																				X						1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																									X	2
Alveolar/bronchiolar carcinoma												X														1
Sarcoma, NOS, metastatic										X																1
Osteosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymus	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	45
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma			X				X																			2
Hepatocellular carcinoma						X																	X			2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma																										1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Malignant lymphoma, mixed type									X																	1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Rectum	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
Osteosarcoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS	X			X							X			X					X					X	X	12
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										1
Parathyroid	–	–	+	+	+	–	+	+	–	+	–	–	–	+	+	–	–	+	–	–	+	–	–	+	+	28
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	N	+	N	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	*50
Adenocarcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																										1
Ovary	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Granulosa cell tumor																										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	*50
Adenoma, NOS																										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	*50
Malignant lymphoma, NOS																										2
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, histiocytic type																						X				4
Malignant lymphoma, mixed type	X																		X		X		X			6

* Animals necropsied

TABLE H2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPC: HIGH DOSE

ANIMAL NUMBER	0 3 6	0 3 9	0 3 2	0 4 1	0 2 0	0 3 1	0 4 8	0 3 3	0 3 4	0 1 6	0 1 2	0 1 8	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 3	0 1 4
WEEKS ON STUDY	0 6 6	0 6 7	0 7 5	0 7 7	0 8 3	0 8 3	0 8 5	0 8 6	0 8 6	0 9 4	0 9 9	1 0 1	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 4	1 0 4	1 0 4	1 0 4	1 0 4
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																									
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Carcinosarcoma, metastatic											X														
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	−	+	+	+	−	+	−	−	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma										X							X								
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																				X					
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS			X																						
Adenoma, NOS												X											X	X	X
Adrenal	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma														X											
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Parathyroid	+	+	+	−	−	+	−	+	−	+	+	+	−	+	+	+	+	−	−	+	−	−	−	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	N	+	+	N	+	+	N	+	N	+	+	+	N	+	+	+	N	N	+	+	N	+
Carcinosarcoma											X														
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma in situ, NOS																									
Endometrial stromal polyp																									
Ovary	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary adenoma																									
Luteoma																									
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
Adenocarcinoma, 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
Adenocarcinoma, NOS, metastatic												X													
Malignant lymphoma, lymphocytic type	X					X										X					X			X	
Malignant lymphoma, histiocytic type								X	X																
Malignant lymphoma, mixed type				X	X								X		X					X					

TABLE H2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	01 15	01 17	01 19	02 21	02 22	02 23	02 24	02 25	02 26	02 27	02 28	02 29	03 30	03 35	03 37	03 38	04 40	04 42	04 43	04 44	04 45	04 46	04 47	04 49	05 50	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic													X													1
Alveolar/bronchiolar adenoma						X																				1
Alveolar/bronchiolar carcinoma																									X	1
Carcinosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, mixed type												X														1
Lymph nodes	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma															X											1
Thymus	–	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	–	40
Malignant lymphoma, mixed type																							X			1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma								X	X						X		X									6
Hepatocellular carcinoma													X													1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, mixed type									X																	1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																										1
Adenoma, NOS									X					X						X		X				8
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	48
Pheochromocytoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid	+	–	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	–	–	–	+	+	+	–	–	32
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	N	N	N	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	*50
Carcinosarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma in situ, NOS								X																		1
Endometrial stromal polyp																									X	1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	48
Papillary adenoma										X																1
Luteoma																	X									1
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	*50
Adenocarcinoma, 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	*50
Adenocarcinoma, NOS, metastatic																										1
Malignant lymphoma, lymphocytic type	X																									6
Malignant lymphoma, histiocytic type																										2
Malignant lymphoma, mixed type							X												X						X	8

* Animals necropsied

TABLE H3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPC

	Vehicle Control	15 mg/kg	30 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	6.6%	5.0%	2.6%
Terminal Rates (c)	0/37 (0%)	2/40 (5%)	1/38 (3%)
Week of First Observation	55	104	104
Life Table Tests (d)	P=0.224N	P=0.478N	P=0.315N
Incidental Tumor Tests (d)	P=0.233N	P=0.596N	P=0.329N
Cochran-Armitage Trend Test (d)	P=0.222N		
Fisher Exact Test (d)		P=0.500N	P=0.309N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	6.6%	7.5%	5.3%
Terminal Rates (c)	0/37 (0%)	3/40 (7%)	2/38 (5%)
Week of First Observation	55	104	104
Life Table Tests (d)	P=0.410N	P=0.634N	P=0.504N
Incidental Tumor Tests (d)	P=0.416N	P=0.587	P=0.520N
Cochran-Armitage Trend Test (d)	P=0.412N		
Fisher Exact Test (d)		P=0.661	P=0.500N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	8/50 (16%)	1/50 (2%)	6/50 (12%)
Adjusted Rates (b)	20.0%	2.5%	14.2%
Terminal Rates (c)	6/37 (16%)	1/40 (3%)	4/38 (11%)
Week of First Observation	76	105	66
Life Table Tests (d)	P=0.298N	P=0.015N	P=0.374N
Incidental Tumor Tests (d)	P=0.306N	P=0.015N	P=0.389N
Cochran-Armitage Trend Test (d)	P=0.309N		
Fisher Exact Test (d)		P=0.016N	P=0.387N
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	2/50 (4%)
Adjusted Rates (b)	4.9%	8.4%	4.7%
Terminal Rates (c)	0/37 (0%)	1/40 (3%)	0/38 (0%)
Week of First Observation	98	68	86
Life Table Tests (d)	P=0.582	P=0.363	P=0.680
Incidental Tumor Tests (d)	P=0.571	P=0.332	P=0.654
Cochran-Armitage Trend Test (d)	P=0.588		
Fisher Exact Test (d)		P=0.339	P=0.691N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	10/50 (20%)	7/50 (14%)	11/50 (22%)
Adjusted Rates (b)	24.4%	17.5%	26.9%
Terminal Rates (c)	7/37 (19%)	7/40 (18%)	9/38 (24%)
Week of First Observation	82	105	77
Life Table Tests (d)	P=0.468	P=0.249N	P=0.518
Incidental Tumor Tests (d)	P=0.484	P=0.357N	P=0.529
Cochran-Armitage Trend Test (d)	P=0.449		
Fisher Exact Test (d)		P=0.298N	P=0.500
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	21/50 (42%)	14/50 (28%)	19/50 (38%)
Adjusted Rates (b)	46.3%	30.4%	42.4%
Terminal Rates (c)	13/37 (35%)	9/40 (23%)	13/38 (34%)
Week of First Observation	76	68	66
Life Table Tests (d)	P=0.373N	P=0.093N	P=0.413N
Incidental Tumor Tests (d)	P=0.369N	P=0.139N	P=0.408N
Cochran-Armitage Trend Test (d)	P=0.377N		
Fisher Exact Test (d)		P=0.104N	P=0.419N

TABLE H3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	15 mg/kg	30 mg/kg
Liver: Hepatocellular Adenoma			
Overall Rates (a)	3/49 (6%)	2/50 (4%)	6/50 (12%)
Adjusted Rates (b)	8.1%	5.0%	15.3%
Terminal Rates (c)	3/37 (8%)	2/40 (5%)	5/38 (13%)
Week of First Observation	104	104	94
Life Table Tests (d)	P=0.174	P=0.464N	P=0.253
Incidental Tumor Tests (d)	P=0.159	P=0.464N	P=0.227
Cochran-Armitage Trend Test (d)	P=0.176		
Fisher Exact Test (d)		P=0.490N	P=0.254
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	4/49 (8%)	4/50 (8%)	7/50 (14%)
Adjusted Rates (b)	10.8%	10.0%	17.8%
Terminal Rates (c)	4/37 (11%)	4/40 (10%)	6/38 (16%)
Week of First Observation	104	104	94
Life Table Tests (d)	P=0.210	P=0.601N	P=0.274
Incidental Tumor Tests (d)	P=0.195	P=0.601N	P=0.249
Cochran-Armitage Trend Test (d)	P=0.211		
Fisher Exact Test (d)		P=0.631N	P=0.274
Pituitary Gland: Adenoma			
Overall Rates (a)	11/50 (22%)	12/49 (24%)	7/50 (14%)
Adjusted Rates (b)	29.7%	29.7%	17.9%
Terminal Rates (c)	11/37 (30%)	11/39 (28%)	6/38 (16%)
Week of First Observation	104	69	101
Life Table Tests (d)	P=0.170N	P=0.557	P=0.198N
Incidental Tumor Tests (d)	P=0.179N	P=0.556	P=0.215N
Cochran-Armitage Trend Test (d)	P=0.191N		
Fisher Exact Test (d)		P=0.478	P=0.218N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	11/50 (22%)	12/49 (24%)	8/50 (16%)
Adjusted Rates (b)	29.7%	29.7%	19.7%
Terminal Rates (c)	11/37 (30%)	11/39 (28%)	6/38 (16%)
Week of First Observation	104	69	75
Life Table Tests (d)	P=0.246N	P=0.557	P=0.285N
Incidental Tumor Tests (d)	P=0.257N	P=0.556	P=0.306N
Cochran-Armitage Trend Test (d)	P=0.269N		
Fisher Exact Test (d)		P=0.478	P=0.306N

(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 vehicle 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 vehicle 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 exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE H4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPC

	Vehicle Control	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, acute/chronic			2 (4%)
*Subcutaneous tissue	(50)	(50)	(50)
Necrosis, fat			1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Hemorrhage	1 (2%)		1 (2%)
Inflammation, acute	2 (4%)	2 (4%)	
Inflammation, chronic	1 (2%)		1 (2%)
Fibrosis, focal	1 (2%)		
Hemosiderosis		1 (2%)	
Alveolar macrophages	7 (14%)	3 (6%)	5 (10%)
Hyperplasia, alveolar epithelium	5 (10%)	4 (8%)	
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(50)	(50)
Necrosis, focal		2 (4%)	
Myelofibrosis	13 (26%)	16 (32%)	20 (40%)
Hyperplasia, granulocytic	5 (10%)	1 (2%)	4 (8%)
#Spleen	(49)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
Fibrosis, focal	1 (2%)		
Necrosis, focal		1 (2%)	
Necrosis, diffuse		1 (2%)	
Angiectasis	1 (2%)		
Hematopoiesis	5 (10%)	3 (6%)	5 (10%)
#Mesenteric lymph node	(49)	(47)	(47)
Necrosis, focal	2 (4%)		
Angiectasis	2 (4%)	2 (4%)	2 (4%)
Hyperplasia, lymphoid	1 (2%)		
#Lung	(50)	(50)	(50)
Leukocytosis, NOS	1 (2%)		2 (4%)
#Liver	(49)	(50)	(50)
Erythrophagocytosis			1 (2%)
Hematopoiesis	2 (4%)	1 (2%)	3 (6%)
CIRCULATORY SYSTEM			
#Heart	(50)	(50)	(50)
Mineralization	1 (2%)		2 (4%)
Periarteritis	1 (2%)		
Degeneration, NOS	1 (2%)		
#Urinary bladder	(49)	(50)	(49)
Periarteritis		1 (2%)	1 (2%)
#Uterus	(50)	(50)	(50)
Thrombus, organized		2 (4%)	
#Ovary	(50)	(48)	(48)
Thrombosis, NOS			1 (2%)
#Thyroid	(48)	(50)	(49)
Periarteritis		1 (2%)	

TABLE H4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM			
#Salivary gland	(49)	(49)	(50)
Atrophy, NOS		1 (2%)	
#Liver	(49)	(50)	(50)
Cyst, NOS	1 (2%)		
Inflammation, chronic	4 (8%)		
Necrosis, focal	2 (4%)	5 (10%)	3 (6%)
Metamorphosis, fatty	1 (2%)	1 (2%)	
Hemosiderosis			1 (2%)
Cytoplasmic vacuolization		42 (84%)	48 (96%)
Focal cellular change	1 (2%)	2 (4%)	1 (2%)
Angiectasis	1 (2%)		
#Pancreas	(48)	(50)	(50)
Dilatation/ducts	1 (2%)		2 (4%)
Inflammation, chronic		1 (2%)	1 (2%)
Degeneration, NOS			1 (2%)
Atrophy, focal	2 (4%)	2 (4%)	2 (4%)
#Glandular stomach	(49)	(50)	(50)
Inflammation, acute	1 (2%)		2 (4%)
#Gastric muscularis	(49)	(50)	(50)
Hyperplasia, NOS			1 (2%)
#Forestomach	(49)	(50)	(50)
Inflammation, acute	1 (2%)		
Hyperplasia, epithelial			1 (2%)
#Jejunum	(47)	(48)	(50)
Inflammation, acute/chronic	1 (2%)		
Amyloid, NOS		1 (2%)	
#Ileum	(47)	(48)	(50)
Inflammation, acute necrotizing		1 (2%)	
Inflammation, acute/chronic			1 (2%)
#Colon	(47)	(50)	(49)
Parasitism		3 (6%)	2 (4%)
URINARY SYSTEM			
#Kidney	(49)	(50)	(50)
Glomerulonephritis, chronic	6 (12%)	5 (10%)	10 (20%)
Infarct, NOS	3 (6%)	2 (4%)	3 (6%)
Metaplasia, osseous	2 (4%)	1 (2%)	1 (2%)
#Kidney/capsule	(49)	(50)	(50)
Inflammation, chronic			1 (2%)
#Kidney/tubule	(49)	(50)	(50)
Dilatation, NOS	1 (2%)		
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(49)	(50)
Hyperplasia, focal	12 (24%)	15 (31%)	10 (20%)
#Adrenal cortex	(50)	(50)	(48)
Degeneration, lipoid	3 (6%)	2 (4%)	
Necrosis, focal			1 (2%)
Hypertrophy, focal	1 (2%)		2 (4%)
Hyperplasia, focal	6 (12%)	1 (2%)	1 (2%)
#Adrenal medulla	(50)	(50)	(48)
Hyperplasia, focal	2 (4%)	1 (2%)	2 (4%)

TABLE H4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(48)	(50)	(49)
Inflammation, acute/chronic	1 (2%)	2 (4%)	4 (8%)
Inflammation, chronic	3 (6%)	5 (10%)	2 (4%)
Cytoplasmic vacuolization		1 (2%)	
Hyperplasia, follicular cell	3 (6%)	5 (10%)	11 (22%)
#Pancreatic islets	(48)	(50)	(50)
Hyperplasia, NOS			1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Inflammation, chronic		2 (4%)	
Hyperplasia, cystic	1 (2%)	2 (4%)	1 (2%)
#Uterus	(50)	(50)	(50)
Dilatation, NOS	4 (8%)	2 (4%)	3 (6%)
Hyperplasia, stromal		1 (2%)	
Angiectasis	1 (2%)	2 (4%)	
#Uterus/endometrium	(50)	(50)	(50)
Inflammation, suppurative	3 (6%)	2 (4%)	2 (4%)
Hyperplasia, cystic	31 (62%)	38 (76%)	35 (70%)
#Fallopian tube	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
#Ovary	(50)	(48)	(48)
Cyst, NOS	23 (46%)	21 (44%)	15 (31%)
Abscess, NOS	4 (8%)	1 (2%)	1 (2%)
Inflammation, chronic	1 (2%)		
NERVOUS SYSTEM			
#Brain/meninges	(50)	(49)	(50)
Inflammation, acute	1 (2%)		
#Brain	(50)	(49)	(50)
Inflammation, chronic	1 (2%)		
Malacia	1 (2%)		
Atrophy, pressure	1 (2%)	3 (6%)	2 (4%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Congenital malformation, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Skeletal muscle	(50)	(50)	(50)
Mineralization			1 (2%)
Inflammation, acute/chronic			1 (2%)

TABLE H4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF THPC (Continued)

	Vehicle Control	Low Dose	High Dose
BODY CAVITIES			
*Peritoneum	(50)	(50)	(50)
Inflammation, acute/chronic	2 (4%)	3 (6%)	
Necrosis, fat			2 (4%)
*Pleura	(50)	(50)	(50)
Vegetable foreign body	1 (2%)		
Inflammation, acute necrotizing	1 (2%)	1 (2%)	1 (2%)
Inflammation, acute/chronic	1 (2%)		1 (2%)
ALL OTHER SYSTEMS			
None			
SPECIAL MORPHOLOGY SUMMARY			
None			

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX I

GENETIC TOXICOLOGY OF THPS

TABLE I1. MUTAGENICITY OF THPS IN L5178Y MOUSE LYMPHOMA CELLS IN THE ABSENCE OF S9
(a)

Compound	Dose (µg/ml)	Total Mutant Clones	Relative Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutation Frequency (mutants/10^6 clonable cells)
Dimethyl sulfoxide		69	132.2	117	17
		53	101.3	100	17
		71	88.5	84	27
		88	96.0	97	31 (23)
Methyl methanesulfonate					
	5	402	97.7	68.9	137
		376	92.8	64.3	135
		439	105.7	88.2	138 (137)
THPS	2	87	83.3	52.2	35
		67	85.5	58.4	26
		59	78.8	85.8	25 (29)
	3	64	88.0	72.5	24
		62	78.0	80.5	26
		94	103.7	68.2	30 (27)
	4	74	102.3	45.9	24
		121	74.7	45.4	54
		71	84.5	41.0	28 (35)
	5	99	89.2	45.3	37
		128	103.8	34.4	41
		112	88.5	42.4	42 (40)
	6	167	96.2	36.4	58
		121	108.5	52.3	37
		156	113.5	41.8	46 (47)
	8	238	71.2	20.5	111
		420	100.7	26.2	139
		368	104.3	28.8	118 (123)

(a) Experiments were performed twice; all doses were tested in duplicate or triplicate. Because the results were similar, data from only one experiment are shown. The protocol was basically that of Clive et al. (1979). Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium to determine the percentage of viable cells.

APPENDIX J

GENETIC TOXICOLOGY OF THPC

TABLE J1. MUTAGENICITY OF THPC IN *SALMONELLA TYPHIMURIUM*

Strain	Dose (µg/plate)	Revertants/plate (a,b) −S9	+S9 (rat)	+S9 (hamster)
TA100	0.00	111 ± 9.8	170 ± 14.7	135 ± 5.5
	0.33	102 ± 5.6	153 ± 10.4	133 ± 6.8
	1.00	114 ± 7.5	142 ± 7.8	130 ± 14.3
	3.30	92 ± 9.1	152 ± 4.3	128 ± 3.5
	10.00	107 ± 13.3	176 ± 14.5	130 ± 8.4
	33.00	104 ± 5.0	154 ± 6.3	135 ± 10.6
TA1535	0.00	4 ± 0.6	7 ± 1.5	6 ± 1.3
	0.33	4 ± 1.0	6 ± 1.5	7 ± 0.6
	1.00	5 ± 2.0	5 ± 0.6	8 ± 0.3
	3.30	5 ± 0.9	4 ± 0.6	10 ± 2.3
	10.00	4 ± 0.9	6 ± 1.2	7 ± 0.7
	33.00	5 ± 1.7	5 ± 0.0	7 ± 0.7
TA1537	0.00	5 ± 0.3	5 ± 1.5	7 ± 1.0
	0.33	3 ± 1.2	7 ± 0.7	7 ± 1.2
	1.00	4 ± 1.5	9 ± 1.5	5 ± 0.7
	3.30	3 ± 0.9	5 ± 1.2	5 ± 2.5
	10.00	6 ± 0.7	5 ± 0.6	8 ± 1.2
	33.00	8 ± 0.6	5 ± 0.6	7 ± 1.7
TA98	0.00	16 ± 0.9	26 ± 4.2	23 ± 1.2
	0.33	9 ± 0.3	17 ± 2.8	20 ± 2.6
	1.00	11 ± 1.2	19 ± 1.2	18 ± 2.4
	3.30	8 ± 0.9	24 ± 2.4	14 ± 1.7
	10.00	11 ± 1.8	20 ± 2.1	25 ± 4.1
	33.00	12 ± 1.2	21 ± 1.7	25 ± 5.1

(a) The S9 fractions were prepared from the liver of Aroclor 1254-induced male Sprague-Dawley rats and male Syrian hamsters. Cells and study compound or solvent (distilled water) were incubated for 20 minutes at 37° C in the presence of either S9 or buffer. 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 (Haworth et al., 1983). The experiment was performed twice, each in triplicate; because the results were similar, data from only one experiment are shown.
(b) Mean ± standard error

TABLE J2. MUTAGENICITY OF THPC IN L5178Y MOUSE LYMPHOMA CELLS IN THE ABSENCE OF S9
(a)

Compound	Dose (μg/ml)	Total Mutant Clones	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutation Frequency (mutants/10^6 clonable cells)
Distilled water		115	84.8	105	45
		111	90.2	107	41
		144	83.5	103	57
		133	65.7	82	68 (53)
Methyl methanesulfonate					
	5	748	38.0	36.5	656
		701	54.5	34.5	429
		655	37.8	24.8	577 (554)
THPC	3	123	72.3	76.4	57
		89	82.8	81.3	36
		114	86.2	75.6	44 (46)
	4	119	75.2	77.6	53
		134	73.3	73.3	61
		123	67.8	63.8	60 (58)
	5	173	93.8	57.8	61
		198	85.5	58.7	77
		188	69.7	31.6	90 (76)
	6	207	57.3	42.8	120
		209	56.5	34.3	123
		371	73.7	33.9	168 (137)
	8	605	63.7	30.0	317
		582	44.0	11.0	441
		502	75.0	38.9	223 (327)

(a) Experiments were performed twice; all doses were tested in triplicate or quadruplicate. Because the results were similar, data from only one experiment are shown. The protocol was basically that of Clive et al. (1979). Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium to determine the percentage of viable cells.

TABLE J3. INDUCTION OF SISTER-CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY THPC (a)

	−S9 (b)		+S9 (c)	
	Dose (µg/ml)	SCE/Cell	Dose (µg/ml)	SCE/Cell (d)
Medium		7.6		6.8
THPC	20.0	11.7	4.99	7.6
	30.0	16.1	15.00	8.1
	39.9	24.4	49.90	19.9
Mitomycin C	0.0015	12.2	Cyclophosphamide 0.50	7.9
	0.010	29.0	2.50	10.7

(a) SCE = sister-chromatid exchange
(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent (medium) at 37° C; 2 hours after initiation of treatment, 10 µM BrdU was added, and incubation was continued for an additional 22-24 hours. Cells were washed, fresh medium containing BrdU (10 µM) and colcemid (0.1 µg/ml) was added, and incubation was continued for 2-3 hours (Galloway et al., 1985).
(c) In the presence of S9, Chinese hamster ovary cells were incubated with study compound or solvent (medium) for 2 hours at 37° C. Then cells were washed, and medium containing 10 µM BrdU was added. Cells were incubated for a further 26 hours, with colcemid (0.1 µg/ml) present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague-Dawley rats (Galloway et al., 1985).
(d) Cells were collected by mitotic shake-off, treated for 3 minutes with potassium chloride (75 mM), washed twice with fixative, and dropped onto slides and air-dried (Galloway et al., 1985).

TABLE J4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY THPC (a)

	−S9 (b)		+S9 (c)	
	Dose (µg/ml)	Abs/100 Cells (percent cells with abs)	Dose (µg/ml)	Abs/100 Cells (percent cells with abs)
Medium				1 (1)
THPC	15.0	2 (2)	10.0	1 (1)
	30.0	7 (6)	30.0	2 (2)
	45.0	20 (19)	50.0	6 (6)
			150.0	33 (27)
Mitomycin C	5.0	96 (56)	Cyclophosphamide 50.0	112 (44)

(a) Abs = aberrations
(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent (medium) for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid (0.1 µg/ml) was added. After a further 2-3 hours of incubation, cells were harvested by mitotic shake-off, fixed, and stained in 6% Giemsa (Galloway et al., 1985).
(c) In the presence of S9, Chinese hamster ovary cells were incubated with study compound or solvent (medium) for 2 hours at 37° C. Cells were then washed, fresh medium was added, and incubation was continued for 8-10 hours. Colcemid (0.1 µg/ml) was added for the last 2-3 hours of incubation; then cells were harvested by mitotic shake-off, fixed, and stained in 6% Giemsa. S9 was from the liver of Aroclor 1254-induced male Sprague-Dawley rats (Galloway et al., 1985).

APPENDIX K

CHEMICAL CHARACTERIZATION OF THPS

APPENDIX K. CHEMICAL CHARACTERIZATION

I. Identity and Purity Determinations of Tetrakis(hydroxymethyl)phosphonium Sulfate (THPS) Lot No. 7340 Performed by the Analytical Chemistry Laboratory

	Determined	Literature Values
A. Physical properties		
1. Appearance:	Clear, colorless liquid	
2. Boiling point:	111° C for the 72% water solution (visual micro boiling point)	No literature value found
B. Spectral data		
1. Infrared		
Instrument:	Beckman IR-12	
Cell:	Thin film between silver chloride plates	
Results:	See Figure 9	No literature reference found; however, the spectrum is consistent with the literature spectrum for THPC (Sadtler Standard Spectra)
2. Ultraviolet/visible		
Instrument:	Cary 118	
Solvent:	Methanol	
	No absorbance between 350 and 800 nm. No maximum between 210 and 350 nm, but a gradual increase in absorbance toward the solvent cutoff.	

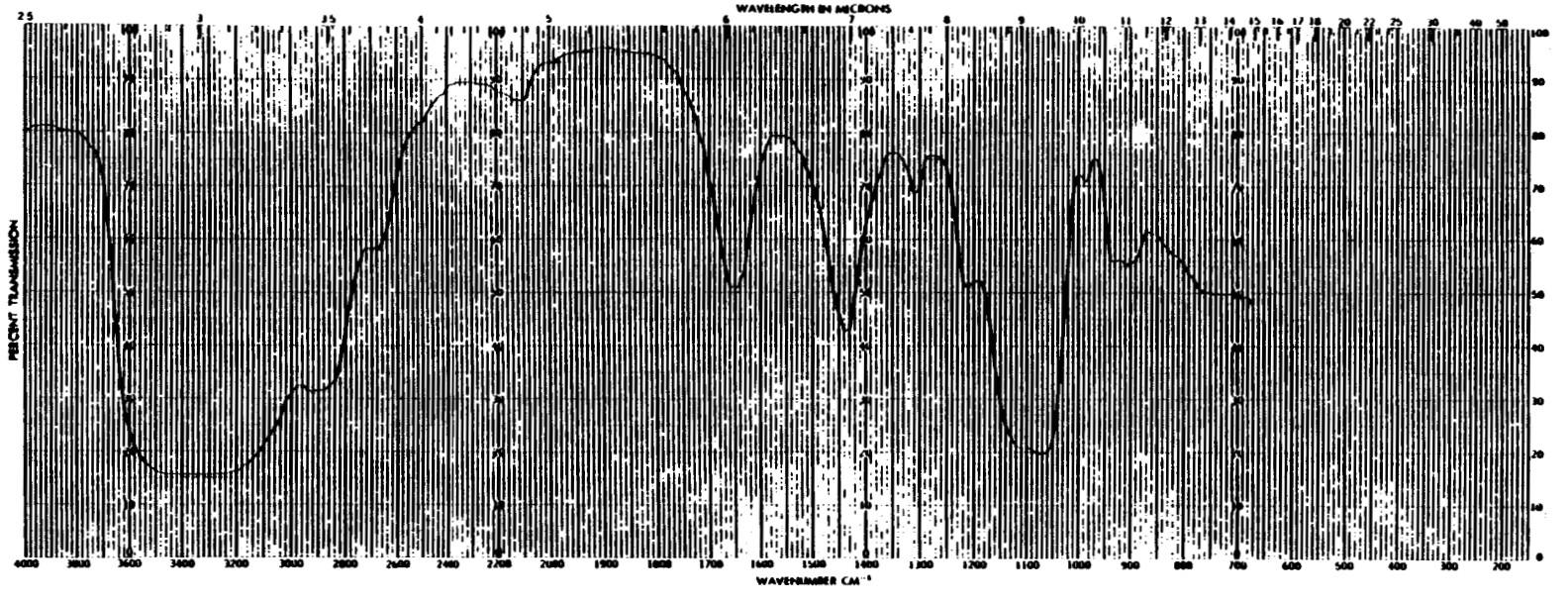


FIGURE 9. INFRARED ABSORPTION SPECTRUM OF THPS (LOT NO. 7340)

	Determined	Literature values
3. Nuclear magnetic resonance		
Instrument:	Varian EM-360A	
Solvent:	Dimethyl sulfoxide-d_6 with tetramethylsilane added	
Assignments:	See Figure 10	No literature reference found. Consistent with the structure.
Chemical shift (δ):	a s, δ 4.53 ppm b s, δ 4.99 ppm c δ 3.26-3.33 ppm d δ 3.81-4.02 ppm	
Integration ratios:	a 8.00 b $-OH, H_2O$ c 0.09 (impurity) d 0.17 (impurity)	

C. **Water analysis (Karl Fischer):** Reagent appeared to react with some component of the formulation. Therefore, the Karl Fischer values were not considered valid.

D. **Iodate-thiosulfate titration** (Frank, 1977)**:** Reaction with potassium iodate and back titration with thiosulfate: 71.7% ± 0.5(δ)% (w/w) oxidizable material

E. **Elemental analysis**

Element	C	H	P	S
Theory (based on 72% THPS and 28% Water) (T)	17.03	7.39	10.98	5.68
Determined (D)	18.42 18.21	7.25 7.26	11.32 11.56	5.51 5.55
Percent D/T	108	98	104	97

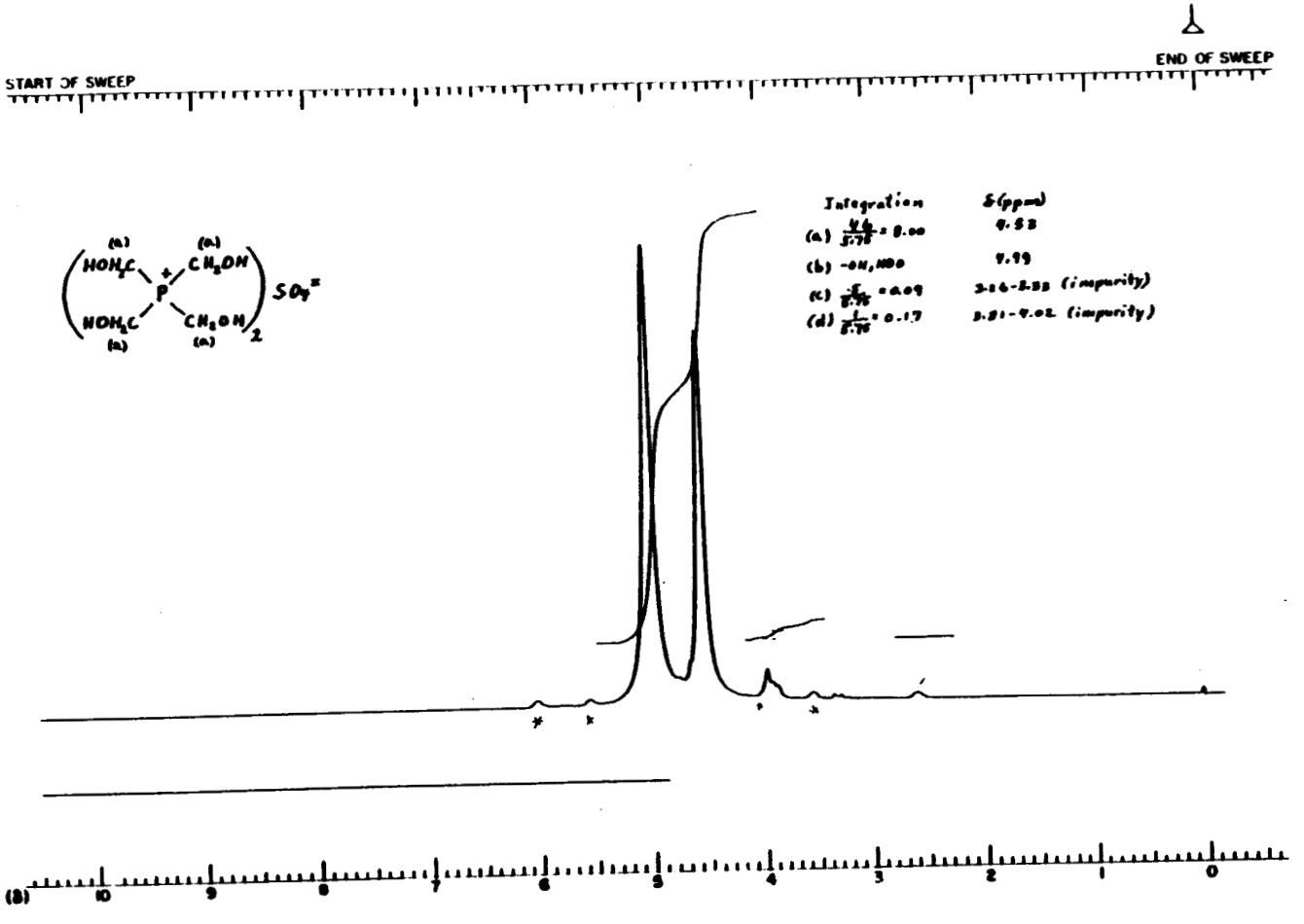


FIGURE 10. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF THPS (LOT NO. 7340)

F. **Thin-layer chromatography**

Plates: Silica Gel 60 F-254
Amount spotted: 200 and 600 µg (20 µg/µl in water)
Reference standard: Triethyl phosphate, 100 µg (10 µg/µl in water)
Visualization: Iodine vapor; ultraviolet at 254 nm

System 1

Solvent: Methanol:water (80:20)

Results: R_f: 0.79 (major)
R_{st}: 0.97

System 2

Solvent: Dioxane:water (80:20)

Results: R_f: 0.89 (major)
origin (trace)
R_{st}: 1.00, origin

G. **Conclusions:** The results of the elemental analysis for carbon and phosphorus were high for theoretical values based on 72% THPS and 28% water, whereas the results for hydrogen and sulfur were in agreement. Titration by reaction with iodate indicated a purity of 71.7% $\pm 0.5(\delta)$%. The manufacturer's nominal specifications were for 75% THPS and 25% water. The titration value is representative of all material in the sample oxidizable by iodate. If any of the THPS was already oxidized, a titration value of less than 75% would be expected. Thin-layer chromatography by one system indicated a major spot only. A second thin-layer chromatographic system indicated a trace impurity at the origin. The infrared, ultraviolet/visible, and nuclear magnetic resonance spectra were consistent with the structure of THPS.

II. Stability Study of THPS Performed by the Analytical Chemistry Laboratory

A. Sample storage: Samples containing 71.7% (w/w) of THPS in water were stored for 2 weeks at −20°, 5°, 25°, or 60° C in glass tubes sealed with Teflon®-lined screw caps.

B. Analytical method: Samples were analyzed by the iodate-thiosulfate titration method described in Section I.D. above.

C. Results

Storage Temperature	Percent of THPS (a)
−20° C	100.0 ± 1.2
5° C	98.6 ± 1.2
25° C	99.2 ± 1.2
60° C	99.3 ± 1.2

(a) Relative to −20° C samples

D. Conclusion: THPS, as a 72% solution in water, is stable for 2 weeks at temperatures up to 60° C.

III. Chemical Stability Study of THPS Performed by the Study Laboratory

A. Storage conditions

Bulk: Room temperature
Reference: −20° C

B. Analytical method

1. Infrared spectroscopy

Instrument: Perkin-Elmer 521 or Digilab FTS-14
Cell: Liquid between plates

2. **Titration:** A 5.00-ml aliquot of 0.2 N samples of THPS was added to 25.00 ml of 0.1 N potassium iodate and 2.0 g of sodium bicarbonate. This mixture was stirred for 1.5 hours. Then 2.0 g of potassium iodide was added with 10.0 ml of 6 N hydrochloric acid. This solution was titrated immediately with 0.1 N sodium thiosulfate to a colorless end point. Starch (2 ml) was added close to the end of the titration to accentuate the color change. The following equation was used to calculate the percent purity.

$$\text{Percent purity} = \frac{(25.00 \times N_{\text{iodate}}) - (\text{Volume}_{(\text{milliliters thio})} \times N_{\text{thio}}) \times 100}{2(5.00)(N_{\text{sample}})}$$

C. Results

1. **Infrared spectroscopy:** All bulk spectra were comparable to the reference spectra and to the spectra supplied by the analytical chemistry laboratory.

2. **Titration**

	Percent Purity	
Date of Analysis	Bulk	Reference
2/7/79	74.8	--
5/8/79	69.8	69.0
9/27/79	72.0	73.7
2/1/80	71.5	71.5
5/2/80	74.7	74.7
2/6/81	72.0	72.5
5/5/81	69.7	70.0
9/11/81	70.2	71.3
1/5/82	70.2	71.3
4/30/82	72.2	74.5
Mean	71.7	72.1
Standard deviation	1.86	1.96

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

APPENDIX L

CHEMICAL CHARACTERIZATION OF THPC

APPENDIX L. CHEMICAL CHARACTERIZATION

I. Identity and Purity Determinations of Tetrakis(hydroxymethyl)phosphonium Chloride (THPC) Lot No. ON2 Performed by the Analytical Chemistry Laboratory

	Determined	Literature Values
A. Physical properties		
1. Transition temperature:	118° C (visual, micro boiling point for 75% water solution)	Melting point: 146°-147° C (nonformulated compound) (Loewengart and Van Duuren, 1977)
2. Appearance:	Slightly viscous, clear yellow liquid	
B. Spectral data		
1. Infrared		
Instrument:	Beckman IR-12	
Cell:	Thin film between silver chloride plates	
Results:	See Figure 11	Consistent with literature spectrum (Sadtler Standard Spectra)
2. Ultraviolet/visible		
Instrument:	Cary 118	
Solvent:	Methanol	
Results:	No absorbance between 350 and 800 nm. No maximum between 210 and 350 nm but a gradual increase in absorbance toward solvent cutoff at 210 nm.	No literature reference found. Spectrum consistent with structure.

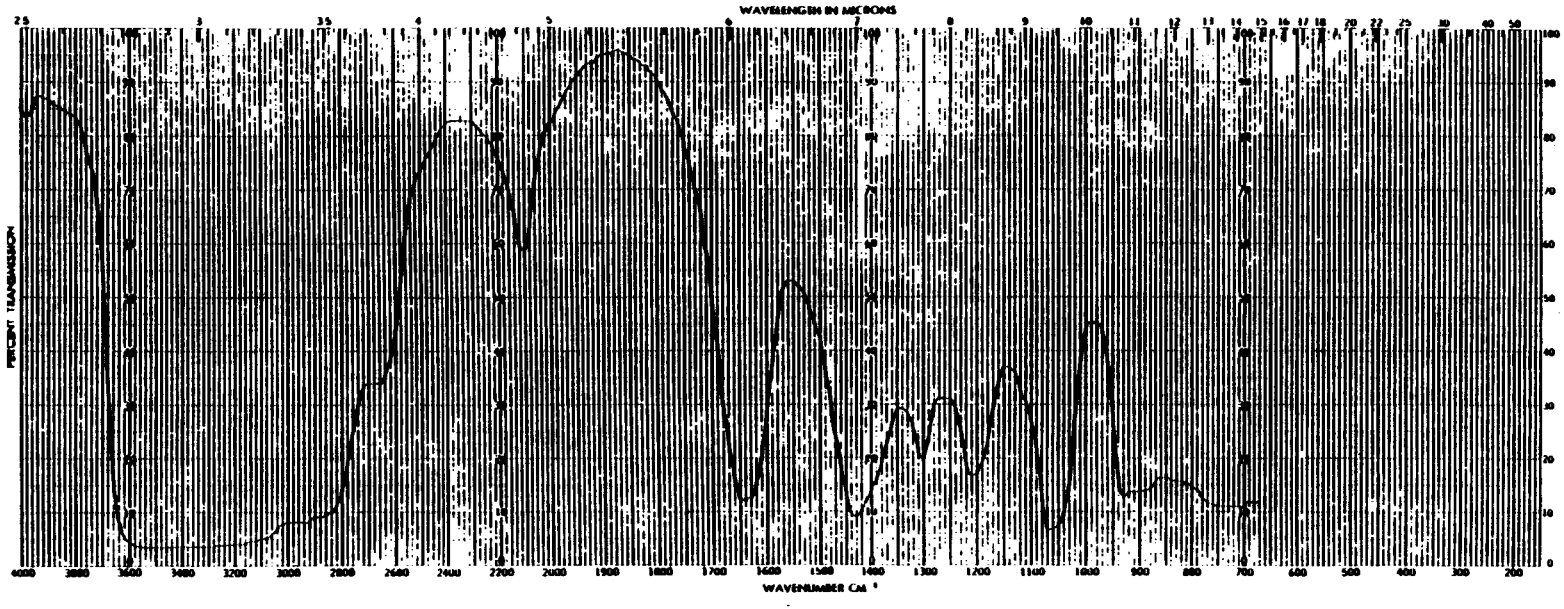


FIGURE 11. INFRARED ABSORPTION SPECTRUM OF THPC (LOT NO. ON2)

	Determined	Literature Values
3. Nuclear magnetic resonance		
Instrument:	Varian EM-360A	
Solvent:	Dimethyl sulfoxide with tetramethylsilane added	
Assignments:	See Figure 12	Consistent with literature spectrum (Sadtler Standard Spectra)
Chemical shift (δ):	a d, 4.52 ppm, $J_{P\text{-}a}$ = 2 Hz b s, 4.90 ppm	
Integration ratios:	a 8.00 b $-OH, H_2O$	

C. **Titration** (Frank, 1977): Reaction with potassium iodate and titration with thiosulfate: 74.7% ± 0.4(δ)% (w/w) oxidizable material

D. **Water analysis (Karl Fischer):** Karl Fischer reagent appeared to react with some component of the compound formulation. Karl Fischer values were not considered valid.

E. **Elemental analysis**

Element	C	H	Cl	P
Theory	25.21	6.35	18.61	16.25
Theory (T) (based on 75% THPC and 25% water)	18.91	7.54	13.96	12.19
Determined (D)	19.55 19.75	7.39 7.32	14.85 14.70	13.30 13.09
Percent D/T	103.91	97.55	105.84	108.24

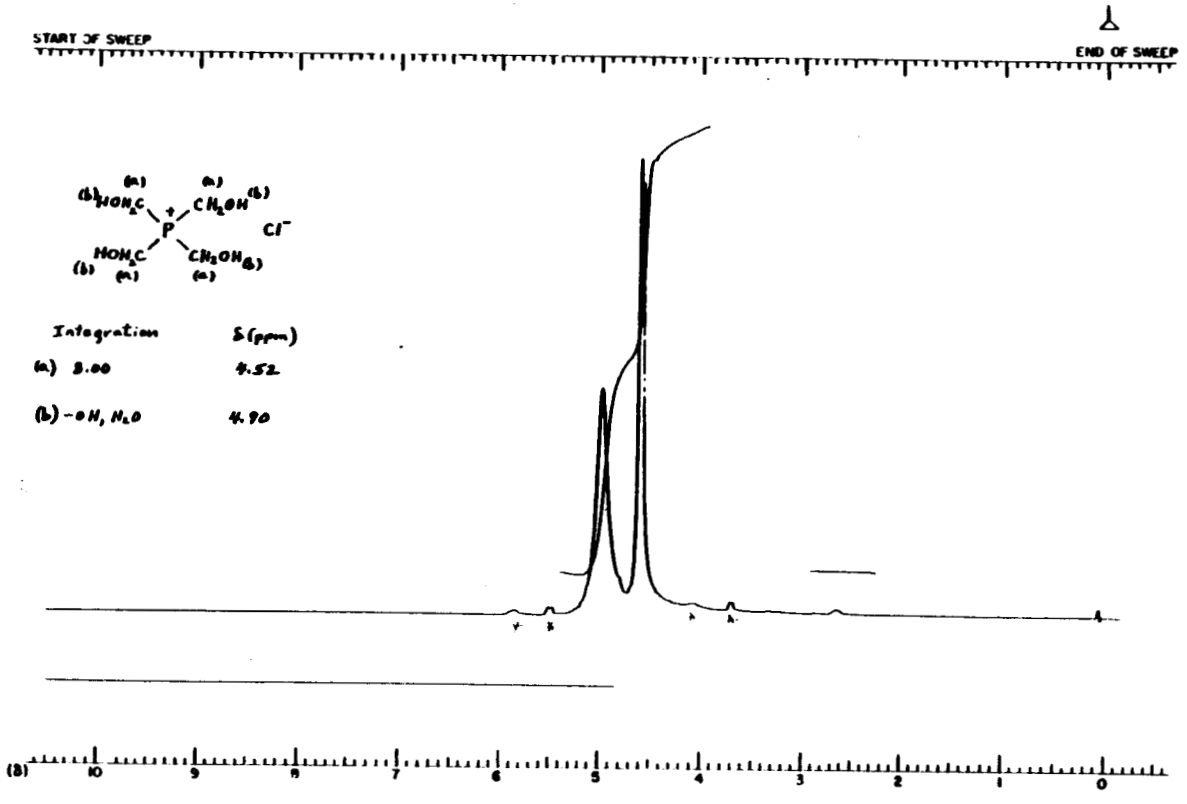


FIGURE 12. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF THPC (LOT NO. ON2)

F. **Thin-layer chromatography**

Plates: Silica Gel 60 F-254
Amount spotted: 200 and 600 µg (20 µg/µl in water)
Reference standard: Triethyl phosphate, 100 µg (10 µg/ml in water)
Visualization: Iodine vapor; ultraviolet, 254 nm

System 1: Methanol:water (80:20)
R_f: 0.78
R_{st}: 0.96

System 2: Dioxane:water (80:20)
R_f: 0.88
R_{st}: 1.00

G. **Conclusions:** The results of the elemental analysis for carbon, chlorine, and phosphorous were slightly high when the theoretical values were based on 75% THPC and 25% water, whereas the result for hydrogen was in agreement. Titration by reaction with iodate indicated a purity of 74.7% ± 0.4(δ)%. Manufacturer specifications for this lot of chemical were 80% THPC and 20% water. The titration value of 74.7% THPC, used to derive the theoretical elemental composition, was representative of material in the sample which was oxidizable by iodate. If any of the THPC had been previously oxidized to the phosphine oxide, a titration value below 80% would be expected. Thin-layer chromatography by two systems indicated major spot only. The infrared, ultraviolet/visible, and nuclear magnetic resonance spectra were consistent with the structure of THPC.

II. Stability Study of THPC Lot No. ON2 Performed by the Analytical Chemistry Laboratory

A. Sample storage: Samples of THPC (75% solution in water) were stored for 2 weeks at −20°, 5°, 25°, or 60° C in glass tubes with Teflon®-lined lids.

B. Analytical method: Samples were analyzed by the iodate-thiosulfate titration method described in Section I.C. of this appendix. Values were compared with the −20° C sample values.

C. Results

Sample Storage Temperature	Percent THPC	Normalized to −20° C Sample
−20° C	74.6 ± 0.6	100.0 ± 0.8
5° C	75.1 ± 0.6	100.6 ± 0.8
25° C	74.6 ± 0.6	100.0 ± 0.8
60° C	74.8 ± 0.6	100.2 ± 0.8

D. Conclusion: Tetrakis(hydroxymethyl)phosphonium chloride is stable as a 75% solution in water when stored for 2 weeks at temperatures of up to 60° C.

III. Stability of THPC at the Study Laboratory

A. Storage conditions

Bulk: Room temperature
Reference: −20° C

B. Analytical method

1. Infrared spectroscopy

Instrument: Perkin-Elmer 521, Digilab FTS-14, or Digilab FTS-10
Cell: Liquid between silver chloride plates

2. **Titration:** A 5.00-ml aliquot of 0.2 N samples of THPC was added to 25.00 ml of 0.1 N potassium iodate and 2.0 g of sodium bicarbonate. This mixture was stirred for 1.5 hours. Then 2.0 g of potassium iodide was added with 10.0 ml of 6 N hydrocholoric acid. This solution was titrated immediately with 0.1 N sodium thiosulfate to a colorless end point. Starch solution (2 ml) was added close to the end of the titration to accentuate the color change. The following equation was used to calculate the percent purity.

$$\text{Percent purity} = \frac{(25.00 \times N_{\text{iodate}}) - (\text{Volume}_{(\text{milliliters thio})} \times N_{\text{thio}}) \times 100}{2(5.00)(N_{\text{sample}})}$$

C. Results

1. **Infrared spectroscopy:** All bulk spectra were comparable to the reference spectra and to the spectra supplied by the analytical chemistry laboratory.

2. **Titration**

Date of Analysis	Percent Purity	
	Bulk	Reference
02/05/79	79.0	--
05/07/79	75.4	75.3
09/27/79	76.5	79.0
02/07/80	76.4	80.0
06/24/80	78.4	78.6
09/30/80	78.0	78.3
01/27/81	79.3	80.5
05/05/81	80.2	80.8
09/10/81	78.8	78.8
01/05/82	79.2	79.8
05/21/82	80.8	81.5
09/28/82	80.5	81.5

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

APPENDIX M

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES OF THPS

APPENDIX M. PREPARATION AND CHARACTERIZATION

I. Studies Conducted at the Analytical Chemistry Laboratory

A. Preparation procedure and homogeneity: Solutions of THPS in water were prepared by the following procedure. One part (1 ml) of THPS (71.7% w/w THPS in water, specific gravity 1.37) was added to three parts (3 ml) water, producing a solution of 24.6% (w/v); equal parts of THPS (1 ml) and of water (1 ml) were mixed, producing a solution 49.1% (w/v); and three parts (3 ml) of THPS were added to one part (1 ml) water, producing a solution 73.7% (w/v).

These solutions were prepared by vigorous manual agitation for 15 seconds followed by 10 seconds in an ultrasonic vibratory bath in 5-ml graduated reaction vials. The solutions were clear when held up to the light.

B. Stability: THPS was supplied as a 72% aqueous solution and was found to be stable when stored for 2 weeks at temperatures from −20° to 60° C (Appendix K, Section II). Because dose mixtures were prepared by dilution of the study chemical with water, additional stability studies were not needed.

II. Studies Conducted at the Study Laboratory

A. Preparation procedure: In the 13-week studies, an appropriate amount of bulk THPS (containing 71.7% THPS) was diluted with distilled water to give a stock solution containing 12.0 mg of THPS per milliliter of solution. A portion of the stock solution and a portion of each resulting dose mixture were diluted with distilled water to prepare solutions containing 8.00, 4.00, 2.00, or 1.00 mg THPS/ml.

For the first 60 weeks of the 2-year studies, the study laboratory prepared the rat and mouse formulations together. Thus, the high dose (2.00 mg/ml) was prepared by diluting 5.85 g of the bulk chemical (containing 4.19 g of THPS) to a total volume of 2,100 ml. The low dose (1.00 mg/ml) was prepared by diluting a 700-ml portion of the stock solution to a total volume of 1,400 ml with distilled water.

Larger quantities of dose mixtures were required for the remainder of the 2-year studies, so the study laboratory prepared the rat and mouse formulations separately. The high dose mixture (2.00 mg/ml) was prepared by diluting a weighed quantity of the study chemical. The low dose mixture (1.00 mg/ml) was prepared by 2:1 dilution of an aliquot of the high dose mixture. All dilutions were made with distilled water.

B. Dose mixture storage and handling: All dose mixtures were prepared weekly in separate quantities that were large enough to dose each different group of animals for 5 days and to provide samples for analysis. Weekly dose preparations were refrigerated at 4° C for 1 week and at room temperatures during the week of administration. The maximum storage time for any dose mixture was 14 days.

APPENDIX N

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES OF THPC

APPENDIX N. PREPARATION AND CHARACTERIZATION

THPC was supplied as a 75% aqueous solution and was found to be stable when stored for 2 weeks at temperatures from −20° C to 60° C (Appendix L, Section II). Because dose mixtures were prepared by dilution of the study material with water, additional stability studies were not needed.

I. **Preparation procedure:** An appropriate amount of bulk THPC was diluted with a small volume of deionized water. This solution was poured into a graduated mixing column and additional deionized water was added. The solution was mixed by inversion to give a stock solution containing 8.0 mg of THPC per milliliter of solution. A portion of the stock solution was diluted with deionized water to prepare solutions containing 4.00 and 2.00 mg THPC/ml.

II. **Dose mixture storage and handling:** All dose mixtures were prepared weekly and stored at 23° C. The maximum storage time for any dose mixture was 14 days.

APPENDIX O

METHODS OF ANALYSIS OF DOSE MIXTURES OF THPS

The same method was used to analyze THPS dose mixtures in water at both the analytical chemistry and the study laboratories. It involved oxidation of the cation of THPS with potassium iodate and back titration with sodium thiosulfate (Frank, 1977).

I. Study Laboratory

Procedure: The concentration of THPS (72% w/v) present in the bulk chemical was used as a correction factor in the preparation of standard solutions of known concentration. Standards were prepared by serial dilution at 4.0 mg, 2.0 mg, and 1.0 mg THPS/ml of deionized water. A 10-ml aliquot of each sample and standard was added to 25.0 ml of 0.1 N potassium iodate followed by the addition of 2.0 g of sodium bicarbonate. Mixtures were sealed and stirred for 1.5 hours. Two grams of potassium iodide was then added followed by a slow addition of 10 ml of 6.0 N hydrochloric acid. Solutions were titrated at once to a clear endpoint with 0.1 N sodium thiosulfate. Concentrations were determined from the linear regression standard curve, and analyses were performed in duplicate.

II. Analytical Chemistry Laboratory

A. **Preparation of spiked water standards:** Two standard solutions of THPS were prepared independently in deionized water. These solutions were diluted with deionized water to make four additional standards.

For the analysis, 10-ml aliquots of the six standard solutions were pipetted into individual 10-ml septum vials. One 10-ml volume of undosed water from the study laboratory was pipetted into a 100-ml septum vial for use as a blank. The spiked water standards and the blank were used in the analysis procedure described below.

B. **Preparation of referee sample:** Two portions (10 ml each) of the referee water sample were pipetted into individual 100-ml septum vials and were analyzed.

C. **Analysis procedure:** A 5-ml volume of 0.05 N potassium iodate solution was pipetted into each standard, blank, and referee sample vial, followed by the addition of 250 mg of sodium bicarbonate powder. The vials were sealed with Telfon®-lined septa and shaken at maximum stroke for 1.5 hours on a wrist-action shaker. From this point on, the sample vials were processed one at a time as described below.

Individual vials were uncapped and were rinsed down with 10 ml of distilled water. A 3-ml volume of 4 N hydrochloric acid was added, followed by 250 mg of potassium iodide crystals. The vial was swirled briefly to dissolve the crystals; then a small magnetic stirring bar was placed in the vial, and the liberated iodine was titrated with 0.01 N sodium thiosulfate while the solution was stirred.

When most of the iodine had been titrated, 1 ml of starch indicator solution was added, and the titration was continued until the blue color was discharged. The volume of thiosulfate required by each standard and sample was subtracted from the blank titration. The weight of THPS in the referee water sample was determined from the linear regression equation obtained from the standard data, relating the net thiosulfate titration for each spiked water standard to the weight of chemical in the respective spiked water standard. Values determined were expressed as both pure anhydrous THPS present in the referee sample and as the weight of bulk chemical (71.7% purity) used to formulate the referee sample.

D. **Quality assurance measures:** The referee water sample was analyzed in duplicate, and the undosed water sample was analyzed once. Individually spiked portions of distilled water (six concentrations) bracketing the specified dose range of the referee sample) were prepared from two independently weighed standards and were used for establishing the titer of the 0.01 N sodium thiosulfate across the specified dose range. The standards, blanks, and referee samples were titrated in a random order. The standard data were evaluated for linearity and correlation coefficient.

APPENDIX P

METHODS OF ANALYSIS OF DOSE MIXTURES OF THPC

The same method was used to analyze THPC doses in water at both the analytical chemistry and the study laboratories. It involved oxidation of the cation of THPC with potassium iodate and back-titration with sodium thiosulfate (Frank, 1977).

I. Study Laboratory

Standards were prepared by serial dilution at 36.0 mg, 16.0 mg (13-week studies), 8.0 mg, 4.0 mg, 2.0 mg, and 1.0 mg (13-week and 2-year studies) THPC per milliliter deionized water. No correction was made for the percent of water in THPC. Samples and standards were then treated in the same manner. Sample aliquots of the THPC solutions were added to 25.0 ml of 0.1 N potassium iodate and 2.0 g of sodium bicarbonate. The mixtures were stirred for 1.5 hours before the addition of 2.0 g of potassium iodide and 10.0 ml of 6 N hydrochloric acid. The liberated iodine was then titrated to a clear end point with 0.1 N sodium thiosulfate. Concentrations were determined from the linear regression standard curve, and the analysis was done in duplicate.

II. Analytical Chemistry Laboratory

A. Preparation of spiked water standards: Two standard solutions of THPC were prepared independently in deionized water. These solutions were diluted with deionized water to make four additional standards. Aliquots (2-10 ml) of the six standard solutions were pipetted into individual 60-ml septum vials to make spiked water standards bracketing the specified concentration range of the referee sample. Undosed water (2-10 ml) was pipetted into a 60-ml septum vial for use as a blank. The spiked water standards and the water blank were analyzed by the procedure described below.

B. Preparation of the referee sample: Three portions (2-10 ml) of the referee water sample were pipetted into individual 60-ml septum vials and were analyzed by the procedure described below.

C. Analysis procedure: A 5-ml volume of 0.05 N potassium iodate solution was pipetted into each standard blank and referee sample vial; then 250 mg of sodium bicarbonate was added to each vial. The vials were sealed with Teflon®-lined septa and were shaken at maximum stroke for 1.5 hours on a wrist-action shaker. Individual vials were uncapped and rinsed down with 5-10 ml of deionized water. A 3-ml volume of 4 N hydrochloric acid was added, followed by 250 mg of potassium iodide crystals. The vial was swirled briefly to dissolve the crystals, a small magnetic stirring bar was placed in the vial, and the liberated iodine was titrated with 0.01 N sodium thiosulfate solution while the solution was stirred. When most of the iodine had been titrated, 1 ml of starch indicator solution was added, and the titration was continued until the blue color was discharged.

The volume of thiosulfate required by each standard and sample was subtracted from the blank titration volume. The amount of THPC in the samples was determined from the linear regression equation obtained from the standard data, relating the net thiosulfate titration volume for each spiked water standard and water blank to the amount of chemical in that standard.

D. Quality assurance measures: The referee water sample was analyzed in triplicate or duplicate, and the undosed water sample was analyzed once. For calibration, six spiked water standards bracketing the specified concentration range of the referee sample were prepared from two independently weighed standards.

APPENDIX Q

RESULTS OF ANALYSIS OF DOSE MIXTURES OF THPS

TABLE Q1. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF THPS

Date Mixed	Concentration of THPS in Water (mg/ml) (a)		Determined as a Percent of Target
	Target	Determined	
07/04/79	12.0	12.2	101.3
	8.00	8.00	100.0
	4.00	4.00	100.0
	2.00	2.01	100.5
	1.00	1.00	100.4

(a) Results of duplicate analysis

TABLE Q2. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF THPS

Date Mixed	Concentration of THPS in Water for Target Concentration (mg/ml) (a)	
	1.0	2.0
04/02/80	1.1	2.1
08/27/80	0.98	2.0
10/17/80	1.0	1.9
12/09/80	1.0	2.0
01/30/81	0.94	2.1
03/31/81	0.95	2.0
05/14/81	1.0	1.9
07/17/81	1.0	2.0
09/18/81	1.0	2.1
11/20/81	1.0	1.9
01/15/82	1.0	2.1
03/12/82	1.0	2.1
Mean (mg/ml)	1.0	2.0
Standard deviation	0.039	0.083
Coefficient of variation (percent)	3.9	4.3
Range (mg/ml)	0.94-1.1	1.9-2.1
Number of samples	12	12

(a) Results of duplicate analysis

TABLE Q3. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF THPS

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (mg/ml)	
		Study Laboratory (a)	Referee Laboratory (b)
01/30/81	1.00	0.94	0.86
03/31/81	1.00	0.95	0.90
07/17/81	2.00	2.0	1.8
03/12/82	2.00	2.1	1.9

(a) Results of duplicate analysis
(b) Results of triplicate analysis

APPENDIX R

RESULTS OF ANALYSIS OF DOSE MIXTURES OF THPC

TABLE R1. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF THPC

Date Mixed	Concentration of THPC in Water (mg/ml) (a,b) Target	Determined	Determined as a Percent of Target
10/24/79	0.4	0.43	107.5
	1.0	1.08	108.0
	1.2	1.42	(c) 118.3
	2.0	2.12	106.0
	4.0 (mouse)	4.60	(c) 115.0
	4.0 (rat)	4.18	104.5
	8.0	7.88	98.5
	12.0	12.73	106.1
	16.0	16.66	104.1
	36.0	35.70	99.2
10/30/79	0.4	0.41	102.5
	1.2	1.31	(d) 108.8
	4.0 (mouse)	4.25	106.3
	12.0	12.00	(d) 100.0
	36.0	35.57	98.8

(a) Results of duplicate analysis
(b) Milligrams of bulk chemical/milliliter of water
(c) Out of specifications. Not used in the studies.
(d) Remix

TABLE R2. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF THPC

Date Mixed	Concentration of THPC in Water for Target Concentration (mg/ml) (a,b)			
	1.0	2.0	4.0	8.0
09/08/80	(c) 0.83	2.08	--	--
10/27/80	0.94	2.07	3.92	7.72
12/22/80	0.90	1.93	3.84	7.89
02/17/81	0.94	(c) 2.22	(c) 4.45	7.80
04/14/81	(c) 1.20	1.99	4.37	8.53
06/08/81	1.00	2.21	4.25	8.00
06/29/81	0.91	2.18	(c) 4.44	7.66
08/11/81	1.07	2.14	4.28	7.90
10/12/81	0.95	2.15	4.18	7.98
12/14/81	1.07	2.18	4.03	7.59
02/01/82	1.01	2.03	4.24	8.02
04/05/82	0.99	2.07	4.25	7.83
06/28/82	0.96	1.93	4.29	7.88
08/03/82	1.00	2.10	3.70	7.20
Mean (mg/ml)	0.98	2.09	4.17	7.85
Standard deviation	0.090	0.096	0.232	0.300
Coefficient of variation (percent)	9.2	4.6	5.6	3.8
Range (mg/ml)	0.83-1.20	1.93-2.22	3.70-4.45	7.20-8.53
Number of samples	14	14	13	13

(a) Results of duplicate or triplicate analysis
(b) Milligrams of bulk chemical/milliliter of water
(c) Out of specifications. Not remixed.

TABLE R3. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF THPC

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (mg/ml) (a)	
		Study Laboratory	Referee Laboratory
09/08/80	1.0	0.83	0.98
10/27/80	8.0	7.72	8.24
04/14/81	4.0	4.37	4.39
10/12/81	1.0	0.95	0.94
04/05/82	2.0	2.07	2.01
08/03/82	8.0	7.20	8.02

(a) Results of duplicate or triplicate analysis

APPENDIX S

SENTINEL ANIMAL PROGRAM

APPENDIX S. SENTINEL ANIMAL PROGRAM

I. 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 study 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 study rooms. These animals are untreated, and these animals and the study 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 vehicle 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:

THPS

	Hemagglutination Inhibition	Complement Fixation
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 (12, 18, 24 mo)	M.Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) MHV (mouse hepatitis virus) Sendai (6 mo)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai (12, 18, 24 mo)	RCV (rat coronavirus) Sendai (6 mo)

THPC

	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) (6, 12 mo)	MHV (mouse hepatitis virus) (18, 24 mo)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai	RCV (rat coronavirus)	

II. Results

Results are presented in Tables S1 and S2.

TABLE S1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF THPS (a)

Interval (months)	Number of Animals	Positive Serologic Reaction for
RATS		
6	--	None positive
12	--	None positive
18	--	None positive
24	--	None positive
MICE		
6	--	None positive
12	--	None positive
18	4/9	MVM
24	6/10	Reo 3

(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.

TABLE S2. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF THPC (a)

Interval (months)	Number of Animals	Positive Serologic Reaction for
RATS		
6	--	None positive
12	--	None positive
18	--	None positive
24	--	None positive
MICE		
6	2/10	MHV
12	--	None positive
18	--	None positive
24	2/10	MHV

(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.

APPENDIX T

INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Pelleted Diet: February 1980 to August 1982

(Manufactured by Zeigler Bros., Inc., Gardners, PA)

TABLE T1. INGREDIENTS OF NIH 07 RAT AND MOUSE RATION (a)

Ingredients (b)	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Brewer's dried yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

(a) NIH, 1978; NCI, 1976
(b) Ingredients ground to pass through a U.S. Standard Screen No. 16 before being mixed

TABLE T2. VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION (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-α-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		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

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

TABLE T3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	24.1 ± 0.85	22.7-26.1	30
Crude fat (percent by weight)	4.92 ± 0.43	4.1-5.7	30
Crude fiber (percent by weight)	3.33 ± 0.45	1.4-4.3	30
Ash (percent by weight)	6.63 ± 0.49	5.7-7.4	30
Essential Amino Acids (percent of total diet)			
Arginine	1.323 ± 0.830	1.21-1.39	4
Cystine	0.310 ± 0.099	0.218-0.400	4
Glycine	1.155 ± 0.069	1.06-1.21	4
Histidine	0.572 ± 0.030	0.530-0.603	4
Isoleucine	0.910 ± 0.033	0.881-0.944	4
Leucine	1.949 ± 0.065	1.85-1.99	4
Lysine	1.279 ± 0.075	1.20-1.37	4
Methionine	0.422 ± 0.187	0.306-0.699	4
Phenylalanine	0.909 ± 0.167	0.665-1.04	4
Threonine	0.844 ± 0.029	0.824-0.886	4
Tryptophan	0.187	0.171-0.211	3
Tyrosine	0.631 ± 0.094	0.566-0.769	4
Valine	1.110 ± 0.050	1.05-1.17	4
Essential Fatty Acids (percent of total diet)			
Linoleic	2.44	2.37-2.52	3
Linolenic	0.274	2.56-0.308	3
Arachidonic	0.008		1
Vitamins			
Vitamin A (IU/kg)	10,797 ± 2,684	6,700-17,000	30
Vitamin D (IU/kg)	3,650	3,000-6,300	2
α-Tocopherol (ppm)	41.53 ± 7.52	31.1-48.9	4
Thiamine (ppm)	16.39 ± 4.12	7.3-27.0	(a) 29
Riboflavin (ppm)	7.50 ± 0.96	6.1-8.2	4
Niacin (ppm)	85.00 ± 14.20	65.0-97.0	4
Pantothenic acid (ppm)	29.3 ± 4.60	23.0-34.0	4
Pyridoxine (ppm)	7.6 ± 1.5	5.6-8.8	4
Folic acid (ppm)	2.80 ± 0.88	1.8-3.7	4
Biotin (ppm)	0.27 ± 0.05	0.21-0.32	4
Vitamin B_{12} (ppb)	21.0 ± 11.9	11.0-38.0	4
Choline (ppm)	3,302 ± 120.0	3,200-3,430	4
Minerals			
Calcium (percent)	1.30 ± 0.19	0.82-1.1	30
Phosphorus (percent)	1.00 ± 0.08	0.82-1.1	30
Potassium (percent)	0.862 ± 0.100	0.772-0.970	3
Chloride (percent)	0.546 ± 0.100	0.442-0.635	4
Sodium (percent)	0.311 ± 0.038	0.258-0.350	4
Magnesium (percent)	0.169 ± 0.133	0.151-0.181	4
Sulfur (percent)	0.316 ± 0.070	0.270-0.420	4
Iron (ppm)	447 ± 57.3	409-523	4
Manganese (ppm)	90.6 ± 8.20	81.7-95.5	4
Zinc (ppm)	53.6 ± 5.27	46.1-58.6	4
Copper (ppm)	10.77 ± 3.19	8.09-15.39	4
Iodine (ppm)	2.95 ± 1.05	1.52-3.82	4
Chromium (ppm)	1.81 ± 0.28	1.44-2.09	4
Cobalt (ppm)	0.68 ± 0.14	0.49-0.80	4

(a) One batch (July 22, 1981) was not analyzed for thiamine.

TABLE T4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminant	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.40 ± 0.21	<0.05-1.06	30
Cadmium (ppm) (a)	0.11 ± 0.06	<0.05-0.40	30
Lead (ppm)	0.98 ± 0.69	0.42-3.37	30
Mercury (ppm) (b)	< 0.05		30
Selenium (ppm)	0.29 ± 0.09	0.10-0.52	30
Aflatoxins (ppb) (b,c)	<10	<5.0-<10.0	30
Nitrate nitrogen (ppm) (d,e)	7.35 ± 3.89	<0.1-17.0	30
Nitrite nitrogen (ppm) (d,e)	1.98 ± 1.59	<0.1-6.9	30
BHA (ppm) (f,g)	3.97 ± 3.59	<0.7-13.0	30
BHT (ppm) (f)	2.80 ± 1.71	0.8-5.9	30
Aerobic plate count (CFU/g) (h)	41,717 ± 31,536	4,900-120,000	29
Aerobic plate count (CFU/g) (i)	50,660 ± 57,960	4,900-310,000	30
Coliform (MPN/g) (j)	31.3 ± 51.8	<3-240	26
Coliform (MPN/g) (k)	217.13 ± 527.46	<3-2,400	30
E. coli (MPN/g) (l)	<3		30
Total nitrosamines (ppb) (m,n)	5.67 ± 5.35	0.8-18.8	27
Total nitrosamines (ppb) (m,o)	23.72 ± 59.53	0.8-279.5	30
N-Nitrosodimethylamine (ppb) (m,n)	4.93 ± 5.26	0.8-16.0	27
N-Nitrosodimethylamine (ppb) (m,o)	22.80 ± 59.09	0.8-278	30
N-Nitrosopyrrolidine (ppb) (p)	1.39 ± 0.75	<0.5-3.5	28
Pesticides (ppm)			
α-BHC (b,q)	<0.01		30
β-BHC (b)	<0.02		30
γ-BHC-Lindane (b)	<0.01		30
δ-BHC (b)	<0.01		30
Heptachlor (b)	<0.01		30
Aldrin (b)	<0.01		30
Heptachlor epoxide (b)	<0.01		30
DDE (b)	<0.01		30
DDD (b)	<0.01		30
DDT (b)	<0.01		30
HCB (b)	<0.01		30
Mirex (b)	<0.01		30
Methoxychlor (r)	<0.05	0.09 (8/26/81)	30
Dieldrin (b)	<0.01		30
Endrin (b)	<0.01		30
Telodrin (b)	<0.01		30
Chlordane (b,s)	<0.05		20
Toxaphene (b)	<0.1		30
Estimated PCBs (b)	<0.2		30
Ronnel (b)	<0.01		30
Ethion (b)	<0.02		30
Trithion (b)	<0.05		30
Diazinon (r)	<0.1	0.02 (4/27/81)	30
Methyl parathion (b)	<0.02		30
Ethyl parathion (b)	<0.02		30
Malathion (t)	0.09 ± 0.06	<0.05-0.27	30
Endosulfan I (b,u)	<0.01		9
Endosulfan II (b,u)	<0.01		9
Endosulfan sulfate (b,u)	<0.03		9

TABLE T4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) Two batches contained more than 0.1 ppm.
(b) All values were less than the detection limit, which is given in the table as the mean.
(c) Detection limit was reduced from 10 ppb to 5 ppb after 7/81.
(d) Source of contamination: Alfalfa, grains, and fish meal
(e) Two batches contained less than 0.1 ppm.
(f) Source of contamination: Soy oil and fish meal
(g) Six batches contained less than 0.5 ppm.
(h) Mean, standard deviation, and range exclude one very high value of 310,000 obtained for the batch produced on 2/26/80. (CFU = colony-forming unit)
(i) Mean, standard deviation, and range include the very high value listed in footnote (h).
(j) Mean, standard deviation, and range exclude the very high value of 1,100 obtained for batches produced on 2/4/80, 5/29/80, and 12/16/80. They also exclude the very high value of 2,400 obtained for the batch produced on 2/26/80. (MPN = most probable number)
(k) Mean, standard deviation, and range include the high value listed in footnote (j).
(l) All values were less than 3 MPN/g.
(m) All values were corrected for percent recovery.
(n) Mean, standard deviation, and range exclude three very high values in the range of 115-280 ppb obtained for batches produced on 1/26/81, 2/23/81, and 4/27/81.
(o) Mean, standard deviation, and range include the very high values given in footnote (n).
(p) Not detectable in batches produced on 3/24/82 and 4/24/82.
(q) BHC = hexachlorocyclohexane or benzene hexachloride
(r) One observation was above the detection limit. The value and the date it was obtained are listed under the range. The detection limit is given as the mean.
(s) Ten batches manufactured from 4/1/80 through 12/16/80 were not analyzed for chlordane.
(t) Thirteen batches contained more than 0.05 ppm.
(u) Twenty-one batches were not analyzed for Endosulfan I, Endosulfan II, and Endosulfan sulfate.

APPENDIX U

DATA AUDIT SUMMARY

APPENDIX U. DATA AUDIT SUMMARY

The experimental data and tables for the NTP Technical Report on the toxicology and carcinogenesis studies of THPS and THPC in F344/N rats and B6C3F$_1$ mice were examined for completeness, consistency, and accuracy and for procedures consistent with Good Laboratory Practice requirements. The audit was conducted by Dynamac Corporation. The following persons were involved in the audit of THPS: R. Ramsey, B.S.; F. Garner, D.V.M.; C. Sexsmith, B.S.; E. Zurek; and M. Perreault, B.S. The following persons were involved in the audit of THPC: J. Albert, M.S.; J. Bhandari, D.V.M., Ph.D.; R.L. Bowman, B.S.; D. Copeland, D.V.M., D.A.C.V.P.; J. Kovach, B.A.; S. Shrivastava, Ph.D.; and S. Taulbee. The 2-year studies in rats and mice were conducted between March 1980 and April 1982 for THPS and between September 1980 and September 1982 for THPC at Battelle Columbus Laboratories, Columbus, Ohio.

The full reports of both audits are on file at the National Toxicology Program, NIEHS. The audits included, but were not limited to, a review of the records of the inlife portion of the studies for 10% of the animals (body weight, clinical observations, palpation, dosing records); all records containing environmental data, mortality data, dose preparation data, and chemical inventory and analysis data; a slide/block match for 100% of the high dose and vehicle control animals; all Individual Animal Data Records containing necropsy and histopathologic findings; and a 10% wet tissue review for animal/carcass identification.

The audit for THPS indicated that the inlife and chemistry portions were complete and without problems that would influence interpretation of study results. Slides and blocks did not match for several rats and mice because tissue samples in blocks had apparently been cut through (5 vehicle control male rats and 6 vehicle control female rats; 22 vehicle control male mice, 15 high dose male mice, 5 vehicle control female mice, and 15 high dose female mice). A number of slides had been marked "deeper" or "recut" indicating resectioning of the blocks. A total of 44 rats and 48 mice had gross observations without corresponding microscopic diagnoses. In nearly all animals, these were determined to be inaccurate observations or to represent minor, age-related, nonneoplastic changes. A single undiagnosed tumor of the anterior pituitary gland was found. Two untrimmed potential lesions were found in the residual wet tissues (one low dose male rat and one vehicle control male mouse); these were not in target organs. A complete review (100%) of residual wet tissues for animal identification revealed two rats and four mice with erroneous toe clips; there was no evidence of misidentified animals.

In the THPC audit the inlife and chemistry portions were complete and without problems that would influence interpretation of study results. The slide and block comparison identified no significant discrepancies. Slides and blocks for several rats and mice did not match (6 vehicle control and 3 high dose male rats, 10 vehicle control and 8 high dose female rats; 5 vehicle control and 11 high dose male mice, 15 vehicle control and 14 high dose female mice). There were 31 rats and 12 mice with gross observations without corresponding diagnoses. Many of these were determined to be inaccurate observations or to represent minor, age-related, nonneoplastic changes. Seven observations in rats and 12 in mice could not be resolved by examination of slides or wet tissues. Eight rats and nine mice had untrimmed potential lesions. Two rats and three mice had erroneous toe clips or ear punches. The identification discrepancy involving one rat could not be resolved and may indicate mislabeling of the wet tissue bag or misidentification of the rat.

Although not every problem identified in the audits was fully resolved, it was concluded that the data reported were adequate to support the conclusions presented in this Technical Report.

 *U.S. GOVERNMENT PRINTING OFFICE:1987-181-296:41317