NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 269

TOXICOLOGY AND CARCINOGENESIS STUDIES OF TELONE II®

(Technical-Grade 1,3-Dichloropropene [CAS No. 542-75-6] Containing 1.0% Epichlorohydrin as a Stabilizer)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

NATIONAL TOXICOLOGY PROGRAM

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

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF TELONE II•

(Technical-Grade 1,3-Dichloropropene [CAS No. 542-75-6]
Containing 1.0% Epichlorohydrin as a Stabilizer)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

May 1985

NTP TR 269

NIH Publication No. 85-2525 NTP-83-22

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. 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.

CONTENTS

TABLES

FIGURES

APPENDIXES

APPENDIXES (Continued)

APPENDIXES (Continued)

APPENDIXES (Continued)

TELONE II®

ClCH = CH-CH_2Cl

**(Technical-Grade 1,3-Dichloropropene [CAS No. 542-75-6]
Containing 1.0% Epichlorohydrin as a Stabilizer)**

$C_3H_4Cl_2$ **Mol. Wt. 110.98**

Synonyms: *cis, trans*-1,3-Dichloropropene; D-D® Soil Fumigant; Telone® Soil Fumigants; Vorlex® Soil Fumigants

ABSTRACT

Toxicology and carcinogenesis studies of Telone II® (a soil fumigant containing approximately 89% *cis*- and *trans*-1,3-dichloropropene, 2.5% 1,2-dichloropropane, 1.5% of a trichloropropene isomer, and 1.0% epichlorohydrin) were conducted by administering the commercial-grade formulation in corn oil by gavage to groups of 52 male and 52 female F344/N rats at doses of 0, 25, or 50 mg/kg and to groups of 50 male and 50 female B6C3F_1 mice at doses of 0, 50, or 100 mg/kg. Doses were administered three times per week for 104 weeks. Ancillary studies were conducted in which dose groups containing five male and five female rats were killed after receiving Telone II® for 9, 16, 21, 24, or 27 months.

Mean body weights of high dose male rats were about 5% lower than those for the vehicle control and low dose male rats; no differences in body weights were observed among groups of female rats. Survival was comparable for the different groups of male and female rats. For male and female mice, the dosed groups initially weighed 6%-22% less than did the vehicle controls; the weight differential decreased to 5%-9% by the end of the studies. Twenty-five vehicle control male mice died during weeks 48-51 from suppurative inflammation of the heart (myocarditis). At the end of the studies, the survival of male mice was as follows: vehicle control, 8/50; low dose, 28/50; high dose, 31/50. Survival of female mice was lower ($P<0.05$) in the high dose group than in the vehicle controls (46/50; 45/50; 36/50).

The primary organs affected were the forestomach (rats and mice), urinary bladder (mice), lung (mice), and liver (rats). Compound-related nonneoplastic lesions included basal cell or epithelial hyperplasia of the forestomach (rats and mice), epithelial hyperplasia of the urinary bladder (mice), and kidney hydronephrosis (mice). Neoplastic lesions associated with administration of Telone II® included squamous cell papillomas of the forestomach (male rats: 1/52; 1/52; 9/52; female rats: 0/52; 2/52; 3/52; female mice: 0/50; 1/50; 2/50), squamous cell carcinomas of the forestomach (male rats: 0/52; 0/52; 4/52; female mice: 0/50; 0/50; 2/50), transitional cell carcinomas of the urinary bladder (female mice: 0/50; 8/50; 21/48), alveolar/bronchiolar adenomas (female mice: 0/50; 3/50; 8/50), and neoplastic nodules of the liver (male rats: 1/52; 6/52; 7/52).

Although the study in male mice was considered inadequate due to the deaths at weeks 48-51 of 25/50 vehicle control animals, 2/50 of the high dose males had transitional cell carcinomas of the urinary bladder. Furthermore, increases were seen in the incidences of alveolar/bronchiolar neoplasms of the lung (1/50; 13/50; 12/50) and of squamous cell papillomas of the forestomach (0/50; 2/50; 3/50). These findings plus the finding of nonneoplastic lesions in two of these organs (basal cell or epithelial hyperplasia of the forestomach: 0/50; 0/50; 4/50; epithelial hyperplasia of the urinary bladder: 0/50; 9/50; 18/50) suggest that Telone II® may have been responsible for the development of these lesions in male mice.

Development of lesions in the forestomach (basal cell hyperplasia and squamous cell papilloma) was observed to be time dependent. The results of the scheduled kills supported the findings of the carcinogenesis studies. When the results from the scheduled kills at all time points were pooled with those of the 24-month carcinogenesis studies, the incidences were as follows: basal cell or epithelial hyperplasia of the forestomach--male rats: 3/77; 13/77; 31/77; female rats: 1/75; 5/77; 35/77; squamous cell papilloma of the forestomach--male rats: 1/77; 1/77; 13/77; female rats: 0/75; 2/77; 8/77; neoplastic nodules of the liver--male rats: 1/77; 6/76; 8/77; female rats: 6/75; 8/77; 12/77.

cis- and *trans*-1,3-Dichloropropene are the principal components (89%) in Telone II®, but the 1.0% epichlorohydrin, a direct-acting mutagen and carcinogen added as a stabilizer, may have influenced the development of forestomach lesions.

1,3-Dichloropropene was mutagenic in *Salmonella typhimurium* strains TA98, TA100, and TA1535 without metabolic activation and in TA100 and TA1535 with metabolic activation by Aroclor-induced male Sprague-Dawley rat and Syrian hamster liver S9. No mutagenic response was seen in TA1537. Sex-linked recessive lethal mutations were observed in *Drosophila melanogaster*, and 1,3-dichloropropene did not induce reciprocal translocations in *D. melanogaster*.

A data audit was conducted on the Telone II® 2-year carcinogenesis studies in rats and mice and the ancillary studies in rats. Except for the already known problem of survival of male vehicle control mice, no other discrepancies or problems that would compromise the validity of the findings or alter the interpretations of these studies were found.

Under the conditions of these gavage studies, there was *clear evidence of carcinogenicity** for male F344/N rats, as indicated by Telone II®-related increased incidences of squamous cell papillomas and carcinomas of the forestomach, as well as an increased incidence of neoplastic nodules of the liver. In female F344/N rats, there was *some evidence of carcinogenicity* because Telone II® caused an increased incidence of squamous cell papillomas of the forestomach. The experiment in male B6C3F$_1$ mice was considered to be an *inadequate study of carcinogenicity* because of reduced survival in the vehicle control group. However, there was some indication in the male mice of Telone II®-related increases of transitional cell carcinomas of the urinary bladder, squamous cell papillomas of the forestomach, and alveolar/bronchiolar adenomas and carcinomas of the lung. There was *clear evidence of carcinogenicity* for female B6C3F$_1$ mice, since Telone II® caused increased incidences of transitional cell carcinomas of the urinary bladder; Telone II® also increased the incidences of alveolar/bronchiolar adenomas of the lung and of squamous cell papillomas or carcinomas of the forestomach in the female mice. Telone II®-related nonneoplastic lesions included basal cell or epithelial cell hyperplasia in the forestomach of male and female rats and male and female mice and epithelial hyperplasia of the urinary bladder in male and female mice.

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

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Telone II® is based on 2-year studies that began in February 1977 (rats) and July 1978 (mice) and ended in February 1979 (rats) and July 1980 (mice) at Frederick Cancer Research Center. Ancillary studies in rats were conducted between February 1977 and May 1979; the results are included in this Technical Report.

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

Raymond S.H. Yang, Ph.D., Chemical Manager

Gary A. Boorman, D.V.M., Ph.D.
Rajendra S. Chhabra, Ph.D.
David M. DeMarini, Ph.D.
Scot L. Eustis, D.V.M., Ph.D.
Joseph K. Haseman, Ph.D.
James Huff, Ph.D.
C.W. Jameson, Ph.D.
W.M. Kluwe, Ph.D.
Mary Kornreich, Ph.D.
Robert R. Maronpot, D.V.M.
E.E. McConnell, D.V.M.
G.N. Rao, D.V.M., Ph.D.
Bernard A. Schwetz, D.V.M., Ph.D.
Raymond W. Tennant, Ph.D.

NTP Pathology Working Group
(Evaluated Slides and Prepared Pathology Report)

First Evaluation: June 5, 1981
G. Boorman, D.V.M., Ph.D. (NTP)
(Chair)
B. Gupta, Ph.D. (NTP)
L. Lomax, D.V.M., Ph.D. (NTP)
E.E. McConnell, D.V.M. (NTP)

Second Evaluation: August 26, 1982
G. Boorman, D.V.M., Ph.D. (NTP)
(Chair)
S. Eustis, D.V.M., Ph.D. (NTP)
E.E. McConnell, D.V.M. (NTP)
R. Kovatch, D.V.M. (Tracor Jitco)
A. Macklin, D.V.M., Ph.D.
(Burroughs-Wellcome)
H. Solleveld, D.V.M., Ph.D. (NTP)

Principal Contributors at Frederick Cancer Research Center
(Conducted Studies and Evaluated Tissues)

Donald Creasia, Ph.D., Toxicologist
Donald D. Cameron Jr., HT, Manager, Histology
James L. Stookey, D.V.M., Pathologist
Susan M. Toms, Data Management

Principal Contributors at Experimental Pathology Laboratory
(Provided Pathology Quality Assurance)

Melvin H. Hamlin II, D.V.M.
Pathologist
Larry J. Ackerman, D.V.M.
Pathologist

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

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated this Technical Report on July 27, 1984, 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

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

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

Ad Hoc Subcommittee Panel of Experts

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

Devra L. Davis, Ph.D.
Board on Toxicology and Environmental Health Hazards
National Academy of Sciences
Washington, D.C.

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

Thomas C. Jones, D.V.M. (Principal Reviewer)
Professor, Comparative Pathology
New England Regional Primate Research Center
Harvard Medical School
Southborough, Massachusetts

Richard J. Kociba, D.V. M., Ph.D.
Dow Chemical USA
Midland, Michigan

David Kotelchuck, Ph.D. (Principal Reviewer)
Research Department
United Electrical, Radio and Machine Workers of America
New York, New York

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

Steven R. Tannenbaum, Ph.D.
Professor, Department of Nutrition and Food Science
Massachusetts Institute of Technology
Cambridge, Massachusetts

Bruce W. Turnbull, Ph.D. (Principal Reviewer)
Professor and Associate Director
College of Engineering
Cornell University
Ithaca, New York

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

---

*Unable to attend meeting

SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF TELONE II®

The review meeting for the Technical Report on the Toxicology and Carcinogenesis Studies of Telone II® began at 9 a.m., July 27, 1984, in the Conference Center, Building 101, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. Members of the Subcommittee were: Drs. Jerry Hook (Chair), Curtis Harper, and James Swenberg. Members of the Panel of Experts were: Mr. Louis Belicksy and Drs. Devra Davis, Seymour Friess, Thomas Jones, Richard Kociba, David Kotelchuck, Tom Slaga, Steven Tannenbaum, Bruce Turnbull, and John Van Ryzin. Drs. Hook, Slaga, and Swenberg were unable to attend this meeting. Dr. Harper served as Acting Chair.

Dr. Turnbull, a principal reviewer, agreed with the conclusions of the Technical Report. He stated that although the design and conduct of the study were less than fully adequate, especially the lack of appropriate randomization and the delay of more than a month in carrying out a scheduled 15-month kill, these drawbacks were well documented and did not compromise the findings.

As a second principal reviewer, Dr. Jones agreed with the findings; however, he questioned the appropriateness of including in the conclusion mention of probable association of Telone II® with a number of tumors in male mice, since this study was considered inadequate because of markedly reduced survival in the vehicle controls.

As a third principal reviewer, Dr. Kotelchuck basically agreed with the conclusions. He said that the failure to randomize initial weights of the mice was an avoidable and potentially serious error, but he did not think it affected the carcinogenicity results. He shared Dr. Jones' concern about association of the chemical with increased incidences of tumors for male mice, since this was judged to be an inadequate study. However, since there were dose trends for some tumors, Dr. Kotelchuck proposed the following conclusion for male mice: "The experiment in male $B6C3F_1$ mice was an *inadequate study of carcinogenicity* because of reduced survival in the vehicle control group. However, there was some indication in the male mice of Telone II®-related increases of squamous cell papillomas of the forestomach and transitional cell carcinomas of the urinary bladder." Dr. Jones and Mr. Beliczky thought that only the first sentence should be included; Dr. Tannenbaum said both sentences were appropriate because the carcinogenicity findings were consistent with those found in female mice and in rats of each sex. Dr. Kotelchuck also suggested not making a reference to the lung tumors, since their incidences fell within the range, albeit the upper limit, of historical control rates. Dr. J. Haseman, NIEHS, argued for retaining mention of the lung tumors based on their being at the upper limit of the historical control range, approximately double the mean historical control rate, and noted that a significant increase was seen in the incidence of lung tumors in female mice. Dr. Friess and Dr. Van Ryzin supported the recommendations, including the comment on the lung tumors.

Dr. Harper asked for a vote on the proposed single sentence conclusion statement for male mice: "The experiment in male $B6C3F_1$ mice was considered to be an *inadequate study of carcinogenicity* because of reduced survival in the vehicle control group." There were two affirmative votes (Drs. Jones and Kociba). Dr. Harper then requested a vote on the conclusion that would include this sentence followed by "However, there was some indication in the male mice of Telone II®-related increases of transitional cell carcinomas of the urinary bladder, squamous cell papillomas of the forestomach, and alveolar/bronchiolar adenomas and carcinomas of the lung." The two-sentence conclusion for the male mouse study was approved with seven affirmative votes.

Dr. Kociba and Dr. Davies asked that either an appendix that would include the hematology and clinical chemistry data or an availability statement be added. [A comment was added on page 34 that these data are available upon request.] The Panel discussed the possible carcinogenic effects of the 1.0% epichlorohydrin included as a stabilizer with the technical-grade 1,3-dichloropropene. Dr. B. Schwetz, NTP, noted that the 1,3-dichloropropene free of epichlorohydrin would not be stable enough to use in a study. Dr. Tannenbaum added that epichlorohydrin is an alkylating agent and a carcinogen in animals. Dr. Kotelchuck stated that the epichlorohydrin probably contributed to the stomach tumors; yet he felt it was important to test the chemical formulation to which humans are exposed. Dr. J. Huff, NTP, observed that the Telone II® formulation induced neoplasms at other sites in addition to those where epichlorohydrin has been reported to induce tumors, although an additive or enhancing interactive effect cannot be completely discounted.

Dr. Turnbull moved that the Technical Report on the toxicology and carcinogenesis studies of Telone II® be accepted with the revised conclusion for male mice and with other modifications as discussed. Dr. Kotelchuck seconded the motion, and the report was approved by eight affirmative votes. There was one abstention (Dr. Kociba).

I. INTRODUCTION

Chemical Background
Production and Use
Fate in Soil
Residue Analysis of Well Water
Metabolism and Disposition
Toxicity of Telone II® and 1,3-Dichloropropene in Animals
Toxicity of D-D® in Animals
Toxicity and Exposure in Humans
Mutagenicity Studies
Carcinogenicity Studies
Rationale for Testing

I. INTRODUCTION

TELONE II®

$ClCH=CH-CH_2Cl$

(Technical-Grade 1,3-Dichloropropene [CAS No. 542-75-6] Containing 1.0% Epichlorohydrin as a Stabilizer)

$C_3H_4Cl_2$ **Mol. Wt. 110.98**

Synonyms: *cis, trans*-1,3-Dichloropropene; D-D® Soil Fumigant; Telone® Soil Fumigants; Vorlex® Soil Fumigants

Chemical Background

1,3-Dichloropropene, the main ingredient of Telone II®, was introduced as a commercial fumigant in 1955 by the Dow Chemical Company (Berry et al., 1980). A preparation containing 1,3-dichloropropene and 1,2-dichloropropane was marketed by Shell Oil Company under the name D-D® (Maddy et al., 1982; Parker et al., 1982).

1,3-Dichloropropene, a mixture of *cis* and *trans* isomers, is a clear, light straw-colored liquid with a penetrating, irritating, chloroform-like odor. The physical properties of a *cis/trans* mixture depend on the ratio of the isomers. 1,3-Dichloropropene is relatively insoluble in water (*trans* isomer, 0.28 g/100 ml water at 20° C; Metcalf, 1978) and is soluble in ether and benzene (Weast, 1976).

Production and Use

Telone II® is widely used in agriculture as a soil fumigant for parasitic plant nematodes (De Lorenzo et al., 1977; Maddy et al., 1982). Before 1978, about 25 million kilograms of 1,3-dichloropropene were produced annually in the United States (Flessel et al., 1978). In California, over one million kilograms of pesticides containing 1,3-dichloropropene were used in 1971 (De Lorenzo et al., 1977). In Italy, over 2 million kilograms were produced in 1972. Current production data are not available.

1,3-Dichloropropene formulations are usually applied undiluted to the soil around vegetable and tobacco crops to control nematodes (Flessel et al., 1978). 1,3-Dichloropropene is believed to act by chemically combining with some nucleophilic center (e.g., sulfhydryl, amine, or hydroxyl groups) in an essential enzyme in the nematode (Metcalf, 1978). As with other fumigants, the performance of 1,3-dichloropropene as a nematocide is dependent on the vapor pressure; diffusion coefficient; the distribution of the fumigant through air, water, and solid phases of the soil; and the temperature and moisture content of the soil.

Fate in Soil

1,3-Dichloropropene was reported to have a half-life in soil of about 10 days (Laskowski et al., 1982). In another study (Van Dijk, 1974), the estimated rates of disappearance of 1,3-dichloropropene isomers under various soil, temperature, and pH conditions differed widely depending on the methods of analyses. When the disappearance of the parent compounds was followed by gas chromatography, the estimated half-lives for *cis*- and *trans*-1,3-dichloropropene ranged from 3 to 37 days. When Cl^- release resulting from the degradation of 1,3-dichloropropene was followed by potentiometric titration, the estimated half-life for *cis*- and *trans*-1,3-dichloropropene was as long as 23 weeks. The *cis*- and *trans*-3-chloroallyl alcohols, presumed degradation products of the corresponding 1,3-dichloropropenes, were biodegraded more rapidly in soil. At 15° C in clay-containing soils, the average half-life for the 3-chloroallyl alcohols was 1-2 days.

Since 1,3-dichloropropene is volatile and insoluble in water, losses are more likely to occur from volatilization than from leaching. The decomposition rate of 1,3-dichloropropene in loam soil was determined to be about 3.5% per day, whereas the decomposition rate in sandy and

peat soils was less than 1% per day (Leistra, 1970). *cis-* and *trans*-1,3-Dichloropropene are hydrolyzed in wet soil to *cis-* and *trans*-3-chloroallyl alcohol (Castro and Belser, 1966). Studies under laboratory and outdoor conditions (Roberts and Stoydin, 1976) confirmed that 3-chloroallyl alcohols were the major degradation products and showed that *cis-* and *trans*-3-chloroacrylic acids were minor products.

Despite the volatility and degradability of 1,3-dichloropropene, both the *cis* and *trans* isomers were detected several months after being applied to soils (Leistra, 1970; Williams, 1968). Twelve weeks after labeled *cis-* or *trans*-1,3-dichloropropene was applied to soils and stored in sealed glass containers, 19% of the *cis* isomer and 18% of the *trans* isomer remained in sandy loam and 10% of the *cis* isomer and 22% of the *trans* isomer remained in medium loam (Roberts and Stoydin, 1976). After 20 weeks, 5% of the *cis* isomer and 4% of the *trans* isomer remained in sandy loam and 3% of the *cis* isomer and 14% of the *trans* isomer remained in medium loam. Eight months after D-D® soil fumigant was applied to a muck soil and to a sandy loam, *cis-* and *trans*-1,3-dichloropropene were detected in both soils (Williams, 1968).

Residue Analysis of Well Water

Fifty-four wells in certain communities in California where Telone® or D-D® had been applied for several years were selected for residue analysis of 1,3-dichloropropene and other pesticides (Maddy et al., 1982). No samples had measurable amounts of 1,3-dichloropropene at a minimum detectable level of 0.1 ppb. A similar study was conducted in which well water samples were taken from areas where 1,2-dibromo-3-chloropropane (DBCP) had been applied. The samples were analyzed for DBCP, 1,3-dichloropropene, 1,2-dibromoethane (EDB), and other pesticides (Peoples et al., 1980). Although DBCP was found in 94 of 262 wells at concentrations ranging from 0.1 to 39 ppb, no detectable levels of 1,3-dichloropropene and/or EDB were found in the 72 well water samples analyzed. However, no data were given to indicate that either 1,3-dichloropropene or EDB was used near the wells.

Metabolism and Disposition

When 2.53-2.70 mg of *cis-* or *trans*-1,3-dichloro[2-^{14}C]propene was administered orally to Carworth Farm E rats, 80%-90% of the radiolabel was eliminated in the feces, urine, or expired air during the first 24 hours of the experiment (Hutson et al., 1971). Within 24 hours, 80.7% of the administered *cis* isomer and 56.5% of the administered *trans* isomer were eliminated in the urine. About 3.9% of the *cis* isomer and 23.6% of the *trans* isomer were recovered as [^{14}C]carbon dioxide. A small amount (1%-4%) of 1,3-dichloropropene was exhaled directly. Rats apparently retain little ingested 1,3-dichloropropene. After 4 days, about 1% of the administered dose of either isomer was found in the carcass.

A glutathione-dependent biotransformation is on the major metabolic pathway of *cis*-1,3-dichloro[^{14}C]propene (Climie et al., 1979). An hepatic glutathione transferase catalyzes the conjugation of *cis*-1,3-dichloropropene with glutathione. The conjugate is further metabolized to a mercapturic acid and is excreted in the urine as N-acetyl-S-[(*cis*)-3-chloroprop-2-enyl]-cysteine. This metabolite accounted for 92% of the 0- to 24-hour cumulative urinary radioactivity. In vitro metabolic studies using rat liver preparations (Climie et al., 1979) revealed that the *cis* isomer of 1,3-dichloropropene was degraded 4-5 times faster than the *trans* isomer.

The metabolic fate of 1,3-dichloropropene was studied in plants by using uniformly labeled [^{14}C]-1,3-dichloropropene (60% *trans* isomer, 40% *cis* isomer) (Berry et al., 1980). 1,3-Dichloropropene was absorbed by the bush bean, tomato, or carrot from the solution culture (vermiculite and sand), rapidly translocated in the plants, and metabolized to 3-chloroallyl alcohol and then to 3-chloro-1-propanol and 3-chloroacrylic acid. The dichloropropene isomers and chloroallyl alcohol had short half-lives in the plant and were not detectable 120 hours after the administration of 1,3-dichloropropene.

With the exception of 3-chloro-1-propanol, metabolites similar to those present in the plant were also found in soil treated with 1,3-dichloropropene. Microbial metabolism by soil

Pseudomonas sp. was responsible for this biotransformation (Castro and Belser, 1966; Belser and Castro, 1971). The overall metabolic pathway of 1,3-dichloropropene is illustrated in Figure 1.

In two recent abstracts (Dietz et al., 1984a, 1984b), the pharmacokinetics of macromolecular binding of 1,3-dichloropropene and its effects on nonprotein sulfhydryl content in the tissues were reported. When oral doses of 1 or 50 mg/kg ^{14}C-*cis*-, *trans*-1,3-dichloropropene were administered to male F344 rats and 1 or 100 mg/kg to male B6C3F$_1$ mice, urinary excretion was the predominant route of elimination in 48 hours, accounting for 51%-61% in rats and 63%-79% in mice. Feces and expired carbon dioxide contained approximately 18% and 6% of the administered dose in rats and 15% and 14% of the administered dose in mice, respectively. Only 2%-6% of the original dose remained in the carcasses at the end of 48 hours. The predominant metabolite was identified as N-acetyl-S-(3-chloroprop-2-enyl)cysteine, confirming the earlier findings of Climie et al. (1979). The sulfoxide or sulfone derivative of the above metabolite was tentatively identified as another major metabolite.

In the second study by Dietz et al. (1984b), the amount of nonprotein sulfhydryl (NPS) and covalent binding to macromolecules was measured in the forestomach, glandular stomach, liver, kidney, and urinary bladder in male F344 rats and male B6C3F$_1$ mice 2 hours following administration of a single oral dose of [^{14}C]-1,3-dichloropropene. The doses given were 0, 1, 5, 25, 50, or 100 mg/kg for NPS studies and 0, 1, 50, or 100 mg/kg for binding studies. Significant depletion of NPS levels was noted in the forestomach of rats and mice dosed with 25 mg/kg or above; the depletion ranged between 17% and 51% of the control values. Effects on NPS in the glandular stomach and liver were also dose dependent but less severe. Macromolecular covalent binding in the forestomach and glandular stomach was greatest at doses that caused the most depletion of tissue NPS. Limited binding was also noted in the liver, kidneys, or urinary bladders.

Toxicity of Telone II® and 1,3-Dichloropropene in Animals
(Torkelson and Oyen, 1977)

The acute oral LD$_{50}$ value for Telone II® was 713 mg/kg body weight in male and 470 mg/kg in female rats (strain unspecified). The liver and kidneys were the primary sites of acute toxicity. Telone II® formulations irritated the skin, causing edema, redness, and necrosis. When a 12.5% solution in propylene glycol was applied under a cuff and allowed to remain undisturbed for 24 hours, Telone II® was absorbed through the skin of rabbits (percent absorption was not reported); deaths occurred with doses of 0.125 and 0.25 g/kg. When undiluted Telone II® was applied in a similar manner to a group of rabbits (both sexes), the dermal LD$_{50}$ value was 504 mg/kg.

Twenty-four hours after a Telone II® formulation was instilled into the eyes of six rabbits for a 30-second exposure period, four of the animals had severe conjunctival irritation and the remaining two rabbits exhibited slight-to-moderate corneal injury. These effects disappeared 8 days after instillation.

A single inhalation exposure of 7 hours at 400 ppm was lethal to male and female guinea pigs; under similar conditions, rats (strain unspecified) survived. Inhalation studies showed that 1,3-dichloropropene at vapor concentrations above 2,700 ppm was irritating to the eyes and nose of rats and caused severe lung, nasal, liver, and kidney injury. At concentrations of 1,000 ppm, it irritated the eyes and nose and was lethal to rats within 2 hours.

Inhalation exposure of rats (strain unspecified) and guinea pigs to 1,3-dichloropropene vapor (46% *cis* isomer, 53% *trans* isomer, and approximately 1% epichlorohydrin) at 11 or 50 ppm for 7 hours per day, 5 days per week for 1 month, produced kidney and liver injury. In another experiment, rats (strain unspecified), guinea pigs, rabbits, and dogs received 7-hour inhalation exposures to 1,3-dichloropropene at either 1 or 3 ppm, 5 days per week for 6 months. The only

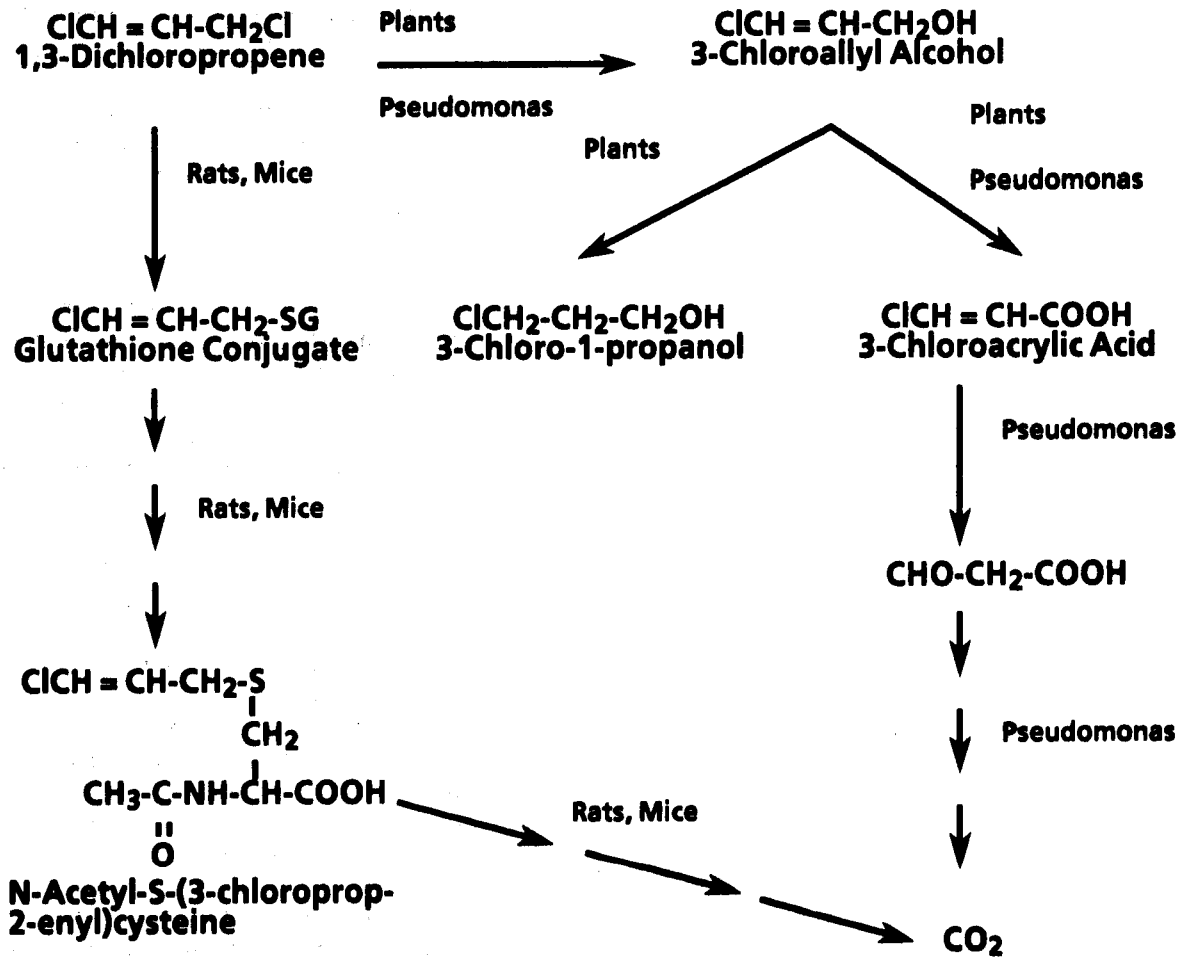


FIGURE 1. METABOLIC PATHWAY OF 1,3-DICHLOROPROPENE

(Castro and Belser, 1966; Belser and Castro, 1971; Climie et al., 1979; Berry et al., 1980; Dietz et al., 1984a,b)

effect attributable to exposure was a cloudy swelling of the renal tubular epithelium in male rats exposed at 3 ppm. Female rats exposed at 3 ppm had marginal increases in liver to body weight ratio.

Toxicity of D-D® in Animals (Parker et al., 1982)

D-D®, a commercial preparation containing 25% *cis*-1,3-dichloropropene, 27% *trans*-1,3-dichloropropene, 29% 1,2-dichloropropane, and other related chlorinated hydrocarbons, was studied to examine inhalation toxicity in CD-1 mice and F344 rats. Exposure concentrations were 0, 5, 14, or 54 ppm, 6 hours per day, 5 days per week for 6 or 12 weeks. Body weights, organ weights, hematologic values, serum chemistry, urinalysis, and gross pathologic and histopathologic findings were evaluated. The only exposure-related effects observed were increased liver-to-body weight ratios (male rats), increased kidney-to-body weight ratios (female rats), and slight-to-moderate diffuse hepatocyte enlargement (male mice), all at the 54-ppm level.

Toxicity and Exposure in Humans

The most likely routes of human exposure to 1,3-dichloropropene are through inhalation and the skin. Irritation of eyes and upper respiratory mucosa, accompanied by lacrimation, appears promptly after exposure to vapors (Gosselin et al., 1976). Inhalation by humans of air containing concentrations greater than 1,500 ppm produces headaches, mucous membrane irritation, dizziness, nausea, vomiting, gasping, coughing, substernal pain, and respiratory distress. Slightly elevated levels of serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, or both were reported (Flessel et al., 1978; Gosselin et al., 1976). The chemical at vapor concentrations lower than 1,500 ppm produces central nervous system depression and moderate irritation of the respiratory system. Dermal exposure causes severe skin irritation with marked inflammatory response. Ingestion produces acute gastrointestinal distress, pulmonary congestion and edema, and central nervous system depression.

A human fatality occurred a few hours after the accidental ingestion of a D-D® mixture (Gosselin et al., 1976). The victim experienced abdominal pain and vomiting. He became semicomatose and exhibited muscle twitching. Death occurred in spite of gastric lavage and therapy for pulmonary edema. Markovitz and Crosby (1984) described three case reports of workers accidentally exposed to 1,3-dichloropropene. Nine firemen were treated for headache, neck pain, nausea, and breathing difficulty after cleaning up 1,3-dichloropropene that had spilled on a road in a tank truck accident. Six years later, two of the firemen developed lymphomas, and both died the following year. In another incident, a farmer injecting 1,3-dichloropropene into the soil was exposed to the chemical for about 1 month through a leaky hose, Within a year, he developed myelomonocytic leukemia and later died from pneumonia.

Torkelson and Oyen (1977) suggested that 7- to 8-hour daily occupational exposures to 1,3-dichloropropene not exceed time-weighted average concentrations of 1 ppm.

Mutagenicity Studies

Neudecker et al. (1977) found that the *cis* and *trans* isomers of 1,3-dichloropropene were mutagenic in strain TA1535 of *Salmonella typhimurium* and that the addition of rat liver S9 reduced the mutagenicity and cytotoxicity of both isomers. The *cis*- and *trans*-1,3-dichloropropene samples were 99.75% and 97.46% pure. The impurities in these samples were characterized as 3,3-dichloropropene and 1,2-dichloropropane. De Lorenzo et al. (1977) also found that *cis*- and *trans*-1,3-dichloropropene as well as Telone II® and D-D® soil fumigant (which contain both isomers of 1,3-dichloropropene) were mutagenic in strains TA1535, TA1978, and TA100 in the presence or absence of S9. Stolzenberg and Hine (1980) confirmed that 1,3-dichloropropene was a direct-acting mutagen in strain TA100 and that S9 reduced the mutagenicity. A mixture of the *cis* and *trans* isomers of 1,3-dichloropropene was mutagenic in strains TA1535 and TA100, was weakly mutagenic in strain TA98, and was not mutagenic in strain TA1537 (Appendix J). S9

reduced the mutagenicity of the isomer mixture, confirming the previous reports. These results suggest that 1,3-dichloropropene is a base-pair substitution mutagen that can be enzymatically detoxified by S9. In vitro studies by Climie et al. (1979) demonstrated that the glutathione-dependent detoxification of the *trans* isomer is four- to fivefold less rapid than that of the *cis* isomer. In addition, a mixture of the two isomers induced sex-linked recessive lethal mutations in Drosophila but gave negative results when tested for its ability to induce reciprocal translocations in Drosophila (Appendix K).

Recently Talcott and King (1984) demonstrated that purification of four separate preparations of 1,3-dichloropropene by silicic acid chromatography, which removes polar impurities, eliminated the mutagenicity of the preparations in *S. typhimurium* strain TA100. Thus, the mutagenicity of 1,3-dichloropropene preparations observed in other studies may have been due to mutagenic polar impurities and not to 1,3-dichloropropene itself. Subsequent studies at NIEHS (Dr. E. Zeiger, unpublished data) with purified and unpurified samples of 1,3-dichloropropene confirmed that the purified 1,3-dichloropropene was not mutagenic in Salmonella TA100.

Carcinogenicity Studies

cis-1,3-Dichloropropene has been tested for carcinogenicity in mice by dermal and subcutaneous routes and in a mouse-skin initiation-promotion experiment (Van Duuren et al., 1979). The only chemical-related positive findings came from the subcutaneous injection experiment. Weekly injections of 3 mg *cis*-1,3-dichloropropene in 0.05 ml trioctanoin for 538 days produced fibrosarcomas at the injection site (left flank) in 6/30 female HA:ICR Swiss mice. Neither the trioctanoin vehicle controls nor the untreated controls had any fibrosarcomas.

Rationale for Testing

Telone II® was tested because of its widespread agricultural use, the structural similarity of 1,3-dichloropropene to vinyl chloride (a known human and animal carcinogen), and the lack of conclusive carcinogenicity studies.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF TELONE II®

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

TWO-YEAR AND ANCILLARY STUDIES

Study Design

Source and Specifications of Test Animals

Animal Maintenance

Clinical Examinations and Pathology

Statistical Methods

PROCUREMENT AND CHARACTERIZATION OF TELONE II®

Telone II® was obtained from Dow Chemical USA (Freeport, TX) as a colorless liquid (Lot no. EXP-N-3993). According to the manufacturer, the 1983 specifications for Telone II® indicate that it contains 92% 1,3-dichloropropene (45% *cis*-isomer and 47% *trans*-isomer), 2% 1,2-dichloropropane, 1% epichlorohydrin, and a 5% mixture of chlorinated propenes and hexenes (Dow Chemical Co., 1983).

Purity and identity analyses of Telone II® were conducted at the Frederick Cancer Research Center. The boiling point was consistent with that for technical-grade 1,3-dichloropropene (CAS No. 542-75-6). The infrared and nuclear magnetic resonance spectra indicated that components other than *cis*- and *trans*-1,3-dichloropropene were present (Appendix H). Gas chromatographic analysis of the test material over the course of the 2-year studies indicated that it contained 88%-90% 1,3-dichloropropene. The two major components (approximately 42% and 46% of the total area by gas chromatographic analysis) were identified as *cis*- and *trans*-1,3-dichloropropene by ^{13}C nuclear magnetic resonance spectrometry and gas chromatography/mass spectrometry (Appendix H). The gas chromatographic/mass spectrometric analysis of the test material indicated that it contained 12 impurities with a combined area that was approximately 12% of the total area. A peak with an area of 2.5% of the total area was identified as 1,2-dichloropropane; a peak with an area of 1.5% was identified as a trichloropropene isomer; and a second trichloropropene isomer was also identified. Epichlorohydrin was not quantitated at the Frederick Cancer Research Center. Reanalysis of Telone II® after 13 months of storage indicated that the composition of the compound was unchanged. The Telone II® preparation had the following composition:

1,3-Dichloropropene	88%-90%
cis-isomer	41.6%
trans-isomer	45.9%
1,2-Dichloropropane	2.5%
Trichloropropene isomer	1.5%
Epichlorohydrin	1.0%
Nine other impurities	Approximately 7.5%

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

Telone II® and corn oil were mixed daily to yield the desired concentrations. Solutions were homogenized for 1-2 minutes in a Lourdes® blender. Dose solutions were analyzed periodically (Appendix I); because 52/68 of the samples were within ± 10% of the target concentrations, it is estimated that the dose solutions were within specifications 76% of the time. Rarely did the dose solutions vary from the target concentration by as much as 20% (Table 1).

TABLE 1. ANALYSIS OF CHEMICAL/VEHICLE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF TELONE II®

	Concentration of Telone II® in Corn Oil for Target Concentrations (a)			
	Rats		Mice	
	5 mg/ml	10 mg/ml	10 mg/ml	20 mg/ml
Mean (mg/ml)	4.8	9.4	10.1	20.8
Standard deviation	0.50	0.54	1.3	2.14
Coefficient of variation (percent)	10.4	5.7	13.0	10.3
Range (mg/ml)	4.0-5.8	8.8-10.6	8.8-13.1	17.8-25.5
Number of samples	19	19	15	15

(a) See Appendix I (Table I1) for results of individual analyses

TWO-YEAR AND ANCILLARY STUDIES

Study Design

In the 2-year carcinogenicity studies, groups of 52 F344/N rats of each sex were administered doses of 0, 25, or 50 mg/kg body weight Telone II® in corn oil 3 days per week for 104 weeks. Groups of 50 B6C3F$_1$ mice of each sex were administered 0, 50, or 100 mg/kg Telone II® on the same schedule. The gavage route was chosen as the simplest method to ensure systemic exposure of quantitated doses and because of the volatility and reactivity (in feed) of Telone II®. Dose selection was based on earlier short-term studies (primarily body weight reduction effects); data and records from these studies are not considered complete enough to report.

In the ancillary studies, the rats were from the same shipment as those in the 2-year studies, were kept in the same room, received the same doses, and were maintained and observed in the same manner.

Interim-Kill Studies: Groups of 28 rats of each sex were assigned to each dose group. At 9, 16, 21, 24, and 27 months of dosing, five rats of each sex in each dose group were killed and necropsies were performed. The three remaining rats of each sex in each dose group served as substitutes for any rats that died prematurely. Visible lesions were described and recorded. Tissues were preserved in 10% neutral buffered formalin. After the histopathologic evaluation of the 2-year carcinogenicity studies was complete, the liver, stomach, adrenal glands, thyroid gland, urinary bladder, kidneys, and mammary gland from interim-kill rats were examined microscopically to evaluate the development of lesions in these tissues with respect to time.

Hematologic and Clinical Chemistry Studies: Groups of 20 rats of each sex were assigned to each dose group. Twelve of the 20 rats were bled intraorbitally approximately once every 4 weeks, and samples were taken for clinical chemistry studies (1-ml samples); eight rats were bled for hematologic studies (0.25-ml samples). The following 18 hematologic and 25 clinical chemistry variables were measured:

Hematology	Clinical Chemistry
Red blood cell	Calcium
Hematocrit	Inorganic phosphate
Hemoglobin	Calcium/inorganic phosphate ratio
Mean cell volume	Total protein
Mean cell hemoglobin	Albumin
Mean cell hemoglobin concentration	Albumin/(protein-albumin) ratio
White blood cell	Triglycerides
Differential-band neutrophils	Cholesterol
Differential-segmented neutrophils	Glucose
Differential lymphocytes	Lactic acid dehydrogenase
Differential monocytes	Creatinine phosphokinase
Differential eosinophils	Hydroxybutyrate dehydrogenase
Differential basophils	Phosphohexoisomerase
Absolute-band neutrophils	Leucine aminopeptidase
Absolute-segmented neutrophils	Cholinesterase
Absolute lymphocytes	Blood urea nitrogen
Absolute monocytes	Creatinine
Absolute eosinophils	Uric acid
	Bilirubin--total
	Glutamic pyruvate transaminase
	Glutamic oxaloacetic transaminase
	Sorbitol dehydrogenase
	Isocitric dehydrogenase
	Gamma glutamyl transpeptidase
	Alkaline phosphatase

The test intervals for rats in the hematology subgroups were minus 1 week and plus 3, 7, 11, 15, 19, 23, 27, 31, 35, and 39 weeks. Those for rats in the clinical chemistry subgroups were minus 1 week and plus 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 39, and 69 weeks.

Source and Specifications of Test Animals

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N, female, × C3H/HeN MTV$^-$, male) mice used in this study were produced under barrier conditions at the Frederick Cancer Research Center under a contract to the Carcinogenesis Program. Breeding starts for the foundation colony at the production facility originated at the National Institutes of Health Repository. Animals used for testing were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Animals were transferred to the testing laboratory at 4-6 weeks of age. The animals were quarantined at the testing facility for 2-5 weeks. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rodents were placed on study at 6-10 weeks of age.

Rats were assigned to cages so that average cage weights were approximately equal. Three shipments of mice were received at 2-week intervals. All vehicle control mice were from the first shipment; low dose mice were from the first and second shipments, and high dose mice were from the second and third shipments. As a result of this procedure, initial body weights of vehicle control mice were greater than those in the dosed groups.

Animal Maintenance

Rats were housed four per cage and mice five per cage. Feed and water were available ad libitum. Details of animal maintenance are summarized in Table 2.

Clinical Examinations and Pathology

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

Examinations for grossly visible lesions were performed on major tissues or organs. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined microscopically are listed in Table 2.

When the pathology examination was completed, the slides, individual animal data records, and summary tables were sent to an independent quality assurance laboratory. Individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assurance pathologist. Slides of all target tissues and those about which the original and quality assurance pathologists disagreed were submitted to the Chairperson of the Pathology Working Group (PWG) for evaluation. Representative coded slides selected by the Chairperson were reviewed by PWG pathologists, who reached a consensus and compared their findings with the original and quality assurance diagnoses. When diagnostic differences were found, the PWG sent the appropriate slides and comments to the original pathologist for review. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group.

Two PWG evaluations were held for these studies. The first PWG determined that the initial pathology report submitted by Frederick Cancer Research Center was inadequate and requested that all pathology records and slides be reread by a second pathologist. The second pathology report was approved with some modifications by the PWG.

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

Statistical Methods

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

Survival Analyses: The probabiiity 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

TABLE 2. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE TWO-YEAR GAVAGE STUDIES OF TELONE II® (a)

EXPERIMENTAL DESIGN	
Size of Test Groups	52 male and 52 female rats; 50 male and 50 female mice
Doses	Rats--0, 25, or 50 mg/kg Telone II® in corn oil via gavage 3 × wk; mice--0, 50, or 100 mg/kg; dose vol: 5.0 ml/kg for both species
Date of First Dose	Rats--2/25/77; mice--7/7/78
Date of Last Dose	Rats--2/21/79; mice--7/2/80
Duration of Dosing	104 wk; 3 × wk (M, W, F)
Type and Frequency of Observation	Observed 2 × d for moribundity and mortality; clinical exam and palpation for masses 1 × wk; weighed 1 × wk
Necropsy and Histologic Examination	Necropsies, consisting of gross examination of major tissues, major organs and all gross lesions, performed on all animals. Tissues/organs examined histopathologically: gross lesions and tissue masses, blood smears, submandibular and mesenteric lymph nodes, salivary glands, femur (including marrow), thyroid gland, parathyroids, small intestine (one section), colon, liver, prostate/testes or ovaries/uterus, lungs and bronchi, mammary gland, skin, esophagus, stomach, brain (cerebellum and cerebrum), heart, thymus, trachea, pancreas, spleen, kidneys, adrenal glands, urinary bladder, pituitary, gallbladder (mice only)
ANIMALS AND ANIMAL MAINTENANCE	
Species	F344/N rats and B6C3F$_1$ mice
Animal Source	Frederick Cancer Research Center (Frederick, MD)
Testing Laboratory	Frederick Cancer Research Center (Frederick, MD)
Time Held Before Start of Test	Rats--3 wk; mice--2-5 wk
Age When Placed on Study	Rats--6 wk; mice--6-10 wk
Age When Killed	Rats--112-113 wk; mice--111-117 wk
Necropsy Dates	Rats--3/6/79-3/20/79; mice--7/10/80-7/25/80
Method of Distribution	Rats--assigned to cages so that average cage weights were approximately equal; mice--assigned to control (first shipment), low dose (first and second shipments), and high dose (second and third shipment) groups as animals arrived
Feed	Wayne Sterilizable Lab Meal® (Allied Mills, Chicago, IL) ad libitum in suspended stainless steel hoppers
Bedding	None; stainless steel wire grids (Lab Products, Rochelle Park, NJ) were placed in the bottom of the cages
Water	Acidified to pH 2.5 with HCl; available ad libitum from glass bottles; changed 2 × wk

TABLE 2. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE TWO-YEAR GAVAGE STUDIES OF TELONE II® (Continued)

ANIMALS AND ANIMAL MAINTENANCE (Continued)	
Cages	Polycarbonate (Lab Products, Inc., Garfield, NJ)
Cage Filters	Nonwoven polyester fiber (Hoeltge, Inc., Cincinnati, OH)
Animals per Cage	Rats--4; mice--5
Animal Room Environment	Rats--temp 22°-24° C; rel humidity about 45%-55%; 15 changes room air/h; fluorescent light 12 h/d; mice--same as rats but 12-15 room air changes/h and 10 h light and 14 h dark cycles
Other Chemicals on Test in Same Room	None
CHEMISTRY	
Lot Numbers Used	EXP-N-3993
Supplier	Dow Chemical USA (Freeport, TX)
CHEMICAL/VEHICLE	
Preparation	Appropriate amounts of Telone II® and corn oil were mixed to give the desired concentrations. The solutions were homogenized for 1-2 minutes in a Lourdes® blender
Maximum Storage Time	Freshly prepared each day of dosing
Storage Conditions	Not stored

(a) Documentation not available for short-term studies; see text for the experimental design of the ancillary studies.

dead of other than natural causes or were found to be missing; animals dying from natural causes (including those killed while moribund) 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. All reported P values for the survival analysis are two-sided.

Calculation of Incidence Rates: 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 necropsies were performed.

Analysis of Tumor Incidence: Three statistical methods are used to analyze tumor incidence data. The two that adjust for intercurrent mortality employ the classical method for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise comparisons of high dose and low dose groups with vehicle controls and tests for overall dose-response trends.

For studies in which compound administration has little effect on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death. All reported P values for tumor analyses are one-sided.

Life Table Analyses--The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and 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 study, were then combined by the Mantel-Haenszel method to obtain an overall P value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975).

Incidental Tumor Analyses--The second method of analysis assumed that all tumors of a given type observed in animals that died before the end of the study were "incidental"; i.e., they were merely observed at necropsy in animals dying of an unrelated cause. According to this approach, the proportions of tumor-bearing animals in dosed and vehicle control groups were compared in each of five time intervals: 0-52 weeks, 53-78 weeks, 79-92 weeks, week 93 to the week before the terminal-kill period, and the terminal-kill period. The denominators of these proportions were the number of animals on which necropsies were actually performed during the time interval. The individual time interval comparisons were then combined by the previously described method to obtain a single overall result. (See Haseman, 1984, for the computational details of both methods.)

All tumors observed in the ancillary study were considered to be incidental; hence the reported "life table analysis" is a combination of a life table analysis applied to tumors observed in animals dying during the course of the study and an incidental tumor test applied to tumors observed in scheduled-kill animals (Haseman, 1984); each scheduled-kill period (9, 16, 21, 24, and 27 months) was considered as a separate time interval. The 24-month data from the ancillary study were combined with the data from the terminal kill in the 2-year study.

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

III. RESULTS

RATS

TWO-YEAR STUDIES AND ANCILLARY STUDIES

Body Weights and Clinical Signs

Survival

Ancillary Studies

Pathology and Statistical Analyses of Results

MICE

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

TWO-YEAR STUDIES AND ANCILLARY STUDIES*

Body Weights and Clinical Signs

Mean body weights of high dose male rats were approximately 5% lower than those of the vehicle controls after about week 28 (Table 3 and Figure 2). Mean body weights of dosed and vehicle control female rats were comparable. The record of weekly clinical observations was incomplete for the first 18 months of the study. Other than a few instances of abnormal signs (e.g., convulsions, "wasting") for individual animals, no extraordinary clinical signs of toxicity were observed.

TABLE 3. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF TELONE II®

Weeks on Study	Vehicle Control		Low Dose			High Dose		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
0	99	52	98	100.0	52	99	101.0	52
2	160	51	160	100.0	52	162	101.3	52
4	211	51	211	100.0	48	210	99.5	52
6	244	51	247	101.2	48	244	100.0	52
8	269	51	274	101.9	48	271	100.7	52
10	290	50	291	100.3	48	283	97.6	52
12	306	50	311	101.6	48	301	98.4	52
16	328	50	332	101.2	48	318	97.0	51
20	344	50	346	100.6	48	336	97.4	51
24	362	50	363	100.3	48	345	95.3	51
28	372	50	375	100.8	48	353	94.9	51
32	386	50	387	100.3	48	361	93.5	51
36	394	50	400	101.5	48	375	95.2	50
40	400	50	409	102.3	48	381	95.3	50
44	409	50	421	102.9	48	390	95.4	50
48	411	50	426	103.6	48	387	94.2	50
52	417	49	428	102.6	46	391	93.8	50
60	420	49	423	100.7	48	390	92.9	49
68	431	49	441	102.3	47	403	93.5	49
76	433	49	440	101.6	47	396	91.5	49
84	428	47	437	102.1	46	390	91.1	49
92	427	47	438	102.6	45	408	95.6	45
100	418	44	423	101.2	42	393	94.0	41
FEMALE								
0	88	52	89	101.1	52	90	102.3	52
2	124	51	125	100.8	52	129	104.0	52
4	145	51	146	100.7	52	149	102.8	52
6	162	51	162	100.0	52	166	102.5	52
8	174	51	174	100.0	52	179	102.9	52
10	182	51	182	100.0	52	189	103.8	52
12	189	51	189	100.0	52	197	104.2	52
16	197	51	198	100.5	50	202	102.5	52
20	202	51	202	100.0	50	209	103.5	52
24	214	51	213	99.5	50	217	101.4	52
28	219	51	219	100.0	50	224	102.3	52
32	227	51	225	99.1	50	233	102.6	52
36	234	51	234	100.0	49	239	102.1	52
40	239	51	241	100.8	49	246	102.9	52
44	245	51	248	101.2	49	252	102.9	52
48	249	51	252	101.2	49	257	103.2	52
52	255	50	258	101.2	49	261	102.4	52
60	262	50	268	102.3	48	267	101.9	52
68	290	49	285	98.3	48	285	98.3	52
76	291	48	301	103.4	47	294	101.0	52
84	303	47	311	102.6	45	301	99.3	48
92	305	45	321	105.2	39	316	103.6	46
100	305	38	324	106.2	39	314	103.0	40

*Unless otherwise stated, all data on body weights and survival were derived from the 2-year carcinogenicity studies; results from the ancillary studies were not used in these measurements and calculations.

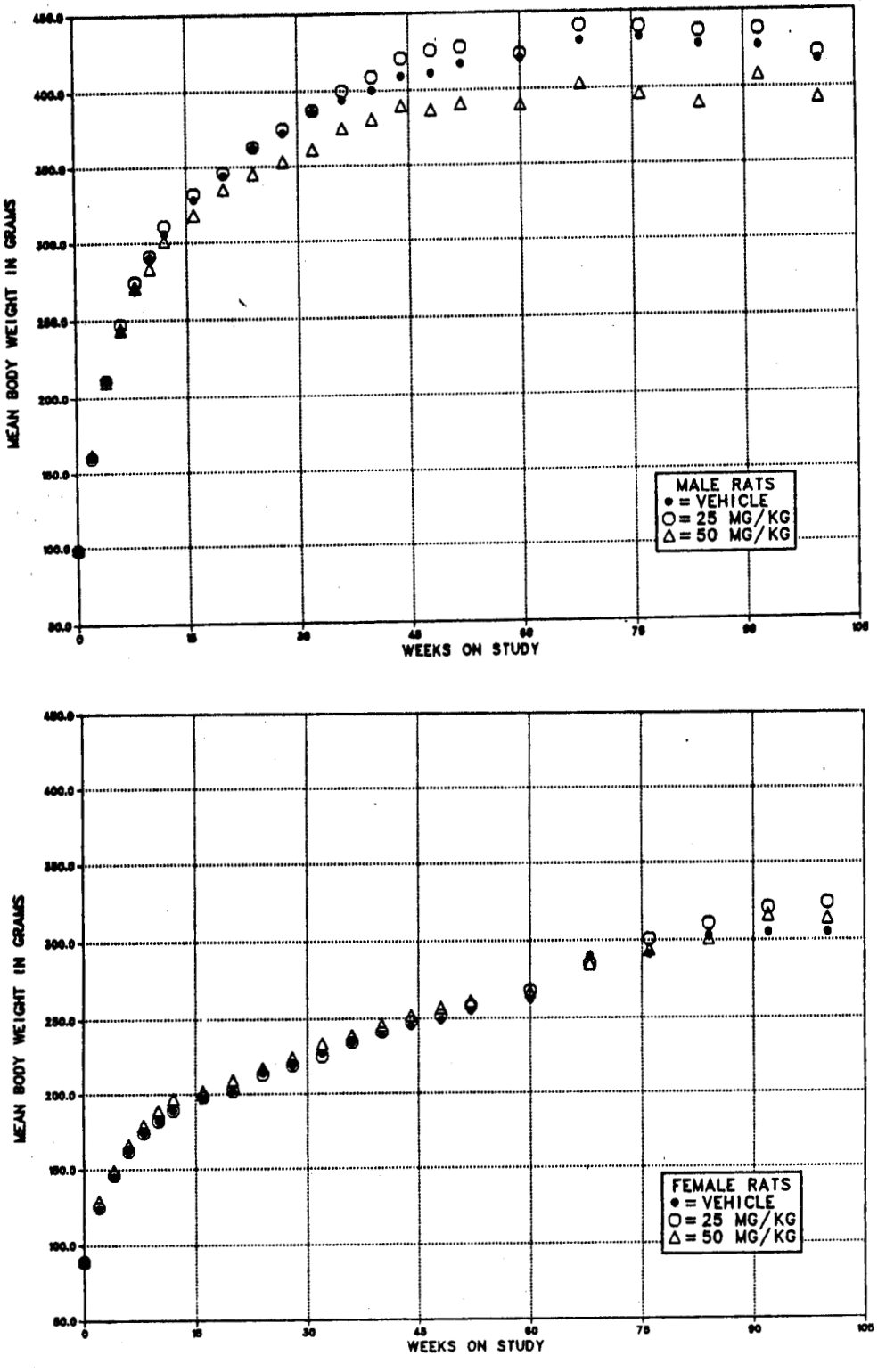


FIGURE 2. GROWTH CURVES FOR RATS ADMINISTERED TELONE II® IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of the survival of male and female rats administered Telone II® at the doses used in the 2-year studies and those of the vehicle controls are shown in Figure 3. No significant differences in survival were observed between any groups of either sex (Table 4).

Ancillary Studies

Initial analyses by Frederick Cancer Research Center of the hematologic and clinical chemistry data revealed certain statistically (*t*-test) significant changes in several analytes, including mean cell volume, cholinesterase, glucose, lactate dehydrogenase, triglycerides, and alpha-hydroxybutyrate dehydrogenase. Because these changes were neither consistent nor progressive over time and since there is a greater than normal variability in the data, these changes are not believed to be toxicologically significant. The data for serum cholinesterase, which had the most statistically significant changes and which also were the most variable, are listed in Appendix L (Table L1); all data for 18 hematologic and 25 clinical chemistry measurements are available from the NTP Archives.

The lesions observed in the rats in the interim-kill groups are discussed along with those found in the 2-year carcinogenesis studies. Generally, the pathology data from the ancillary studies supported the results from the 2-year studies. The only instance in which the inclusion of data from the ancillary studies markedly affected the statistical significance of observed tumor increases was squamous cell papilloma of the forestomach in female rats.

TABLE 4. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF TELONE II®

	Vehicle Control	25 mg/kg	50 mg/kg
MALE (a)			
Animals initially in study	52	52	52
Nonaccidental deaths before termination (b)	7	13	11
Accidentally killed	2	1	1
Killed at termination	42	37	40
Died during termination period	1	1	0
Survival P values (c)	0.414	0.222	0.459
FEMALE (a)			
Animals initially in study	52	52	52
Nonaccidental deaths before termination (b)	17	13	14
Accidentally killed	1	4	0
Killed at termination	34	35	38
Survival P values (c)	0.560	0.655	0.626

(a) Terminal kill period: weeks 106-108
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and those of the life table exact pairwise comparisons with the vehicle controls are in the dosed columns.

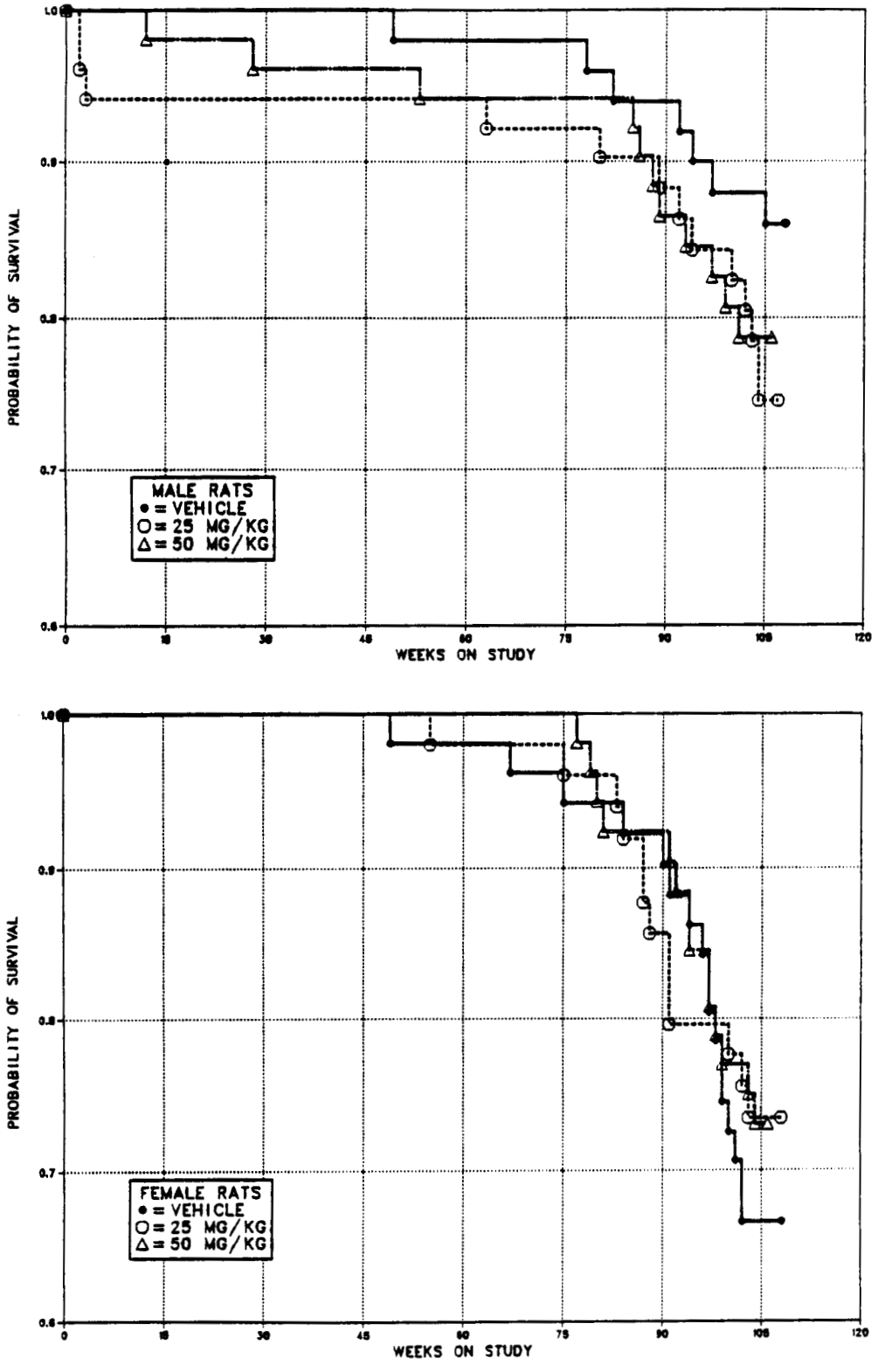


FIGURE 3. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED TELONE II® IN CORN OIL BY GAVAGE FOR TWO YEARS

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidence of rats with neoplastic or nonneoplastic lesions in the forestomach, liver, adrenal gland, thyroid gland, urinary bladder, and kidney. Histopathologic findings on neoplasms in rats are summarized in Appendix A (Tables A1 and A2); the survival and tumor status for individual male and female rats also are summarized in Appendix A (Tables A3 and A4). Findings on nonneoplastic lesions are summarized in Appendix C (Tables C1 and C2). Appendix E (Tables E1, E2, and E3) gives the incidences of neoplasms and nonneoplastic lesions in rats in the interim-kill groups at 9, 16, 21, 24, and 27 months; the serum cholinesterase data are presented in Appendix L (Table L1). Appendix F (Tables F1 and F2) contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix F (footnotes). Historical incidences of tumors in corn oil vehicle control animals are listed in Appendix G.

Forestomach (reported as "stomach" or "forestomach" in the Carcinogenesis Bioassay Data System): Basal cell hyperplasia occurred at increased incidences in dosed male and female rats (Table 5). The pooling of data from the 2-year studies and the interim-kill studies reaffirmed the dose-related increases of basal cell hyperplasia in both sexes. Most hyperplastic lesions involved only the basal layer of the squamous epithelium and were diagnosed as basal cell hyperplasia rather than epithelial hyperplasia.

Squamous cell papillomas, squamous cell carcinomas, and squamous cell papillomas or carcinomas (combined) occurred with significant positive trends in male rats; the incidences of squamous cell papillomas and squamous cell papillomas or carcinomas in the high dose group were significantly greater than those in the vehicle controls (Table 5). When data from the 2-year and interim-kill studies were combined, the positive findings were reinforced. The increased incidences of squamous cell papillomas in female rats were not significant in the 2-year study, but the pooled results of the 2-year and interim-kill studies showed significant dose-related increases.

TABLE 5. ANALYSIS OF FORESTOMACH LESIONS IN RATS IN THE TWO-YEAR AND ANCILLARY GAVAGE STUDIES OF TELONE II® (a)

	Vehicle Control		25 mg/kg		50 mg/kg	
	2-Year Study	2-Year and Ancillary Studies (b)	2-Year Study	2-Year and Ancillary Studies	2-Year Study	2-Year and Ancillary Studies
MALE						
Basal Cell or Epithelial Hyperplasia						
Overall Rates	2/52 (4%)	3/77 (4%)	5/52 (10%)	13/77 (17%)	13/52 (25%)	31/77 (40%)
Squamous Cell Papilloma						
Overall Rates	1/52 (2%)	1/77 (1%)	1/52 (2%)	1/77 (1%)	9/52 (17%)	13/77 (17%)
Adjusted Rates	2.3%		2.4%		21.3%	
Terminal Rates	1/43 (2%)		0/38 (0%)		7/40 (18%)	
Life Table Tests	P=0.002	P<0.001	P=0.739	P=0.742	P=0.008	P<0.001
Incidental Tumor Tests	P=0.002	P<0.001	P=0.702N	P=0.739N	P=0.011	P<0.001
Squamous Cell Carcinoma						
Overall Rates	0/52 (0%)	0/77 (0%)	0/52 (0%)	0/77 (0%)	4/52 (8%)	4/77 (5%)
Adjusted Rates	0.0%		0.0%		10.0%	
Terminal Rates	0/43 (0%)		0/38 (0%)		4/40 (10%)	
Life Table Tests	P=0.014	P=0.014	(c)	(c)	P=0.054	P=0.056
Incidental Tumor Tests	P=0.014	P=0.014	(c)	(c)	P=0.054	P=0.056
Squamous Cell Papilloma or Carcinoma (d)						
Overall Rates	1/52 (2%)	1/77 (1%)	1/52 (2%)	1/77 (1%)	13/52 (25%)	17/77 (22%)
Adjusted Rates	2.3%		2.4%		30.8%	
Terminal Rates	1/43 (2%)		0/38 (0%)		11/40 (28%)	
Life Table Tests	P<0.001	P<0.001	P=0.739	P=0.742	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P<0.001	P=0.702N	P=0.739N	P<0.001	P<0.001
FEMALE						
Basal Cell or Epithelial Hyperplasia						
Overall Rates	1/52 (2%)	1/75 (1%)	0/52 (0%)	5/77 (6%)	16/52 (31%)	35/77 (45%)
Squamous Cell Papilloma (e)						
Overall Rates	0/52 (0%)	0/75 (0%)	2/52 (4%)	2/77 (3%)	3/52 (6%)	8/77 (10%)
Adjusted Rates	0.0%		4.9%		7.4%	
Terminal Rates	0/34 (0%)		1/36 (3%)		2/38 (5%)	
Life Table Tests	P=0.097	P=0.002	P=0.241	P=0.245	P=0.138	P=0.006
Incidental Tumor Tests	P=0.093	P=0.002	P=0.350	P=0.309	P=0.116	P=0.005

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix F (footnotes).
(b) Pooled results from the 2-year and the ancillary studies (9-, 16-, 21-, 24-, and 27-month kills)
(c) No *P* value is presented because no tumors were observed in the 25 mg/kg and vehicle control groups.
(d) Historical incidence in NTP studies: 6/1,114 (0.5%)
(e) Historical incidence of squamous cell papilloma or carcinoma in NTP studies: 5/1,125 (0.4%)

Liver: Neoplastic nodules were classified according to the recommendations of Squire and Levitt (1975) and the National Academy of Sciences (1980) with some modification; that is, small focal lesions causing only minimal compression, with little or no cytologic atypia in livers or with toxic or anoxic hepatic change (such as occurs with mononuclear cell leukemia), were classified in this study as nodular hyperplasia. Neoplastic nodules in male rats occurred with a significant positive trend, and the incidences in the dosed groups were significantly greater than that in the vehicle controls (Table 6). When the data from the 2-year and interim-kill studies were pooled, the significance of the increased incidences persisted. One other high dose male had an hepatocellular carcinoma. Incidences of neoplastic nodules in dosed female rats were not significantly increased in the 2-year study (vehicle control, 6/52, 12%; low dose, 6/52, 12%; high dose, 10/52, 19%) and in the pooled data from the 2-year and interim-kill studies (vehicle control, 6/75, 8%; low dose, 8/77, 10%; high dose, 12/77 16%).

TABLE 6. ANALYSIS OF LIVER TUMORS IN MALE RATS IN THE TWO-YEAR AND ANCILLARY GAVAGE STUDIES OF TELONE II[a]

	Vehicle Control		25 mg/kg		50 mg/kg	
	2-Year Study	2-Year and Ancillary Studies (a)	2-Year Study	2-Year and Ancillary Studies	2-Year Study	2-Year and Ancillary Studies
Neoplastic Nodule						
Overall Rates	1/52 (2%)	1/77 (1%)	6/52 (12%)	6/76 (8%)	7/52 (13%)	8/77 (10%)
Adjusted Rates	2.3%		15.8%		17.5%	
Terminal Rates	1/43 (2%)		6/38 (16%)		7/40 (18%)	
Life Table Tests	P=0.023	P=0.012	P=0.040	P=0.043	P=0.025	P=0.014
Incidental Tumor Tests	P=0.023	P=0.012	P=0.040	P=0.043	P=0.025	P=0.014
Neoplastic Nodule or Carcinoma (b)						
Overall Rates	1/52 (2%)	1/77 (1%)	6/52 (12%)	6/76 (8%)	8/52 (15%)	9/77 (12%)
Adjusted Rates	2.3%		15.8%		20.0%	
Terminal Rates	1/43 (2%)		6/38 (16%)		8/40 (20%)	
Life Table Tests	P=0.011	P=0.006	P=0.040	P=0.043	P=0.013	P=0.007
Incidental Tumor Tests	P=0.011	P=0.006	P=0.040	P=0.043	P=0.013	P=0.007

(a) Pooled results from the 2-year and the ancillary studies (9-, 16-, 21-, 24-, and 27-month kills)
(b) Historical incidence in NTP studies: 40/1,141 (3.5%) ± 4%

Time-Dependent Development of Forestomach and Liver Lesions: The development of forestomach lesions (basal cell hyperplasia, squamous cell papilloma) in rats in the interim-kill groups followed a time-dependent trend in high dose males and females (Table 7). Basal cell hyperplasia of the forestomach was seen as early as 9-16 months after dosing began. The neoplasms of the forestomach and liver were not seen until 24 months after dosing began.

Adrenal Gland: Pheochromocytomas occurred in low dose males with a significantly increased incidence when compared with the vehicle controls (Table 8).

TABLE 7. INCIDENCE OF FORESTOMACH AND LIVER LESIONS IN RATS IN THE ANCILLARY STUDIES OF TELONE II[a]

	Vehicle Control (a)					25 mg/kg (a)					50 mg/kg (a)				
	9	16	21	24	27	9	16	21	24	27	9	16	21	24	27
	(months on study)					(months on study)					(months on study)				
MALE															
Stomach: Basal Cell Hyperplasia	0/5	0/5	1/5	0/5	0/5	0/5	1/5	3/5	3/5	1/5	1/5	5/5	4/5	4/5	4/5
Stomach: Squamous Cell Papilloma	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	2/5	2/5
Liver: Neoplastic Nodule	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/4	0/5	0/5	0/5	0/5	0/5	1/5	0/5
FEMALE															
Stomach: Basal Cell Hyperplasia	0/5	0/5	0/5	0/5	0/3	0/5	2/5	2/5	1/5	0/5	0/5	5/5	5/5	4/5	5/5
Stomach: Squamous Cell Papilloma	0/5	0/5	0/5	0/5	0/3	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	5/5
Liver: Neoplastic Nodule	0/5	0/5	0/5	0/5	0/3	0/5	0/5	0/5	2/5	0/5	0/5	0/5	0/5	0/5	2/5

(a) Scheduled kills

TABLE 8. ANALYSIS OF ADRENAL GLAND TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TELONE II[a]

	Vehicle Control	25 mg/kg	50 mg/kg
Pheochromocytoma			
Overall Rates	2/52 (4%)	8/52 (15%)	6/52 (12%)
Adjusted Rates	4.7%	21.1%	13.6%
Terminal Rates	2/43 (5%)	8/38 (21%)	3/40 (7%)
Life Table Tests	P=0.110	P=0.029	P=0.123
Incidental Tumor Tests	P=0.141	P=0.029	P=0.192

Thyroid Gland: Follicular cell adenomas or carcinomas (combined) occurred in female rats with a significant positive trend; the incidences in the dosed groups were not significantly greater than that in the vehicle controls (Table 9). The increased incidences of follicular cell adenomas or carcinomas (combined) were not significant in dosed male rats.

Urinary Bladder: Edema of the submucosa of the urinary bladder was observed at increased incidences in high dose males and high dose females (males: vehicle control, 0/52; low dose, 0/52; high dose, 9/52, 17%; females: vehicle control, 0/52; low dose, 0/52; high dose, 3/52, 6%).

Kidney: Nephropathy was increased in dosed female rats (vehicle control, 15/52, 29%; low dose 24/52, 46%; high dose, 25/52, 48%). No increases were observed in male rats (vehicle control, 38/52, 73%; low dose, 35/52, 67%; high dose, 42/52, 81%).

TABLE 9. ANALYSIS OF THYROID GLAND LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF TELONE II[a]

	Vehicle Control	25 mg/kg	50 mg/kg
MALE			
Follicular Cell Adenoma or Carcinoma			
Overall Rates	0/52 (0%)	4/51 (8%)	1/51 (2%)
FEMALE			
Follicular Cell Hyperplasia			
Overall Rates	0/52 (0%)	0/52 (0%)	2/52 (4%)
Follicular Cell Adenoma			
Overall Rates	0/52 (0%)	1/52 (2%)	2/52 (4%)
Follicular Cell Carcinoma			
Overall Rates	0/52 (0%)	1/52 (2%)	2/52 (4%)
Follicular Cell Adenoma or Carcinoma			
Overall Rates	0/52 (0%)	2/52 (4%)	4/52 (8%)
Adjusted Rates	0.0%	5.6%	10.1%
Terminal Rates	0/34 (0%)	2/36 (6%)	3/38 (8%)
Life Table Tests	P=0.047	P=0.251	P=0.077
Incidental Tumor Tests	P=0.043	P=0.251	P=0.064

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Initial mean body weights of dosed mice were 6%-22% lower than those of the vehicle controls; these differences were caused by failure to fully randomize the distribution of the animals. Three shipments of mice were received at 2-week intervals on 5/30/78, 6/13/78, and 6/27/78.

The mice were approximately 4-6 weeks of age when received. In most cases, weights of dosed mice remained lower than those of the vehicle controls throughout the study (Table 10 and Figure 4); final body weights were 5% lower than those of the vehicle controls, except in low dose females (9% lower). The weekly clinical observation record was available from approximately 10 weeks after dosing began until the end of the study. No extraordinary clinical signs were observed.

TABLE 10. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF TELONE II®

Weeks on Study	Vehicle Control		Low Dose			High Dose		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
0	23	50	20	87.0	50	20	87.0	50
2	27	50	26	96.3	50	25	92.6	50
4	29	50	28	96.6	49	27	93.1	49
6	31	50	30	96.8	49	29	93.5	49
8	32	50	30	93.8	49	30	93.8	49
10	33	50	31	93.9	49	31	93.9	49
12	35	50	33	94.3	49	32	91.4	49
16	33	50	34	103.0	49	31	93.9	49
20	37	50	36	97.3	49	35	94.6	49
24	39	50	36	92.3	49	35	89.7	49
28	39	50	36	92.3	49	34	87.2	49
32	40	50	37	92.5	49	36	90.0	49
36	40	50	37	92.5	49	36	90.0	49
40	41	50	37	90.2	48	36	87.8	49
44	40	48	37	92.5	48	36	90.0	49
48	42	48	39	92.9	48	35	83.3	49
52	40	23	38	95.0	47	37	92.5	47
60	41	23	39	95.1	42	38	92.7	46
68	41	22	37	90.2	40	36	87.8	46
76	43	22	39	90.7	40	37	86.0	44
84	41	21	39	95.1	39	37	90.2	42
92	40	15	38	95.0	38	37	92.5	40
100	40	12	38	95.0	35	38	95.0	38
FEMALE								
0	18	50	17	94.4	50	14	77.8	50
2	20	50	20	100.0	50	19	95.0	49
4	23	50	22	95.7	50	21	91.3	49
6	23	50	23	100.0	50	22	95.7	49
8	24	50	23	95.8	50	23	95.8	49
10	25	50	25	100.0	50	25	100.0	49
12	26	50	25	96.2	50	25	96.2	49
16	25	50	25	100.0	50	24	96.0	49
20	28	50	27	96.4	50	27	96.4	49
24	29	50	27	93.1	50	27	93.1	49
28	29	50	28	96.6	50	27	93.1	48
32	30	50	30	100.0	50	28	93.3	47
36	30	50	29	96.7	50	29	96.7	47
40	31	50	29	93.5	50	29	93.5	47
44	30	50	29	96.7	50	29	96.7	47
48	31	50	29	93.5	50	29	93.5	47
52	32	50	30	93.8	50	30	93.8	47
60	32	50	31	96.9	50	31	96.9	45
68	33	50	30	90.9	50	31	93.9	43
76	35	49	32	91.4	49	32	91.4	41
84	35	49	32	91.4	49	33	94.3	41
92	33	48	32	97.0	48	33	100.0	40
100	35	47	32	91.4	47	33	94.3	37

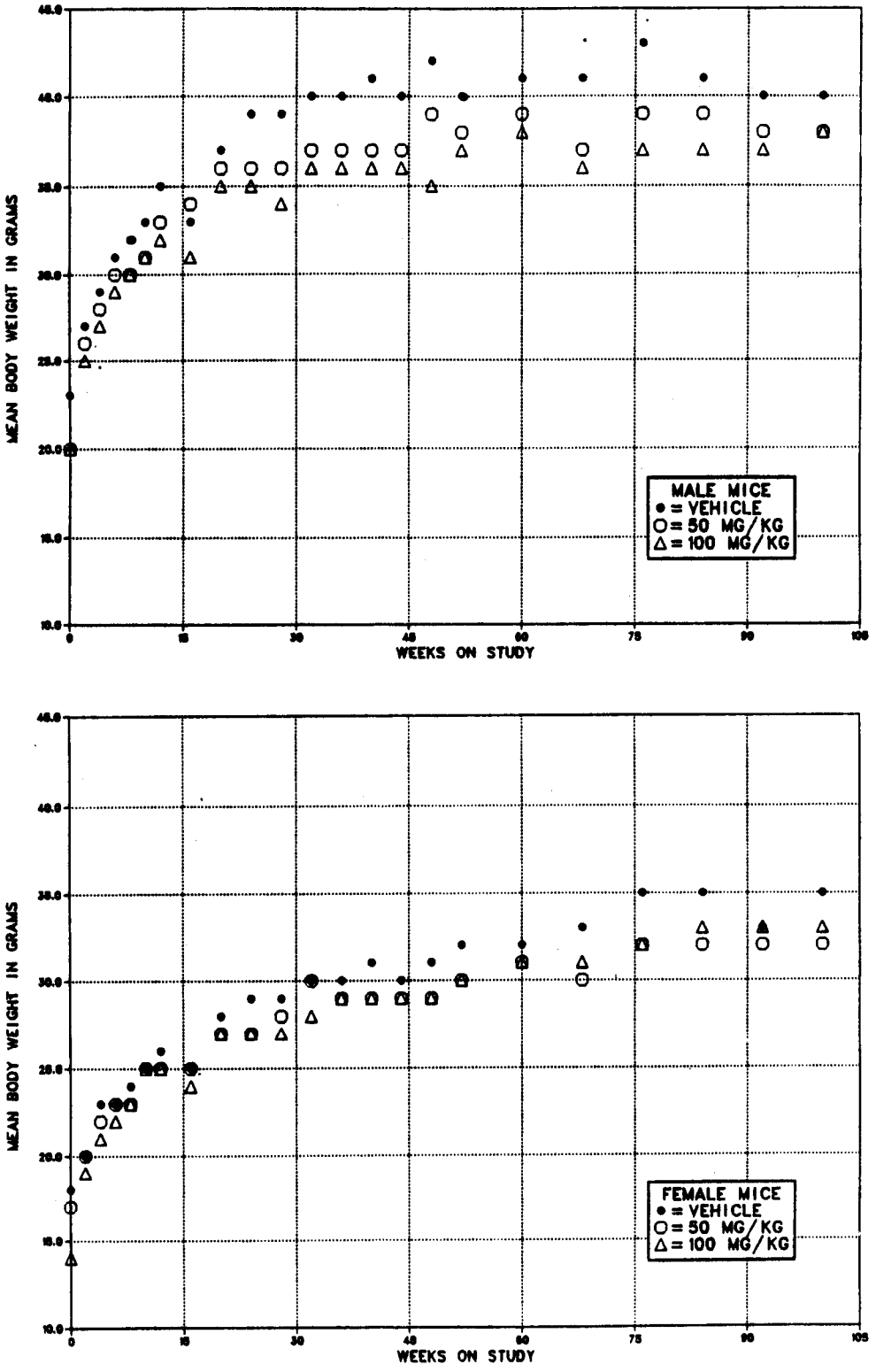


FIGURE 4. GROWTH CURVES FOR MICE ADMINISTERED TELONE II® IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival of male and female mice administered Telone II® at the doses used in the 2-year studies and those of the vehicle controls are shown in Figure 5. The survival of vehicle control male mice was significantly lower than that of either dose group (Table 11). The deaths of 39 male mice in the vehicle control group were attributed to suppurative inflammation of the heart (myocarditis); 25 of these mice died between weeks 48 and 51. In the survival analysis, these early deaths resulted in a precipitous drop in the Kaplan-Meier survival curve for the male control group (Figure 5). In male mice, myocarditis was diagnosed in 39 vehicle controls, 13 low dose animals, and 5 high dose animals; some of the same animals also had related heart lesions such as myocardial necrosis (Appendix D, Table D1). In female mice, the survival of the high dose group was significantly lower than that of the vehicle control group. None of the female mice had myocarditis.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidence of animals with neoplastic or nonneoplastic lesions in the urinary bladder, lung, forestomach, and liver. Histopathologic findings on neoplasms in mice are summarized in Appendix B (Tables B1 and B2); the survival and tumor status for individual male and female mice also are summarized in Appendix B (Tables B3 and B4). Findings on nonneoplastic lesions are summarized in Appendix D (Tables D1 and D2). Appendix F (Tables F3 and F4) contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix F (footnotes). Historical incidences of tumors in corn oil vehicle control animals are listed in Appendix G. Since only eight vehicle control male mice lived to the end of the study, only analyses that account for differences in survival are considered for male mice.

TABLE 11. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF TELONE II®

	Vehicle Control	50 mg/kg	100 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	(c) 42	22	19
Accidentally killed	0	1	0
Died during termination period	4	0	2
Killed at termination	4	28	29
Survival P values (d)	<0.001	<0.001	<0.001
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	4	5	14
Died during termination period	0	3	1
Killed at termination	46	42	35
Survival P values (d)	0.006	0.991	0.015

(a) Terminal kill period: males--weeks 105-107; females--weeks 106-107
(b) Includes animals killed in a moribund condition
(c) Twenty-five male mice died between weeks 48 and 51; the cause was given as suppurative inflammation of the heart (myocarditis).
(d) The result of the life table trend test is in the vehicle control column, and the life table exact pairwise comparisons with the vehicle controls are in the dosed columns.

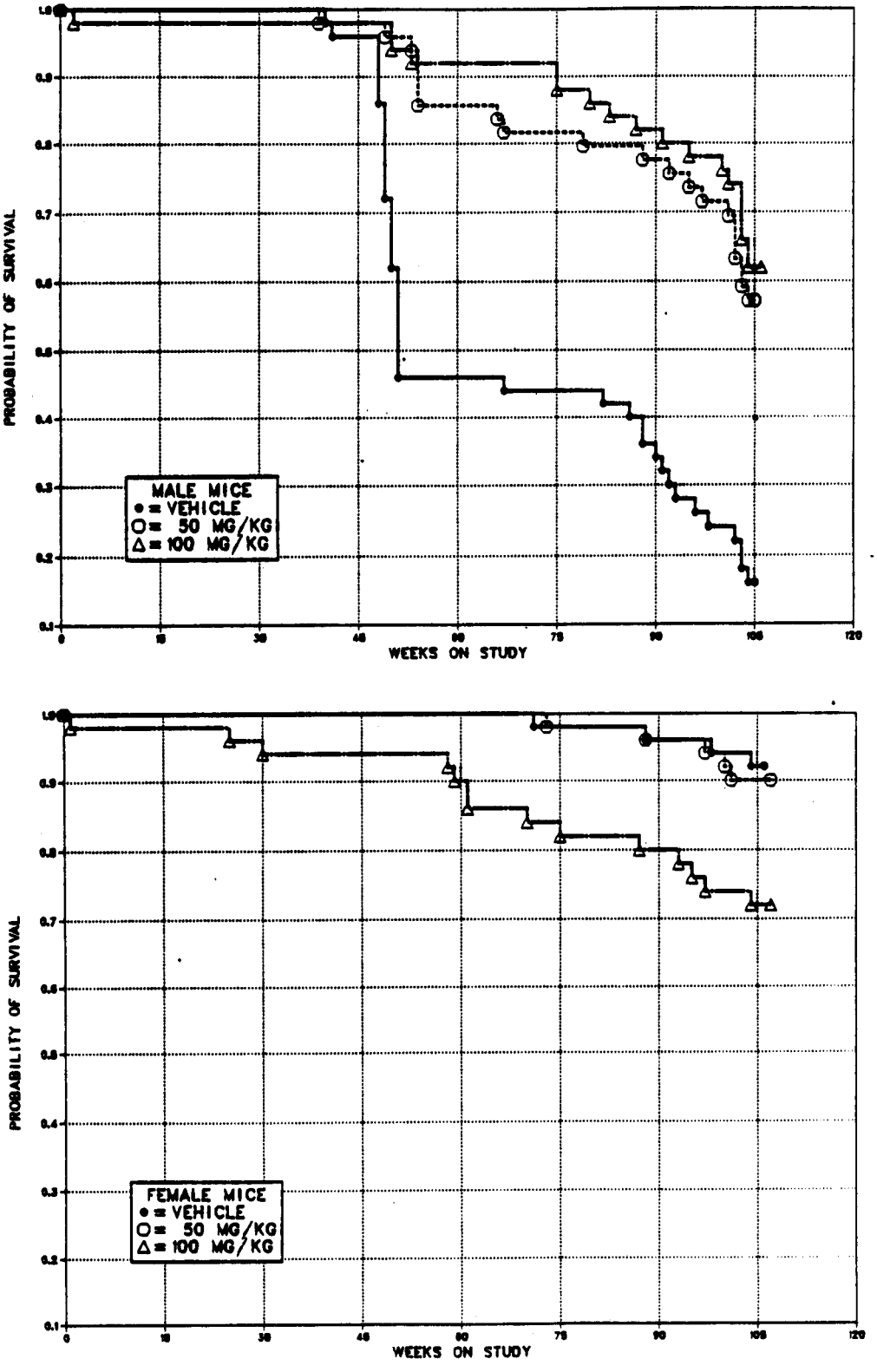


FIGURE 5. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED TELONE II® IN CORN OIL BY GAVAGE FOR TWO YEARS

Urinary Bladder: Epithelial hyperplasia occurred at dose-related increased incidences in male and female mice (Table 12). The low survival rate of vehicle control male mice should be considered when the increases in dosed male mice are evaluated.

Transitional cell carcinomas in female mice occurred with a significant positive trend, and the incidences in the dosed groups were greater than that in the vehicle controls (Table 12). Two male mice in the high dose group had transitional cell carcinomas of the urinary bladder. Rather than proliferating outward as do papillomas, these neoplasms were characterized by solid or glandular growth that extended downward from the transitional epithelium into the submucosa and muscular layer and occasionally to the serosa of the bladder.

TABLE 12. ANALYSIS OF URINARY BLADDER LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF TELONE II® (a)

	Vehicle Control	50 mg/kg	100 mg/kg
MALE			
Epithelial Hyperplasia			
Overall Rates	(b) 0/50 (0%)	9/50 (18%)	18/50 (36%)
Transitional Cell Carcinoma (c)			
Overall Rates	0/50 (0%)	0/50 (0%)	2/50 (4%)
FEMALE			
Epithelial Hyperplasia			
Overall Rates	2/50 (4%)	15/50 (30%)	19/48 (40%)
Transitional Cell Carcinoma (d)			
Overall Rates	0/50 (0%)	8/50 (16%)	21/48 (44%)
Adjusted Rates	0.0%	17.4%	56.5%
Terminal Rates	0/46 (0%)	7/45 (16%)	19/35 (54%)
Life Table Tests	P<0.001	P=0.005	P<0.001
Incidental Tumor Tests	P<0.001	P=0.006	P<0.001

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix F (footnotes).
(b) At approximately 1 year of the study, 25 vehicle control male mice died from suppurative inflammation of the heart (myocarditis); only 8 mice in the group lived to the end of the study.
(c) Historical incidence in NTP studies: 0/1,033
(d) Historical incidence in NTP studies: 0/1,025

Lung: Alveolar/bronchiolar adenomas occurred in female mice with significant positive trends (Table 13). The incidences of alveolar/bronchiolar adenomas in low dose male mice and high dose female mice were greater than those in the vehicle controls. Incidences of alveolar/bronchiolar adenomas or carcinomas (combined) in dosed male mice and in high dose female mice were greater than those in the vehicle controls.

TABLE 13. ANALYSIS OF LUNG TUMORS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF TELONE II®

	Vehicle Control	50 mg/kg	100 mg/kg
MALE			
Alveolar/Bronchiolar Adenoma			
Overall Rates	(a) 1/50 (2%)	11/50 (22%)	9/50 (18%)
Adjusted Rates	11.1%	33.4%	27.0%
Terminal Rates	0/8 (0%)	7/28 (25%)	7/31 (23%)
Life Table Tests	P=0.419	P=0.147	P=0.312
Incidental Tumor Tests	P=0.185	P=0.026	P=0.162
Alveolar/Bronchiolar Adenoma or Carcinoma (b)			
Overall Rates	1/50 (2%)	13/50 (26%)	12/50 (24%)
Adjusted Rates	11.1%	39.8%	33.5%
Terminal Rates	0/8 (0%)	9/28 (32%)	8/31 (26%)
Life Table Tests	P=0.264	P=0.097	P=0.166
Incidental Tumor Tests	P=0.072	P=0.015	P=0.040
FEMALE			
Alveolar/Bronchiolar Adenoma			
Overall Rates	0/50 (0%)	3/50 (6%)	8/50 (16%)
Adjusted Rates	0.0%	6.7%	21.3%
Terminal Rates	0/46 (0%)	3/45 (7%)	7/36 (19%)
Life Table Tests	P<0.001	P=0.118	P=0.002
Incidental Tumor Tests	P=0.001	P=0.118	P=0.003
Alveolar/Bronchiolar Adenoma or Carcinoma (c)			
Overall Rates	2/50 (4%)	4/50 (8%)	8/50 (16%)
Adjusted Rates	4.3%	8.9%	21.3%
Terminal Rates	2/46 (4%)	4/45 (9%)	7/36 (19%)
Life Table Tests	P=0.011	P=0.327	P=0.020
Incidental Tumor Tests	P=0.019	P=0.327	P=0.032

(a) At approximately 1 year of the study, 25 vehicle control male mice died from suppurative inflammation of the heart (myocarditis); only 8 mice in the group lived to the end of the study.
(b) Historical incidence in NTP studies: 155/1,082 (14%) ± 6%
(c) Historical incidence in NTP studies: 52/1,103 (5%) ± 3%

Forestomach (reported as "stomach" in the Carcinogenesis Bioassay Data System): Epithelial hyperplasia of the stomach was observed at increased incidences in high dose female mice (Table 14). Squamous cell papillomas or carcinomas (combined) occurred in female mice with a positive trend (Table 14). The incidences of high dose females with squamous cell papillomas or carcinomas (combined) and of high dose males with squamous cell papillomas were greater than those in the vehicle controls.

TABLE 14. ANALYSIS OF FORESTOMACH LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF TELONE II®

		Vehicle Control	50 mg/kg	100 mg/kg
MALE				
Epithelial Hyperplasia				
Overall Rates	(a)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Squamous Cell Papilloma (b)				
Overall Rates		0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted Rates		0.0%	6.7%	7.4%
Terminal Rates		0/8 (0%)	1/28 (4%)	1/31 (3%)
Life Table Tests		P=0.234	P=0.510	P=0.280
Incidental Tumor Tests		P=0.051	P=0.403	P=0.037
FEMALE				
Epithelial Hyperplasia				
Overall Rates		1/50 (2%)	1/50 (2%)	21/50 (42%)
Squamous Cell Papilloma or Carcinoma (c)				
Overall Rates		0/50 (0%)	1/50 (2%)	(d) 4/50 (8%)
Adjusted Rates		0.0%	2.2%	10.6%
Terminal Rates		0/46 (0%)	1/45 (2%)	3/36 (8%)
Life Table Tests		P=0.014	P=0.496	P=0.040
Incidental Tumor Tests		P=0.021	P=0.496	P=0.059

(a) At approximately 1 year of the study, 25 vehicle control male mice died from suppurative inflammation of the heart (myocarditis); only 8 mice in the group lived to the end of the study.
(b) Historical incidence of squamous cell papillomas or carcinomas in NTP studies: 7/1,055 (0.7%)
(c) Historical incidence in NTP studies: 4/1,077 (0.4%)
(d) Two female mice had squamous cell papillomas, and two others had squamous cell carcinomas.

Liver: The incidences of hepatocellular adenomas and hepatocellular adenomas or carcinomas (combined) in low dose female mice were greater than those in the vehicle controls (Table 15). Incidences of these neoplasms in dosed males were not significantly increased (carcinoma: vehicle control, 4/50; low dose, 6/50; high dose, 10/50; adenoma or carcinoma: vehicle control, 5/50; low dose, 7/50; high dose, 13/50).

Kidney: Hydronephrosis occurred at increased incidences in dosed female mice (vehicle control, 0/50; low dose, 2/50, 4%; high dose, 14/50, 28%). One vehicle control male and no dosed males had this lesion. No renal tumors were observed.

TABLE 15. ANALYSIS OF LIVER TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TELONE II®

	Vehicle Control	50 mg/kg	100 mg/kg
FEMALE			
Hepatocellular Adenoma			
Overall Rates	0/50 (0%)	5/50 (10%)	3/50 (6%)
Adjusted Rates	0.0%	10.8%	7.8%
Terminal Rates	0/46 (0%)	4/45 (9%)	2/36 (6%)
Life Table Tests	P=0.082	P=0.033	P=0.088
Incidental Tumor Tests	P=0.164	P=0.040	P=0.164
Hepatocellular Carcinoma			
Overall Rates	1/50 (2%)	3/50 (6%)	0/50 (0%)
Hepatocellular Adenoma or Carcinoma (a)			
Overall Rates	1/50 (2%)	8/50 (16%)	3/50 (6%)
Adjusted Rates	2.2%	17.4%	7.8%
Terminal Rates	1/46 (2%)	7/45 (16%)	2/36 (6%)
Life Table Tests	P=0.183	P=0.018	P=0.232
Incidental Tumor Tests	P=0.291	P=0.021	P=0.361

(a) Historical incidence in NTP studies: 80/1,176 (7%) ± 3%

IV. DISCUSSION AND CONCLUSIONS

Body Weight and Survival Data
Toxicity and Carcinogenesis
The Potential Influencing Effects of 1,2-Dichloropropane and Epichlorohydrin
Mutagenicity
Structure/Activity Relationships
Conclusions

IV. DISCUSSION AND CONCLUSIONS

This report describes mainly the results of the 2-year carcinogenesis studies of Telone II® in F344/N rats and B6C3F$_1$ mice. Ancillary studies were conducted in F344/N rats to follow the time-dependent development of certain lesions as well as to perform hematologic and clinical chemistry evaluations. Commercial-grade Telone II® containing approximately 89% *cis*- and *trans*-1,3-dichloropropene, 2.5% 1,2-dichloropropane, 1.5% of a trichloropropene isomer, and 1.0% epichlorohydrin was administered by gavage in corn oil three times a week to the rats at 0, 25, or 50 mg/kg and to the mice at 0, 50, or 100 mg/kg. Ancillary studies were conducted in which dose groups containing five male and five female rats were killed after receiving Telone II® for 9, 16, 21, 24, or 27 months. These studies were conducted by Frederick Cancer Research Center (FCRC; present name: Frederick Cancer Research Facility) under the National Cancer Institute (NCI) Bioassay Program. Short-term studies were conducted by FCRC in advance of these long-term studies, but the data and records were considered incomplete; consequently, no final reports were written and the results are not recorded in this Technical Report.

Body Weight and Survival Data

Administration of Telone II® did not have any significant effect on the body weights or survival of male or female rats. There was a marginal depression (5%-9%) of mean body weight in the high dose male rats during the study, beginning at about week 25.

The mice in the Telone II® carcinogenicity studies were from three different groups that were received at 2-week intervals: vehicle control mice were from the first group; low dose mice were from the first and second groups, and high dose mice were from the second and third groups. The lack of randomization and the age differential among the dosed and vehicle control groups led to lower initial mean body weights in the dosed groups, especially in high dose females, as compared with the vehicle control group (male: low dose, −13%; high dose, −13%; female: low dose, −6%; high dose, −22%). Mean body weights of dosed mice remained lower (5%-9%) than those of the vehicle controls throughout the study. This discrepancy in body weight was not considered to be serious enough to compromise the conclusions of the study.

Survival of vehicle control male mice was low; only 8/50 (16%) were alive at the end of the study. Thirty-nine of the 42 early deaths were attributed to suppurative inflammation of the heart (myocarditis). The cause of this lesion is unknown. Although suppurative inflammation is most characteristic of a bacterial infection, the observed high incidence of myocarditis is not typical of common contagious bacterial infections of mice. The male mice study was considered inadequate because of the low survival in the vehicle control group. The female vehicle control (46/50) and low dose (45/50) groups had greater than usual survival rates at the end of the study, whereas 36/50 survived in the high dose group.

Toxicity and Carcinogenesis

The forestomach (rat, mouse), liver (rat), urinary bladder (mouse), lung (mouse), and kidney (mouse) were the primary organs affected in the 2-year studies of Telone II®. A summary of the incidences of lesions in rats and mice is given in Table 16.

Stomach Lesions: Hyperplasia and benign and malignant neoplasms of the squamous epithelium of the forestomach were observed in both rats and mice. These lesions were probably the result of interaction between Telone II® and the epithelium of the forestomach. When the incidences of squamous cell papillomas of the forestomach in male rats in the 2-year and ancillary studies were combined, statistical evidence for a dose-related effect was strengthened (Tables 5 and 16). The incidence of squamous cell carcinoma of the forestomach showed a positive trend. No squamous cell carcinomas of the forestomach were observed in scheduled-kill rats.

Comparison of these findings with tumor incidence data from previous studies indicates that the observed incidence is well above the background level. The historical incidence for squamous cell papilloma or carcinoma of the forestomach in male F344/N rats is low (6/1,114, 0.5%, Appendix G, Table G9). In addition, a dose-response trend for basal cell hyperplasia of

TABLE 16. SUMMARY OF THE INCIDENCE OF SELECTED LESIONS IN RATS AND MICE IN THE TWO-YEAR AND ANCILLARY GAVAGE STUDIES OF TELONE II®

	Male			Female		
	Vehicle Control	Low Dose	High Dose	Vehicle Control	Low Dose	High Dose
RATS						
Forestomach						
Basal cell or epithelial hyperplasia	(a) **2/52**	**5/52**	**13/52**	**1/52**	**0/52**	**16/52**
	(b) (3/77)	(13/77)	(31/77)	(1/75)	(5/77)	(35/77)
Squamous cell papilloma	**1/52**	**1/52**	**9/52**	**0/52**	**2/52**	**3/52**
	(1/77)	(1/77)	(13/77)	(0/75)	(2/77)	(8/77)
Squamous cell carcinoma	**0/52**	**0/52**	**4/52**	0/52	0/52	0/52
	(0/77)	(0/77)	(4/77)	(0/75)	(0/77)	(0/77)
Liver						
Neoplastic nodule	**1/52**	**6/52**	**7/52**	6/52	6/52	10/52
	(1/77)	(6/76)	(8/77)	(6/75)	(8/77)	(12/77)
Hepatocellular carcinoma	0/52	0/52	1/52	0/52	0/52	0/52
	(0/77)	(0/76)	(1/77)	(0/75)	(0/77)	(0/77)
MICE (c)						
Forestomach						
Epithelial hyperplasia	**0/50**	**0/50**	**4/50**	**1/50**	**1/50**	**21/50**
Squamous cell papilloma	**0/50**	**2/50**	**3/50**	**0/50**	**1/50**	**2/50**
Squamous cell carcinoma	0/50	0/50	0/50	**0/50**	**0/50**	**2/50**
Lung						
Alveolar/bronchiolar adenoma	**1/50**	**11/50**	**9/50**	**0/50**	**3/50**	**8/50**
carcinoma	**0/50**	**2/50**	**3/50**	**2/50**	**1/50**	**0/50**
Urinary Bladder						
Epithelial hyperplasia	**0/50**	**9/50**	**18/50**	**2/50**	**15/50**	**19/48**
Transitional cell carcinoma	**0/50**	**0/50**	**2/50**	**0/50**	**8/50**	**21/48**
Kidney						
Hydronephrosis	**1/50**	**0/50**	**0/50**	**0/50**	**2/50**	**14/50**

(a) Bold type indicates areas of probable biologic significance.
(b) Values in parentheses represent incidence rates for the pooled data of 2-year rat carcinogenesis and ancillary (five rats per dose per sex were killed at 9, 16, 21, 24, and 27 months) studies.
(c) At approximately 1 year of the study, 25 vehicle control male mice died from suppurative inflammation of the heart (myocarditis); only 8 mice in the group lived to the end of the study.

the stomach further supports the effects of Telone II® on the forestomach in the male rats.

In female rats, when the data from the 2-year studies were considered alone, an increasing trend (not statistically significant) appeared to be present for the squamous cell papilloma of the forestomach (vehicle control, 0/52; low dose, 2/52; high dose, 3/52). When the data from the ancillary studies were combined with those from the 2-year studies, the five tumors in the high dose group strengthened the dose-response trend (vehicle control, 0/75; low dose, 2/77; high dose, 8/77); a significant difference ($P \leq 0.006$) was present between the vehicle controls and the high dose groups. Since squamous cell papillomas or carcinomas are uncommon in female F344/N rats (5/1,125, 0.4%, Appendix G, Table G10) and a clear dose-response trend of basal cell hyperplasia of the forestomach was also observed, Telone II® is considered responsible for the effects in the forestomach in the female rats.

The study involving male $B6C3F_1$ mice was considered inadequate because of the early deaths in the vehicle control group, which were probably due to myocarditis. Nonetheless, the squamous cell papillomas of the forestomach observed in the male mice (vehicle control, 0/50; low dose, 2/50; high dose, 3/50) are uncommon lesions (7/1,055, 0.7%, Appendix G, Table G11). Epithelial hyperplasia of the forestomach was also observed in 4/50 male mice in the high dose group.

In the female mice, the incidence of squamous cell papillomas or carcinomas of the forestomach (combined) was increased. The relatively low incidences of squamous cell papillomas of the forestomach in dosed female mice were greater than those normally seen in female $B6C3F_1$ mice (4/1,077, 0.4%, Appendix G, Table G12). In high dose female mice, epithelial hyperplasia of the forestomach was prevalent. The findings in mice suggest that the effects observed in the forestomach were related to administration of Telone II®.

Liver lesions: Telone II®-related lesions in the liver were observed mainly in male rats. In the 2-year studies, a positive trend in the incidence of neoplastic nodules was observed in the male rats. When the data from the scheduled-kill studies were combined with those from the 2-year studies, the dose-response trend of neoplastic nodules in the male rats remained significant. In the female mice, an increased incidence of hepatocellular adenoma or hepatocellular adenoma or carcinoma was seen in the low dose group (Table 15). Since no increase was observed in high dose females, this increase is not considered compound related.

Lung lesions: Telone II®-related lesions in the lung were observed mainly in female mice. The incidence of alveolar/bronchiolar adenomas in the high dose female mice was significantly increased; the significance was reduced when adenomas and carcinomas were combined (Table 15). The male mice showed a similar trend, but because of the early deaths in the vehicle controls and the late appearance of this tumor, a direct comparison of these rates might be misleading.

Urinary bladder lesions: The transitional cell carcinomas of the urinary bladder observed in the Telone II®-dosed mice are uncommon (0/1,033 for males and 0/1,025 for females, Appendix G, Table G13). The tumors did not proliferate outward in a papillary manner but were characterized by solid to glandular growths extending downward from the transitional epithelium into the submucosa and muscular layer and in a few cases to the serosa of the bladder. Urinary bladder tumors have often been associated with exposure to aromatic amines (Cohen et al., 1982; Hicks, 1983); however, the components of Telone II® are chemically and physically different from those of aromatic amines. No calculi were observed in the urinary bladder of the mice with transitional cell carcinomas. In the dosed female mice, epithelial hyperplasia of the urinary bladder was also increased. The prevalence of these neoplastic and nonneoplastic lesions in the dosed female mice indicates that the effects were related to administration of Telone II®. The increased incidence of epithelial hyperplasia and transitional cell carcinoma of the urinary bladder (2/50) in high dose males as compared with 0/50 in concurrent controls and 0/1,033 (for transitional cell carcinoma of the urinary bladder) in historical controls suggests that the effects are related to administration of

Telone II®. Lesions of the urinary bladder were not seen in rats.

Kidney lesions: Hydronephrosis was observed in dosed female mice. Since 8 of the 14 high dose females with hydronephrosis also had transitional cell carcinoma of the urinary bladder and 3 of the remaining 6 had hyperplasia of the urinary bladder, this lesion might have been a secondary effect of the urinary bladder lesions (i.e., restricted urine flow at the renal pelvis and/or ureter). Thirteen female mice had transitional cell carcinomas without hydronephrosis. The complete dilation of the pelvic area in the affected animals supports the possibility of hydronephrosis being secondary to the bladder lesions. Torkelson and Oyen (1977) reported that after male rats were exposed to 1,3-dichloropropene at a concentration of 3 ppm for 7 hours per day, 5 days per week for 6 months, only cloudy swelling of the renal tubular epithelium was found to be compound related.

Other organs: The incidence of pheochromocytomas of the adrenal gland (vehicle control, 2/52; low dose, 8/52; high dose, 6/52) was increased marginally ($P<0.05$) in low dose male rats compared with that in the vehicle controls (Table 8). There was no dose-response relationship, and the mean historical incidence is 17% (Appendix G, Table G1). The combined incidence of follicular cell adenoma or carcinoma of the thyroid gland in female rats showed a marginal trend (vehicle control, 0/52; low dose, 2/52; high dose, 4/52). In both cases, the additional data from the ancillary studies strengthened the effects slightly (male--pheochromocytomas: vehicle control, 4/77; low dose, 14/77; high dose, 10/76; female--follicular cell adenomas or carcinomas: vehicle control, 0/75; low dose, 2/77; high dose, 5/77), but the increases remained marginal.

The Potential Influencing Effects of 1,2-Dichloropropane and Epichlorohydrin

The material tested, Telone II®, contains primarily isomers of 1,3-dichloropropene. The added stabilizer or impurities present in Telone II® are epichlorohydrin (1.0%) and 1,2-dichloropropane (2.5%). Both chemicals have been shown to be carcinogenic (Laskin et al., 1980; Konishi et al., 1980; NTP, 1985). These studies are described briefly below. An additional impurity, a trichloropropene isomer (1.5%), has not been tested for carcinogenicity.

1,2-Dichloropropane was administered in corn oil by gavage to F344/N rats and $B6C3F_1$ mice (NTP, 1985). Doses of 0, 62, 125, or 250 mg/kg body weight were given five times per week for 103 weeks. Under these conditions, 1,2-dichloropropane caused an increased incidence of hepatocellular adenomas in male and female mice (male: vehicle control, 7/50; low dose, 10/49; high dose, 16/50; female: vehicle control, 0/50; low dose, 4/50; high dose, 5/50) and a marginally increased incidence of adenocarcinomas in the mammary gland in female rats (vehicle control, 1/50; low dose, 2/50; high dose, 5/50). These neoplasms are different from the principal neoplastic lesions observed in the Telone II® studies. Furthermore, the highest level of 1,2-dichloropropane that could be achieved with the dose regimen in the present studies is 2.5 mg/kg (i.e., 2.5% of the highest dose at 100 mg/kg) per administration. This level is approximately thirtyfold less than the dose levels used in the 1,2-dichloropropane study in which the dosing frequency was five times per week. Therefore, the 2.5% 1,2-dichloropropane in the Telone II® preparation was not considered to be responsible for any of the toxic responses.

Konishi et al. (1980) reported that male Wistar rats offered epichlorohydrin in drinking water at 0, 375, 750, or 1,500 ppm for 81 weeks developed forestomach hyperplasia (vehicle control, 0/10; low dose, 7/9; mid dose, 9/10; high dose, 12/12) and, at the two highest concentrations, forestomach papillomas (1/10, 7/12) and carcinomas (1/10, 2/12). Thus, forestomach hyperplasia was induced in male Wistar rats with long term intake of water containing as low as 0.375 mg epichlorohydrin/ml (i.e., 375 ppm), whereas forestomach papillomas and carcinomas were induced with 0.75-1.5 mg epichlorohydrin/ml water (750-1,500 ppm). In comparison, the present studies used 50 mg/kg Telone II® for rats and 100 mg/kg for mice as the high doses. Epichlorohydrin was present at a concentration of 1.0% in Telone II®; thus, the high dose rats or mice would have received epichlorohydrin at doses of 0.5 mg/kg or 1.0 mg/kg. Since the

gavage dose volume was 5 ml/kg, the epichlorohydrin concentrations for the high dose rats and mice would have been between 0.1 mg/ml or 0.2 mg/ml. Although these concentrations were several times lower than those calculated from the study by Konishi et al. (1980), the following factors suggest that epichlorohydrin, in addition to 1,3-dichloropropene, may have a role in the chronic toxicity (including carcinogenicity) in the present studies:

(1) The kinetics of a single gavage administration is such that the exposure to epichlorohydrin at the site of application is relatively brief but concentrated. In contrast, incorporation of epichlorohydrin in the drinking water means that the daily dose would be distributed throughout the day as the animals drink. The exposure, therefore, would be multiple and at lower epichlorohydrin concentrations. Thus, the gavage dosing in the Telone II® studies would probably produce epichlorohydrin concentrations at the site of application similar to those in the drinking water study by Konishi et al. (1980), albeit for much shorter periods.

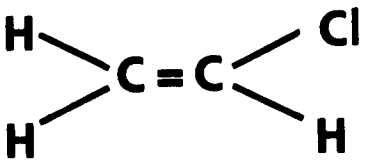
(2) The same lesions (e.g., forestomach hyperplasia, papillomas, carcinomas) were seen in both the study by Konishi et al. (1980) and the present studies.

Mutagenicity

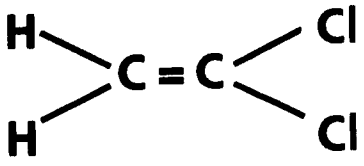
Recently Talcott and King (1984) demonstrated that purification of four separate preparations of 1,3-dichloropropene by silicic acid chromatography (which removes polar impurities) eliminated the mutagenicity of the preparations in *Salmonella typhimurium* strain TA100. The authors showed that purified 1,3-dichloropropene was not mutagenic. The unpurified preparations contained a mixture of polar impurities that accounted for the mutagenic activity of three of the four preparations. Two oxidation products of 1,3-dichloropropene were tentatively identified in one of the mixtures of polar impurities: these were epichlorohydrin and 1,3-dichloro-2-propanol--both of which are mutagenic in Salmonella (McCann et al., 1975; Stolzenberg and Hine, 1980). These results suggest that mutagenic impurities rather than 1,3-dichloropropene itself account for the mutagenic activity of preparations of 1,3-dichloropropene. Nonetheless, Telone II® was mutagenic in Salmonella strains TA100, TA1535, and TA1978 in the presence or absence of S9 (De Lorenzo et al., 1977).

Structure/Activity Relationships

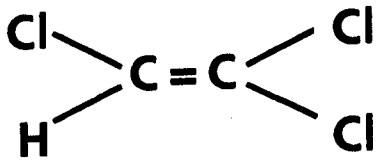
Chu and Milman (1981) have reviewed the carcinogenesis data on vinyl chloride (a structural analog of 1,3-dichloropropene), vinylidine chloride, trichloroethylene, 1,2-dichloroethane, 1,2-dibromoethane, tetrachloroethylene, and epichlorohydrin. These compounds have been shown to be carcinogenic in at least one study, although controversy regarding carcinogenicity for some of these compounds may still exist. The structural formulae of these compounds are presented in Figure 6. These chemicals have two common features: they are all small molecules with a short carbon chain, and they are all chlorinated or brominated. Chu and Milman (1981) pointed out that direct-acting compounds such as 1,2-dibromoethane, 1,2-dichloroethane, and epichlorohydrin produced forestomach tumors when given by gavage or nasal cavity tumors when given by inhalation. 1,2-Dibromoethane and 1,2-dichloroethane also induced tumors distant from the site of application. 1,3-Dichloropropene has an allylic carbon that should be reactive and could account for the induction of tumors of the forestomach. In addition, metabolic activation is probable at the carbon-carbon double bond. The development of tumors at locations distant from the site of application may be related to the formation of reactive intermediates.



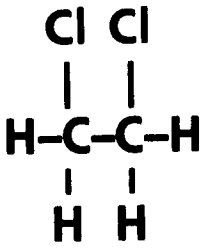
Vinyl Chloride



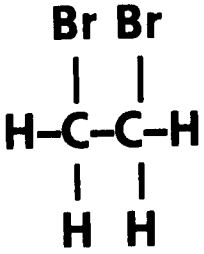
Vinylidine Chloride



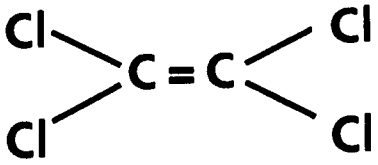
Trichloroethylene



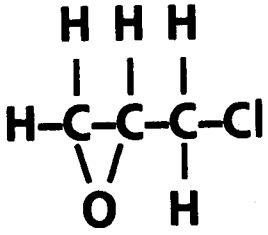
1,2-Dichloroethane



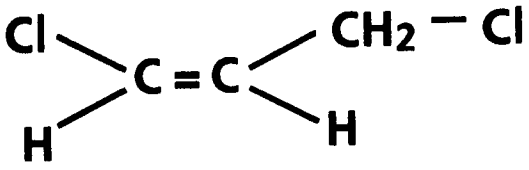
1,2-Dibromoethane (EDB)



Tetrachloroethylene



Epichlorohydrin



1,3-Dichloropropene
(*cis*-form shown)

FIGURE 6. STRUCTURES OF 1,3-DICHLOROPROPENE AND RELATED COMPOUNDS

Conclusions

Under the conditions of these gavage studies, there was *clear evidence of carcinogenicity** for male F344/N rats, as indicated by Telone II®-related increased incidences of squamous cell papillomas and carcinomas of the forestomach, as well as an increased incidence of neoplastic nodules of the liver. In female F344/N rats, there was *some evidence of carcinogenicity* because Telone II® caused an increased incidence of squamous cell papillomas of the forestomach. The experiment in male B6C3F$_1$ mice was considered to be an *inadequate study of carcinogenicity* because of reduced survival in the vehicle control group. However, there was some indication in the male mice of Telone II®-related increases of transitional cell carcinomas of the urinary bladder, squamous cell papillomas of the forestomach, and alveolar/bronchiolar adenomas and carcinomas of the lung. There was *clear evidence of carcinogenicity* for female B6C3F$_1$ mice, since Telone II® caused increased incidences of transitional cell carcinomas of the urinary bladder; Telone II® also increased the incidences of alveolar/bronchiolar adenomas of the lung and of squamous cell papillomas or carcinomas of the forestomach in the female mice. Telone II®-related nonneoplastic lesions included basal cell or epithelial cell hyperplasia in the forestomach of male and female rats and male and female mice and epithelial hyperplasia of the urinary bladder in male and female mice.

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

V. REFERENCES

V. REFERENCES

1. Abrahamson, S.; Lewis, E. (1971) The detection of mutations in *Drosophila melanogaster*. Hollaender, A., Ed.: Chemical Mutagens: Principles and Methods for Their Detection, Vol. 2. New York: Plenum Press, pp. 461-487.

2. Ames, B.; McCann, J.; Yamasaki, E. (1975) Methods for detecting carcinogens and mutagens with the *Salmonella*/mammalian-microsome mutagenicity test. Mutat. Res. 31:347-364.

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

4. Belser, N.; Castro, C. (1971) Biodehalogenation--the metabolism of the nematocides cis- and trans-3-chloroallyl alcohol by a bacterium isolated from soil. J. Agric. Food Chem. 19:23-26.

5. 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.

6. Berry, D.; Campbell, W.; Street, J.; Salunkhe, D. (1980) Uptake and metabolism of 1,3-dichloropropene in plants. J. Food Safety 4:247-255.

7. Boorman, G.; Montgomery, C., Jr.; Hardisty, J.; Eustis, S.; Wolfe, M.; McConnell, E. (1985) Quality assurance in pathology for rodent toxicology and carcinogenicity tests. Milman, H.; Weisburger, E., Eds.: Handbook of Carcinogen Testing. Park Ridge, NJ: Noyes Publications (in press).

8. Castro, C.; Belser, N. (1966) Hydrolysis of *cis*- and *trans*-1,3-dichloropropene in wet soil. J. Agric. Food Chem. 14:69-70.

9. Chu, K.; Milman, H. (1981) Review of experimental carcinogenesis by compounds related to vinyl chloride. Environ. Health Perspect. 41:211-220.

10. Chukovskaya, E.; Dostovolova, V.; Vasil'eva, T.; Freidlina, R. (1976) Org. Mag. Res. 8:229.

11. Climie, I.; Hutson, D.; Morrison, B.; Stoydin, G. (1979) Glutathione conjugation in the detoxication of (Z)-1,3-dichloropropene (a component of the nematocide D-D) in the rat. Xenobiotica 9:149-156.

12. Cohen, S.; Greenfield, R.; Friedell, G. (1982) Urinary bladder carcinogenesis. Pathobiol. Ann. 12:267-280.

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

14. De Lorenzo, F.; Degl'Innocenti, S.; Ruocco, A.; Silengo, L.; Cortese, R. (1977) Mutagenicity of pesticides containing 1,3-dichloropropene. Cancer Res. 37:1915-1917.

15. Dietz, F.; Hermann, E.; Ramsey, J. (1984a) The pharmacokinetics of ^{14}C-1,3-dichloropropene in rats and mice following oral administration. The Toxicologist 4:147 (Abstract No. 585).

16. Dietz, F.; Dittenber, D.; Kirk, H.; Ramsey, J. (1984b) Non-protein sulfhydryl content and macromolecular binding in rats and mice following administration of 1,3-dichloropropene. The Toxicologist 4:147 (Abstract No. 586).

17. Dow Chemical Co. (1983) Personal communication from Ms. Frances C. Omelia, Dow Chemical, to Dr. John A. Moore, NTP, June 16, 1983.

18. Flessel, P.; Goldsmith, J.; Kahn, E.; Wesolowski, J.; Maddy, K.; Peoples, S. (1978) Acute and possible long-term effects of 1,3-dichloropropene--California. Morbidity and Mortality Weekly Report 27:50, 55.

19. Gart, J.; Chu, K.; Tarone, R. (1979) Statistical issues in interpretation of chronic bioassay tests for carcinogenicity. J. Natl. Cancer Inst. 62(4):957-974.

20. Gosselin, R.; Hodge, H.; Smith, R.; Gleason, M. (1976) Clinical Toxicology of Commercial Products, 4th ed. Baltimore: Williams-Wilkins, pp. 119-121.

21. Graselli, J.; Ritchy, W., Eds. (1975) Atlas of Spectral Data and Physical Constants of Organic Compounds, 2nd ed. Cleveland: CRC Press, Inc., pp. 301, 2939-2940.

22. Haseman, J. (1984) Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies. Environ. Health Perspect. (in press).

23. Hicks, R. (1983) Multi-stage tumor development in the urinary bladder. 13th International Cancer Congress, Part B. Biology of Cancer 1:205-218.

24. Hutson, D., Moss, J.; Pickering, B. (1971) The excretion and retention of components of the soil fumigant D-D® and their metabolites in the rat. Food Cosmet. Toxicol. 9:677-680.

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

26. Kastenbaum, M.; Bowman, K. (1970) Tables for determining the statistical significance of mutation frequencies. Mutat. Res. 9:527-549.

27. Konishi, Y.; Kawabata, A.; Denda, A.; Ikeda, T.; Katada, H.; Maruyama, H.; Higashiguchi, R. (1980) Forestomach tumors induced by orally administered epichlorohydrin in male Wistar rats. Gann 71:922-923.

28. Laskin, S.; Sellakumar, A.; Kuschner, M.; Nelson, N.; La Mendola, S.; Rusch, G.; Katz, G.; Dulak, N.; Albert, R. (1980) Inhalation carcinogenicity of epichlorohydrin in noninbred Sprague-Dawley rats. J. Natl. Cancer Inst. 65:751-757.

29. Laskowski, D.; Goring, C.; McCall, P.; Swann, R. (1982) Terrestrial environment. Environ. Risk Anal. Chem. 25:198-240.

30. Leistra, M. (1970) Distribution of 1,3-dichloropropene over the phases in soil. J. Agric. Food Chem. 18:1124-1126.

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

32. Maddy, K.; Fong, H.; Lowe, J.; Conrad, D.; Fredrickson, A. (1982) A study of well water in selected California communities for residues of 1,3-dichloropropene, chloroallyl alcohol, and 49 organophosphate or chlorinated hydrocarbon pesticides. Bull. Environ. Contam. Toxicol. 29:354-359.

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

34. Margolin, B.; Collins, B.; Mason, J. (1983) Statistical analysis and sample-size determinations for mutagenicity experiments with binomial responses. Environ. Mutagen. 5:705-716.

35. Markovitz, A.; Crosby, W. (1984) Chemical carcinogenesis. A soil fumigant, 1,3-dichloropropene, as possible cause of hematologic malignancies. Arch. Intern. Med. 144:1409-1411.

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

37. McCann, J.; Choi, E.; Yamasaki, E.; Ames, B. (1975) Detection of carcinogens as mutagens in the Salmonella/microsome test: Assay of 300 chemicals. Proc. Natl. Acad. Sci. (USA) 72:5135-5139.

38. Merck Index (1968) 8th ed. Stecher, P.G., Ed. Rahway, NJ: Merck and Co., p. 353.

39. Metcalf, R. (1978) Fumigants. White-Stevens, R., Ed.: Pesticides in the Environment. New York: Marcel Dekker, Inc.

40. National Academy of Sciences (NAS) (1980) Histologic typing of liver tumors of the rat. J. Natl. Cancer Inst. 64:179-206.

41. National Toxicology Program (NTP) (1985) Carcinogenesis Studies of 1,2-Dichloropropane (Propylene Dichloride) (CAS No. 78-87-5) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies). NTP TR 263. Research Triangle Park, NC (in press).

42. Neudecker, T.; Stefani, A.; Henschler, D. (1977) In vitro mutagenicity of soil nematicide 1,3-dichloropropene. Experientia 33:1084-1085.

43. Parker, C.; Coate, W.; Voelker, R. (1982) Subchronic inhalation toxicity of 1,3-dichloropropene/1,2-dichloropropane (D-D)® in mice and rats. J. Toxicol. Environ. Health 9:899-910.

44. Peoples, S.; Maddy, K.; Cusick, W.; Jackson, T.; Cooper, C.; Frederickson, A. (1980) A study of samples of well water collected from selected areas in California to determine the presence of DBCP and certain other pesticide residues. Bull. Environ. Contam. Toxicol. 24:611-618.

45. Roberts, T.; Stoydin, G. (1976) The degradation of (*Z*)- and (*E*)-1,3-dichloropropene and 1,2-dichloropropane in soil. Pestic. Sci. 7:325-335.

46. Squire, R.; Levitt, M. (1975) Report of a workshop on classification of specific hepatocellular lesions in rats. Cancer Res. 35:3214-3223.

47. Stolzenberg, S.; Hine, C. (1980) Mutagenicity of 2- and 3-carbon halogenated compounds in the Salmonella/mammalian-microsome test. Environ. Mutagenesis 2:59-66.

48. Talcott, R.; King, J. (1984) Mutagenic impurities in 1,3-dichloropropene preparations. J. Natl. Cancer Inst. 72:1113-1116

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

50. Torkelson, T.; Oyen, F. (1977) The toxicity of 1,3-dichloropropene as determined by repeated exposure of laboratory animals. Am. Ind. Hyg. Assoc. J. 38:217-223.

51. Van Dijk, H. (1974) Degradation of 1,3-dichloropropenes in the soil. Agro-Ecosystems 1:193-204.

52. Van Duuren, B.L.; Goldschmidt, B.M.; Loewengart, G.; Smith, A.C.; Meichionne, S.; Seldman, I.; Roth, D. (1979) Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. J. Natl. Cancer Inst. 63:1433-1439.

53. Weast, R. (1976) Chemical Rubber Handbook. Boca Raton, FL: CRC Press Inc.

54. Williams, I. (1968) Recovery of *cis*- and *trans*-dichloropropene residues from two types of soil and their detection and determination by electron capture gas chromatography. J. Econ. Entomol. 61:1432-1435.

55. Woodruff, R.; Mason, J.; Valencia, R; Zimmering, S. (1984) Chemical mutagenesis testing in Drosophila: I. Comparison of positive and negative control data for sex-linked recessive lethal mutations and reciprocal translocations in three laboratories. Environ. Mutagen. 6:189-202.

56. Yahagi, T.; Degawa, M.; Seino, Y.; Matsushima, T.; Nagao, M.; Sugimura, T.; Hashimoto, Y. (1975) Mutagenicity of carcinogenic azo dyes and their derivatives. Cancer Lett. 1:91-96.

APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF TELONE II®

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	52	52	52
ANIMALS NECROPSIED	52	52	52
ANIMALS EXAMINED HISTOPATHOLOGICALLY	52	52	52
INTEGUMENTARY SYSTEM			
*ABDOMINAL CAVITY	(52)	(52)	(52)
FIBROUS HISTIOCYTOMA, MALIGNANT		1 (2%)	
*SKIN	(52)	(52)	(52)
SQUAMOUS CELL CARCINOMA		1 (2%)	
BASAL-CELL CARCINOMA	1 (2%)		1 (2%)
TRICHOEPITHELIOMA		1 (2%)	1 (2%)
*SUBCUT TISSUE	(52)	(52)	(52)
FIBROMA	3 (6%)	1 (2%)	
FIBROUS HISTIOCYTOMA, MALIGNANT			1 (2%)
LEIOMYOSARCOMA		1 (2%)	
NEURILEMOMA, MALIGNANT			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(52)	(52)	(52)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	2 (4%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)		
C-CELL CARCINOMA, METASTATIC		2 (4%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(52)	(52)	(52)
MALIGNANT LYMPHOMA, NOS			1 (2%)
MONOCYTIC LEUKEMIA	12 (23%)	12 (23%)	10 (19%)
#BONE MARROW	(52)	(52)	(52)
SARCOMA, NOS			1 (2%)
#SPLEEN	(52)	(52)	(52)
MONOCYTIC LEUKEMIA	1 (2%)		
#LYMPH NODE	(52)	(52)	(52)
C-CELL CARCINOMA, METASTATIC		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
*TONGUE	(52)	(52)	(52)
SQUAMOUS CELL PAPILLOMA			2 (4%)
#LIVER	(52)	(52)	(52)
NEOPLASTIC NODULE	1 (2%)	6 (12%)	7 (13%)
HEPATOCELLULAR CARCINOMA			1 (2%)
SARCOMA, NOS, METASTATIC			1 (2%)
FIBROUS HISTIOCYTOMA, METASTATIC			1 (2%)
#PANCREAS	(52)	(52)	(52)
ACINAR-CELL ADENOMA	2 (4%)		2 (4%)
#STOMACH	(52)	(52)	(52)
SQUAMOUS CELL PAPILLOMA	1 (2%)		8 (15%)
SQUAMOUS CELL CARCINOMA			4 (8%)
#FORESTOMACH	(52)	(52)	(52)
SQUAMOUS CELL PAPILLOMA		1 (2%)	1 (2%)
URINARY SYSTEM			
#KIDNEY	(52)	(52)	(52)
TUBULAR-CELL ADENOCARCINOMA			1 (2%)
LIPOSARCOMA		1 (2%)	

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(52)	(50)	(50)
CARCINOMA,NOS			1 (2%)
ADENOMA, NOS	1 (2%)		
CHROMOPHOBE ADENOMA	23 (44%)	13 (26%)	16 (32%)
ACIDOPHIL ADENOMA		1 (2%)	
#ADRENAL	(52)	(52)	(52)
CORTICAL ADENOMA	2 (4%)	1 (2%)	
PHEOCHROMOCYTOMA	2 (4%)	7 (13%)	6 (12%)
#ADRENAL MEDULLA	(52)	(52)	(52)
PHEOCHROMOCYTOMA		1 (2%)	
#THYROID	(52)	(51)	(51)
FOLLICULAR-CELL ADENOMA		2 (4%)	
FOLLICULAR-CELL CARCINOMA		2 (4%)	1 (2%)
C-CELL ADENOMA	3 (6%)		2 (4%)
C-CELL CARCINOMA	3 (6%)	4 (8%)	2 (4%)
#PARATHYROID	(39)	(32)	(39)
CARCINOMA,NOS			1 (3%)
ADENOMA, NOS	1 (3%)		
#PANCREATIC ISLETS	(52)	(52)	(52)
ISLET-CELL ADENOMA	10 (19%)	7 (13%)	9 (17%)
ISLET-CELL CARCINOMA	2 (4%)	6 (12%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(52)	(52)	(52)
FIBROADENOMA	1 (2%)	5 (10%)	1 (2%)
*PREPUTIAL GLAND	(52)	(52)	(52)
CARCINOMA,NOS	1 (2%)		
ADENOMA, NOS			1 (2%)
ADENOCARCINOMA, NOS	2 (4%)		
#TESTIS	(52)	(52)	(52)
INTERSTITIAL-CELL TUMOR	46 (88%)	46 (88%)	48 (92%)
NERVOUS SYSTEM			
#BRAIN	(52)	(52)	(52)
GLIOMA, NOS		1 (2%)	
OLIGODENDROGLIOMA		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*LUMBAR VERTEBRA	(52)	(52)	(52)
OSTEOSARCOMA			1 (2%)
BODY CAVITIES			
*ABDOMINAL CAVITY	(52)	(52)	(52)
RHABDOMYOSARCOMA		1 (2%)	
*TUNICA VAGINALIS	(52)	(52)	(52)
MESOTHELIOMA, NOS	2 (4%)	1 (2%)	1 (2%)
MESOTHELIOMA, MALIGNANT	1 (2%)		2 (4%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(52)	(52)	(52)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)
MALIGNANT MELANOMA, METASTATIC	1 (2%)		
FIBROUS HISTIOCYTOMA, METASTATIC		1 (2%)	
MESOTHELIOMA, MALIGNANT		1 (2%)	
OSTEOSARCOMA, METASTATIC		1 (2%)	1 (2%)
SITE UNKNOWN			
ADENOCARCINOMA, NOS			1
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	52	52	52
NATURAL DEATH	8	12	10
MORIBUND SACRIFICE		2	1
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	42	37	40
DOSING ACCIDENT	2	1	1
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS			
ANIMAL MISSING			
ANIMAL MISSEXED			
OTHER CASES			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	51	47	50
TOTAL PRIMARY TUMORS	123	127	135
TOTAL ANIMALS WITH BENIGN TUMORS	50	46	49
TOTAL BENIGN TUMORS	96	88	97
TOTAL ANIMALS WITH MALIGNANT TUMORS	23	26	27
TOTAL MALIGNANT TUMORS	24	32	30
TOTAL ANIMALS WITH SECONDARY TUMORS##	1	5	4
TOTAL SECONDARY TUMORS	1	5	4
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	3	7	8
TOTAL UNCERTAIN TUMORS	3	7	8
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TELONE II®

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	52	52	52
ANIMALS NECROPSIED	52	52	52
ANIMALS EXAMINED HISTOPATHOLOGICALLY	52	52	52
INTEGUMENTARY SYSTEM			
*SKIN	(52)	(52)	(52)
SQUAMOUS CELL CARCINOMA			1 (2%)
*SUBCUT TISSUE	(52)	(52)	(52)
FIBROMA		1 (2%)	
RHABDOMYOSARCOMA	1 (2%)		
CARCINOSARCOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(52)	(52)	(52)
ALVEOLAR/BRONCHIOLAR ADENOMA			2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	1 (2%)	1 (2%)
GRANULOSA-CELL CARCINOMA, METAST			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(52)	(52)	(52)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
MONOCYTIC LEUKEMIA	9 (17%)	9 (17%)	5 (10%)
LEUKEMIA, MONONUCLEAR CELL		1 (2%)	
#MANDIBULAR L. NODE	(52)	(52)	(52)
CARCINOSARCOMA, INVASIVE			1 (2%)
#THYMUS	(52)	(52)	(50)
THYMOMA		1 (2%)	
CIRCULATORY SYSTEM			
#SPLEEN	(52)	(51)	(52)
HEMANGIOSARCOMA			1 (2%)
DIGESTIVE SYSTEM			
*TONGUE	(52)	(52)	(52)
SQUAMOUS CELL CARCINOMA	1 (2%)		
#LIVER	(52)	(52)	(52)
NEOPLASTIC NODULE	6 (12%)	6 (12%)	10 (19%)
#PANCREAS	(52)	(52)	(52)
FIBROSARCOMA, METASTATIC			1 (2%)
#STOMACH	(52)	(52)	(52)
SQUAMOUS CELL PAPILLOMA		2 (4%)	3 (6%)
URINARY SYSTEM			
#URINARY BLADDER	(52)	(52)	(52)
TRANSITIONAL-CELL CARCINOMA	1 (2%)		
ADENOMATOUS POLYP, NOS		1 (2%)	

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TELONE II® (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(51)	(52)
CHROMOPHOBE ADENOMA	28 (56%)	26 (51%)	30 (58%)
CHROMOPHOBE CARCINOMA	2 (4%)	1 (2%)	1 (2%)
#ADRENAL	(52)	(52)	(52)
CORTICAL ADENOMA	2 (4%)		1 (2%)
CORTICAL CARCINOMA		1 (2%)	
PHEOCHROMOCYTOMA	1 (2%)	2 (4%)	
#THYROID	(52)	(52)	(52)
FOLLICULAR-CELL ADENOMA		1 (2%)	2 (4%)
FOLLICULAR-CELL CARCINOMA		1 (2%)	2 (4%)
C-CELL ADENOMA	4 (8%)	6 (12%)	2 (4%)
C-CELL CARCINOMA	2 (4%)	2 (4%)	1 (2%)
#PANCREATIC ISLETS	(52)	(52)	(52)
ISLET-CELL ADENOMA	3 (6%)	1 (2%)	
ISLET-CELL CARCINOMA			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(52)	(52)	(52)
ADENOMA, NOS	1 (2%)		
ADENOCARCINOMA, NOS	2 (4%)		1 (2%)
FIBROADENOMA	14 (27%)	20 (38%)	24 (46%)
*PREPUTIAL GLAND	(52)	(52)	(52)
CARCINOMA,NOS		1 (2%)	2 (4%)
*CLITORAL GLAND	(52)	(52)	(52)
CARCINOMA,NOS		1 (2%)	
ADENOMA, NOS		1 (2%)	
#UTERUS	(52)	(52)	(52)
ADENOCARCINOMA, NOS			1 (2%)
LEIOMYOMA	1 (2%)		
ENDOMETRIAL STROMAL POLYP	16 (31%)	10 (19%)	12 (23%)
ENDOMETRIAL STROMAL SARCOMA	2 (4%)		
#OVARY	(52)	(52)	(52)
GRANULOSA-CELL CARCINOMA			1 (2%)
FIBROSARCOMA			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*ZYMBAL GLAND	(52)	(52)	(52)
CARCINOMA,NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(52)	(52)	(52)
LEIOMYOSARCOMA, METASTATIC			1 (2%)
SITE UNKNOWN			
LEIOMYOSARCOMA			1

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

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TELONE II® (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	52	52	52
NATURAL DEATH	16	13	13
MORIBUND SACRIFICE	1		1
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	34	35	38
DOSING ACCIDENT	1	3	
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS		1	
ANIMAL MISSING			
ANIMAL MISSEXED			
OTHER CASES			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	45	44	44
TOTAL PRIMARY TUMORS	98	96	108
TOTAL ANIMALS WITH BENIGN TUMORS	38	39	39
TOTAL BENIGN TUMORS	70	72	76
TOTAL ANIMALS WITH MALIGNANT TUMORS	18	15	19
TOTAL MALIGNANT TUMORS	22	18	22
TOTAL ANIMALS WITH SECONDARY TUMORS##			4
TOTAL SECONDARY TUMORS			4
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	6	6	10
TOTAL UNCERTAIN TUMORS	6	6	10
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TELONE II®: VEHICLE CONTROL

ANIMAL NUMBER	00011	00035	00057	00079	00111	00135	00157	00179	00211	00235	00257	00291	00311	00335	00357	00391	00411	00435	00457	00499
WEEKS ON STUDY	10707	10707	10707	10707	09707	10707	10707	10707	10707	10707	10606	10707	00101	10707	10708	10907	10707	10707	08202	07808	10707
INTEGUMENTARY SYSTEM																					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																					
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																					
RESPIRATORY SYSTEM																					
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					
Alveolar/bronchiolar carcinoma											X										
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																					
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Monocytic leukemia															X						
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
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																X					
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																					
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																					
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																					
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS									X												
Chromophobe adenoma							X	X	X			X		X			X		X	X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma		X																			
Pheochromocytoma			X																		
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma						X															
C-cell carcinoma			X																		X
Parathyroid	+	+	+	+	+	+	–	+	+	–	–	+	+	+	–	–	+	–	+	+	–
Adenoma, NOS					X																
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma		X					X		X									X			
Islet cell carcinoma																X					
REPRODUCTIVE SYSTEM																					
Mammary gland	+	+	+	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
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
Carcinoma, NOS			X																		
Adenocarcinoma, NOS																	X				
NERVOUS SYSTEM																					
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BODY CAVITIES																					
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS			X							X											
Mesothelioma, malignant																			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
Malignant melanoma, metastatic																			X		
Monocytic leukemia							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 A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0051	0053	0055	0057	0059	0061	0063	0065	0067	0069	0071	0073	0075	0077	0079	0081	0083	0085	0087	0089	0091	0093	0095	0097	0099	0101	0103	TOTAL
WEEKS ON STUDY	107	107	107	107	107	107	107	107	107	107	107	107	105	107	107	107	092	107	107	107	049	094	107	108	108	108	108	TISSUES TUMORS
INTEGUMENTARY SYSTEM																												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Basal cell carcinoma																											X	1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Fibroma	X														X								X					3
RESPIRATORY SYSTEM																												
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Alveolar/bronchiolar adenoma																											X	1
Alveolar/bronchiolar carcinoma																												1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
HEMATOPOIETIC SYSTEM																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Monocytic leukemia																												1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																												
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
DIGESTIVE SYSTEM																												
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Neoplastic nodule																												1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Acinar cell adenoma								X																				2
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Squamous cell papilloma												X																1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
URINARY SYSTEM																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
ENDOCRINE SYS																												
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenoma, NOS																												1
Chromophobe adenoma		X		X		X	X									X	X	X		X	X		X	X	X		X	23
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Cortical adenoma		X																										2
Pheochromocytoma						X																						2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
C-cell adenoma											X							X										3
C-cell carcinoma				X																								3
Parathyroid	-	+	+	-	-	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	-	+	+	+	39
Adenoma, NOS																												1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Islet cell adenoma						X			X								X						X	X	X			10
Islet cell carcinoma										X																		2
REPRODUCTIVE SYSTEM																												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	*52
Fibroadenoma																				X								1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
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	X	46
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
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	N	N	*52
Carcinoma, NOS																												1
Adenocarcinoma, NOS	X																											2
NERVOUS SYSTEM																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
BODY CAVITIES																												
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Mesothelioma, NOS																												2
Mesothelioma, malignant																												1
ALL OTHER SYSTEMS																												
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Malignant melanoma, metastatic																												1
Monocytic leukemia		X			X				X		X	X	X					X							X			12

* Animals Necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TELONE II®: LOW DOSE

ANIMAL NUMBER	20 01	20 03	20 05	20 07	20 09	21 11	21 13	21 15	21 17	21 19	22 21	22 23	22 25	22 27	22 29	23 31	23 33	23 35	23 37	23 39	24 41	24 43	24 45	24 47	24 49
WEEKS ON STUDY	10 06	10 02	06 03	10 06	00 03	00 02	10 04	10 06	10 06	10 06	10 06	10 06	10 06	10 06	10 04	10 06	10 06	10 06	09 04	10 06	10 06	10 06	10 00	10 06	10 06
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																							X		
Trichoepithelioma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																							X		
Leiomyosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X								X					
C-cell carcinoma, metastatic				X																					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell carcinoma, metastatic																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liposarcoma		X																							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chromophobe adenoma								X			X	X	X		X										
Acidophil adenoma																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma															X						X				
Thyroid	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma										X															
Follicular cell carcinoma				X																					
C-cell carcinoma				X																					
Parathyroid	–	+	–	+	+	+	–	–	+	+	–	–	–	+	+	+	–	+	+	+	+	+	–	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma		X		X																					
Islet cell carcinoma															X		X				X				
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma, NOS																									
Oligodendroglioma																									
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
Fibrous histiocytoma, malignant																			X						
Rhabdomyosarcoma																									
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						
Mesothelioma, malignant																									
Osteosarcoma, metastatic																									
Monocytic leukemia							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 A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	25 51	25 53	25 55	25 57	25 59	26 01	26 03	26 05	26 07	26 09	27 01	27 03	27 05	27 07	27 09	28 01	28 03	28 05	28 07	28 09	29 01	29 03	29 05	29 07	29 09	30 01	30 03	TOTAL
WEEKS ON STUDY	10 06	10 06	10 06	10 06	08 00	09 02	10 06	10 06	10 06	10 06	08 09	10 06	10 06	10 06	10 06	10 07	10 07	10 07	10 07	10 07	10 07	10 07	10 07	10 07	10 07	09 02	09 02	TISSUES TUMORS
INTEGUMENTARY SYSTEM																												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Squamous cell carcinoma																		X										1
Trichoepithelioma																												1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Fibroma																												1
Leiomyosarcoma																					X							1
RESPIRATORY SYSTEM																												
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Alveolar/bronchiolar adenoma																												2
C-cell carcinoma, metastatic										X																		2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
HEMATOPOIETIC SYSTEM																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
C-cell carcinoma, metastatic																					X							1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
CIRCULATORY SYSTEM																												
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
DIGESTIVE SYSTEM																												
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Neoplastic nodule								X								X		X		X	X							6
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Squamous cell papilloma																								X				1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
URINARY SYSTEM																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Liposarcoma																												1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
ENDOCRINE SYSTEM																												
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	50
Chromophobe adenoma							X		X	X			X		X						X	X				X		13
Acidophil adenoma											X																	1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Cortical adenoma																				X								1
Pheochromocytoma	X											X			X	X		X						X				8
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Follicular cell adenoma													X															2
Follicular cell carcinoma																								X				2
C-cell carcinoma								X		X												X						4
Parathyroid	+	+	+	–	–	–	–	+	+	+	+	+	+	–	–	+	–	+	+	–	–	+	+	+	+	–	+	32
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Islet cell adenoma				X												X	X				X			X				7
Islet cell carcinoma		X											X					X										6
REPRODUCTIVE SYSTEM																												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Fibroadenoma				X			X													X				X				5
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
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	X		46
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
NERVOUS SYSTEM																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Glioma, NOS																								X				1
Oligodendroglioma																					X							1
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	N	N	*52
Fibrous histiocytoma, malignant																												1
Rhabdomyosarcoma																										X		1
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
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	N	N	*52
Fibrous histiocytoma, metastatic																												1
Mesothelioma, malignant																		X										1
Osteosarcoma, metastatic					X																							1
Monocytic leukemia	X			X						X					X	X									X			12

* Animals Necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TELONE II®: HIGH DOSE

ANIMAL NUMBER	401	403	405	407	409	411	413	415	417	419	421	423	425	427	429	431	433	435	437	439	441	443	445	447	449
WEEKS ON STUDY	106	106	106	106	106	106	106	096	106	106	089	106	106	106	106	085	106	106	106	106	106	106	106	053	106
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Trichoepithelioma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, malignant																									
Neurilemoma, malignant											X														
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																		X							
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										X													
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule						X			X	X			X												
Hepatocellular carcinoma																									
Sarcoma, NOS, metastatic																		X							
Fibrous histiocytoma, metastatic																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma												X								X					
Squamous cell carcinoma	X		X											X											
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–
Carcinoma, NOS												X													
Chromophobe adenoma			X	X		X			X					X		X									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma		X						X		X															
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																									
C-cell adenoma					X																X				
C-cell carcinoma																									
Parathyroid	–	+	+	+	+	+	+	–	+	–	+	+	+	–	+	–	–	+	–	+	+	+	+	+	+
Carcinoma, NOS																									
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma			X						X					X		X					X				
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	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																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Osteosarcoma																								X	
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS											X														
Mesothelioma, malignant																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												
Osteosarcoma, metastatic																								X	
Malignant lymphoma, NOS																									
Monocytic leukemia	X			X					X	X			X												
Site unknown																									
Adenocarcinoma, NOS													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 A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	4 6 1	4 5 3	4 5 5	4 5 7	4 5 9	4 6 1	4 6 3	4 6 5	4 6 7	4 6 9	4 7 1	4 7 3	4 7 5	4 7 7	4 7 9	4 8 1	4 8 3	4 8 5	4 8 7	4 8 9	4 9 1	4 9 3	4 9 5	4 9 7	4 9 9	5 0 1	5 0 3	TOTAL
WEEKS ON STUDY	1 0 8	1 0 8	1 0 8	0 8 8	1 0 6	0 2 8	0 9 9	0 9 7	0 8 6	1 0 1	1 0 6	1 0 6	1 0 6	1 0 6	1 0 8	0 1 2	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	0 9 3	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	TISSUES TUMORS
INTEGUMENTARY SYSTEM																												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Basal cell carcinoma															X													1
Trichoepithelioma		X																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Fibrous histiocytoma, malignant	X																											1
Neurilemoma, malignant																												1
RESPIRATORY SYSTEM																												
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
HEMATOPOIETIC SYSTEM																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Sarcoma, NOS																												1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
CIRCULATORY SYSTEM																												
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
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	N	N	*52
Squamous cell papilloma																												2
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Neoplastic nodule													X							X					X		7
Hepatocellular carcinoma					X																							1
Sarcoma, NOS, metastatic																												1
Fibrous histiocytoma, metastatic	X																											1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Acinar cell adenoma																		X			X							2
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Squamous cell papilloma					X					X							X					X	X		X	X	9
Squamous cell carcinoma																											X	4
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
URINARY SYSTEM																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Tubular cell adenocarcinoma																			X									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
ENDOCRINE SYSTEM																												
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																												1
Chromophobe adenoma		X		X			X				X		X	X				X					X		X	X	10
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Pheochromocytoma							X														X	X						6
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Follicular cell carcinoma										X																		1
C-cell adenoma																												2
C-cell carcinoma														X			X											2
Parathyroid	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	-	+	-	+	+	+	-	+	+	+	+	-	39
Carcinoma, NOS								X																				1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Islet cell adenoma	X							X										X										3
REPRODUCTIVE SYSTEM																												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Fibroadenoma																												1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*	+	+	+	+	+	+	+	+	+	+	+	46
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	53
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
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	N	N	*52
Adenoma, NOS			X																									1
NERVOUS SYSTEM																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
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	N	N	*52
Osteosarcoma																												1
BODY CAVITIES																												
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Mesothelioma, NOS																												1
Mesothelioma, malignant																				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	N	N	*52
Adenocarcinoma, NOS, metastatic																												1
Osteosarcoma, metastatic																												1
Malignant lymphoma, NOS									X																			1
Monocytic leukemia			X																	X	X	X			X			10
Site unknown																												
Adenocarcinoma, NOS																												1

*Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TELEONE II®: VEHICLE CONTROL

ANIMAL NUMBER	0002	0004	0006	0008	0010	0012	0014	0016	0018	0020	0022	0024	0026	0028	0030	0032	0034	0036	0038	0040	0042	0044	0046	0048	0050
WEEKS ON STUDY	108	084	108	099	108	108	108	108	108	098	097	108	108	102	108	097	108	075	002	108	108	108	108	091	108
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rhabdomyosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
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 carcinoma											X														
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule								X								X				X		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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chromophobe adenoma			X		X		X	X				X	X	X						X	X	X	X		X
Chromophobe carcinoma		X																							
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																X									
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma			X						X																
C-cell carcinoma										X															
Parathyroid	+	–	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma														X			X								
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adenocarcinoma, NOS																									
Fibroadenoma								X					X			X	X			X					
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Endometrial stromal polyp					X			X	X	X				X	X						X	X		X	
Endometrial stromal sarcoma							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
Malignant lymphoma, NOS																									
Monocytic leukemia														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 A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL
(Continued)

ANIMAL NUMBER	0052	0054	0056	0058	0060	0062	0064	0066	0068	0070	0072	0074	0076	0078	0080	0082	0084	0086	0088	0090	0092	0094	0096	0098	0100	0102	0104	TOTAL
WEEKS ON STUDY	108	108	102	108	080	094	108	108	108	090	108	108	108	101	100	049	108	108	108	108	108	108	096	099	067	108	108	TISSUES TUMORS
INTEGUMENTARY SYSTEM																												
Subcutaneous tissue																												*52
Rhabdomyosarcoma																												1
RESPIRATORY SYSTEM																												
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Alveolar/bronchiolar carcinoma													X															1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
HEMATOPOIETIC SYSTEM																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	51
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
CIRCULATORY SYSTEM																												
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
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	N	N	*52
Squamous cell carcinoma																												1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Neoplastic nodule																		X										6
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Large intestine	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	50
URINARY SYSTEM																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Transitional cell carcinoma										X																		1
ENDOCRINE SYSTEM																												
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	50
Chromophobe adenoma		X		X	X	X	X	X	X		X			X	X		X	X		X		X	X				X	28
Chromophobe carcinoma			X																									2
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Cortical adenoma												X																2
Pheochromocytoma			X																									1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
C-cell adenoma			X																								X	4
C-cell carcinoma																					X							2
Parathyroid	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–		46
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–		52
Islet cell adenoma																					X							3
REPRODUCTIVE SYSTEM																												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Adenoma, NOS					X																							1
Adenocarcinoma, NOS											X						X											2
Fibroadenoma		X	X	X													X	X				X	X	X			X	14
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Leiomyoma						X																						1
Endometrial stromal polyp					X				X		X				X			X			X	X						16
Endometrial stromal sarcoma																												2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
NERVOUS SYSTEM																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
ALL OTHER SYSTEMS																												
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Malignant lymphoma, NOS																								X				1
Monocytic leukemia					X	X			X		X			X	X						X							9

* Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TELEONE II®: LOW DOSE

ANIMAL NUMBER	202	204	206	208	210	212	214	216	218	220	222	224	226	228	230	232	234	236	238	240	242	244	246	248	250
WEEKS ON STUDY	107	107	087	107	107	107	107	107	103	087	107	107	107	107	107	102	107	012	107	107	083	075	107	107	106
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma												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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma			X	X																					
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS													X												
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Chromophobe adenoma			X			X	X		X	X			X	X		X	X			X		X			
Chromophobe carcinoma																					X				
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical carcinoma								X																	
Pheochromocytoma																								X	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Follicular cell carcinoma								X																	
C-cell adenoma												X	X						X						
C-cell carcinoma																									
Parathyroid	+	–	+	–	+	–	+	–	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	–	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma				X																					
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma					X	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	N
Carcinoma, NOS																	X								
Adenoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Monocytic leukemia								X	X																
Leukemia, mononuclear cell																									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 A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	25252	25546	25588	26802	26624	26666	26868	27040	27212	27476	27678	28090	28202	28414	28668	28810	29021	29494	29668	29808	30002	30404	TOTAL
WEEKS ON STUDY	10707	10115	10901	10907	10707	10907	10701	10804	10707	10701	10911	10707	10707	10707	10707	10327	10808	10558	10908	10808	10808	10808	TISSUES TUMORS
INTEGUMENTARY SYSTEM																							
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Fibroma													X										1
RESPIRATORY SYSTEM																							
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Alveolar/bronchiolar carcinoma																							1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
HEMATOPOIETIC SYSTEM																							
Bone marrow	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spleen	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Thymoma								X															1
CIRCULATORY SYSTEM																							
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
DIGESTIVE SYSTEM																							
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Neoplastic nodule	X						X										X			X			6
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
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	*52
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Squamous cell papilloma																							2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Large intestine	+	+	+	+	+	+	+	+	–	–	–	+	+	+	–	+	+	+	+	+	+	+	48
URINARY SYSTEM																							
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenomatous polyp, NOS																							1
ENDOCRINE SYSTEM																							
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Chromophobe adenoma	X			X	X	X	X	X	X	X	X			X	X	X		X			X		26
Chromophobe carcinoma																							1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Cortical carcinoma																							1
Pheochromocytoma													X										2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Follicular cell adenoma											X												1
Follicular cell carcinoma																							1
C-cell adenoma						X			X					X									6
C-cell carcinoma					X			X															2
Parathyroid	+	–	+	+	–	+	+	+	+	+	+	+	+	+	–	–	+	–	+	–	+	+	39
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Islet cell adenoma																							1
REPRODUCTIVE SYSTEM																							
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Fibroadenoma					X			X							X	X		X			X	X	20
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	*52
Carcinoma, NOS																						X	2
Adenoma, NOS																			X				1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Endometrial stromal polyp					X		X		X				X		X	X					X		10
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
NERVOUS SYSTEM																							
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
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	*52
Monocytic leukemia				X								X		X					X	X		X	9
Leukemia, mononuclear cell								X															1

* Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TELONE II®: HIGH DOSE

ANIMAL NUMBER	402	404	406	408	410	412	414	416	418	420	422	424	426	428	430	432	434	436	438	440	442	444	446	448	450
WEEKS ON STUDY	106	106	106	106	099	080	106	106	106	097	106	098	106	106	106	106	106	081	106	106	104	106	106	094	106
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma						X																			
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma									X																
Alveolar/bronchiolar carcinoma								X																	
Granulosa cell carcinoma, metas																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma									X																
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinosarcoma, *invasive*																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule	X		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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic					X																				
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chromophobe adenoma			X		X				X			X	X						X	X	X	X	X	X	X
Chromophobe carcinoma																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Follicular cell carcinoma												X													
C-cell adenoma						X																			
C-cell carcinoma																				X					
Parathyroid	+	+	+	+	–	+	–	+	+	–	+	–	–	–	–	+	+	+	+	+	+	+	+	+	+
Pancreatic *islets*	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell carcinoma																	X								
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Fibroadenoma	X	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	N
Carcinoma, NOS							X		X																
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS					X																				
Endometrial stromal polyp				X															X			X			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell carcinoma																									
Fibrosarcoma					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																									
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
Leiomyosarcoma, metastatic																		X							
Monocytic leukemia										X										X					
Site unknown																									
Leiomyosarcoma																		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 A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	45 52	45 54	45 56	45 58	46 60	46 62	46 64	46 66	46 68	47 10	47 12	47 74	47 76	47 78	48 00	48 02	48 04	48 06	48 08	49 00	49 92	49 94	49 96	49 98	50 00	50 02	50 04	TOTAL
WEEKS ON STUDY	10 06	10 06	10 06	10 06	10 06	10 06	09 91	09 97	07 79	10 06	10 06	10 06	10 06	10 06	10 06	10 06	10 06	10 06	10 06	10 06	10 06	09 92	10 06	09 94	10 06	07 77	10 03	TISSUES TUMORS
INTEGUMENTARY SYSTEM																												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Squamous cell carcinoma																												1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Carcinosarcoma																				X								1
RESPIRATORY SYSTEM																												
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Alveolar/bronchiolar adenoma										X																		2
Alveolar/bronchiolar carcinoma																												1
Granulosa cell carcinoma, metastatic																									X			1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
HEMATOPOIETIC SYSTEM																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Hemangiosarcoma																												1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Carcinosarcoma, invasive																				X								1
Thymus	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	50
CIRCULATORY SYSTEM																												
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
DIGESTIVE SYSTEM																												
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Neoplastic nodule	X	X			X							X		X				X							X			10
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*52
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Fibrosarcoma, metastatic																												1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Squamous cell papilloma					X		X										X											3
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
URINARY SYSTEM																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
ENDOCRINE SYSTEM																												
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Chromophobe adenoma	X	X	X		X	X		X		X	X	X	X	X	X		X	X			X		X		X		X	30
Chromophobe carcinoma																						X						1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Cortical adenoma						X																						1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Follicular cell adenoma		X											X															2
Follicular cell carcinoma	X																											2
C-cell adenoma				X																								2
C-cell carcinoma																												1
Parathyroid	–	+	+	+	+	+	–	–	+	–	+	–	–	+	+	–	–	+	+	+	+	+	+	+	+	+	+	37
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Islet cell carcinoma																												1
REPRODUCTIVE SYSTEM																												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*52
Adenocarcinoma, NOS														X														1
Fibroadenoma			X		X			X	X		X	X	X		X			X			X				X			24
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	N	N	*52
Carcinoma, NOS																												2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Adenocarcinoma, NOS																												1
Endometrial stromal polyp	X			X	X					X	X	X	X				X	X										12
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	52
Granulosa cell carcinoma																									X			1
Fibrosarcoma																												1
NERVOUS SYSTEM																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
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	N	*52
Carcinoma, 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	N	N	*52
Leiomyosarcoma, metastatic																												1
Monocytic leukemia					X																			X		X		5
Site unknown																												
Leiomyosarcoma																												1

*Animals Necropsied

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF TELONE II®

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TELONE II®

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
LEIOMYOSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
ADENOCARCINOMA, NOS, UNC PRIM OR MET			1 (2%)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	11 (22%)	9 (18%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		2 (4%)	3 (6%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS		2 (4%)	2 (4%)
#SPLEEN	(50)	(49)	(49)
MALIGNANT LYMPHOMA, NOS		2 (4%)	2 (4%)
#LYMPH NODE	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
CIRCULATORY SYSTEM			
#BONE MARROW	(49)	(49)	(50)
HEMANGIOSARCOMA		1 (2%)	
#SPLEEN	(50)	(49)	(49)
HEMANGIOMA		3 (6%)	
HEMANGIOSARCOMA	1 (2%)	2 (4%)	1 (2%)
#THYMUS	(49)	(48)	(47)
HEMANGIOSARCOMA		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
HEPATOCELLULAR ADENOMA	1 (2%)	1 (2%)	3 (6%)
HEPATOCELLULAR CARCINOMA	4 (8%)	6 (12%)	10 (20%)
#STOMACH	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		2 (4%)	3 (6%)
URINARY SYSTEM			
#URINARY BLADDER	(50)	(50)	(50)
TRANSITIONAL-CELL CARCINOMA			2 (4%)
ENDOCRINE SYSTEM			
#PITUITARY	(42)	(48)	(45)
CHROMOPHOBE ADENOMA		1 (2%)	
#ADRENAL	(50)	(50)	(48)
CORTICAL ADENOMA	1 (2%)		2 (4%)
#PANCREATIC ISLETS	(50)	(50)	(50)
ISLET-CELL ADENOMA	1 (2%)		
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TELONE II® (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(50)	(50)	(50)
ADENOMA, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
HEPATOCELLULAR CARCINOMA, METAST			1 (2%)
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	44	21	21
MORIBUND SACRIFICE	2		
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	4	28	29
DOSING ACCIDENT		1	
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS			
ANIMAL MISSING			
ANIMAL MISSEXED			
OTHER CASES			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	8	28	30
TOTAL PRIMARY TUMORS	9	36	39
TOTAL ANIMALS WITH BENIGN TUMORS	4	15	17
TOTAL BENIGN TUMORS	4	18	18
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	17	16
TOTAL MALIGNANT TUMORS	5	18	20
TOTAL ANIMALS WITH SECONDARY TUMORS##		1	2
TOTAL SECONDARY TUMORS		1	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			1
TOTAL UNCERTAIN TUMORS			1

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

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TELONE II®

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
OSTEOSARCOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC		1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA		3 (6%)	8 (16%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	2 (4%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS		8 (16%)	9 (18%)
MALIG. LYMPHOMA,HISTIOCYTIC TYPE	2 (4%)		
#SPLEEN	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
#LYMPH NODE	(50)	(50)	(50)
LEIOMYOSARCOMA, METASTATIC		1 (2%)	
MALIGNANT LYMPHOMA, NOS	2 (4%)	1 (2%)	
#LIVER	(50)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)		
CIRCULATORY SYSTEM			
#SPLEEN	(50)	(50)	(50)
HEMANGIOMA		1 (2%)	
HEMANGIOSARCOMA	1 (2%)		2 (4%)
#LIVER	(50)	(50)	(50)
HEMANGIOSARCOMA	2 (4%)	1 (2%)	1 (2%)
#UTERUS	(50)	(50)	(49)
HEMANGIOMA		1 (2%)	
#OVARY	(50)	(50)	(48)
HEMANGIOMA		1 (2%)	1 (2%)
HEMANGIOSARCOMA			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
HEPATOCELLULAR ADENOMA		5 (10%)	3 (6%)
HEPATOCELLULAR CARCINOMA	1 (2%)	3 (6%)	
SARCOMA, NOS, METASTATIC			1 (2%)
OSTEOSARCOMA, METASTATIC	1 (2%)		
#STOMACH	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	2 (4%)
SQUAMOUS CELL CARCINOMA			2 (4%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC		1 (2%)	
#URINARY BLADDER	(50)	(50)	(48)
TRANSITIONAL-CELL CARCINOMA		8 (16%)	21 (44%)
ENDOCRINE SYSTEM			
#PITUITARY	(48)	(48)	(41)
CHROMOPHOBE ADENOMA	4 (8%)	6 (13%)	2 (5%)
#ADRENAL	(50)	(50)	(50)
CORTICAL ADENOMA		1 (2%)	
PHEOCHROMOCYTOMA	1 (2%)	1 (2%)	1 (2%)

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TELONE II® (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS	2 (4%)	1 (2%)	1 (2%)
FIBROADENOMA		2 (4%)	
#UTERUS	(50)	(50)	(49)
SARCOMA, NOS			1 (2%)
LEIOMYOSARCOMA		1 (2%)	
#OVARY	(50)	(50)	(48)
ADENOCARCINOMA, NOS			1 (2%)
TERATOMA, NOS			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY			
* NUMBER OF ANIMALS NECROPSIED			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	4	8	15
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	46	42	35
DOSING ACCIDENT			
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS			
ANIMAL MISSING			
ANIMAL MISSEXED			
OTHER CASES			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	16	33	34
TOTAL PRIMARY TUMORS	19	47	57
TOTAL ANIMALS WITH BENIGN TUMORS	5	17	13
TOTAL BENIGN TUMORS	5	22	17
TOTAL ANIMALS WITH MALIGNANT TUMORS	13	22	29
TOTAL MALIGNANT TUMORS	14	25	39
TOTAL ANIMALS WITH SECONDARY TUMORS##	1	2	2
TOTAL SECONDARY TUMORS	1	3	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			1
TOTAL UNCERTAIN TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TELONE II®: VEHICLE CONTROL

ANIMAL NUMBER	00101	00103	00105	00107	00109	00111	00113	00115	00117	00119	00121	00123	00125	00127	00129	00131	00133	00135	00137	00139	00141	00143	00145	00147	00149
WEEKS ON STUDY	041	093	105	048	067	049	105	049	039	049	051	051	040	051	051	096	090	082	105	049	051	105	051	051	088
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
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
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	−	+	+	+	+	+	+	−	−	+	+	+	−	+	+	+	+	+	−	−	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									X
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	+	+	+	−	−	+	+	+	+	−	−	+	+	−	+	+	+	−	−	−	−	+	−	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma									X																
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

ANIMAL NUMBER	0051	0053	0055	0057	0059	0061	0063	0065	0067	0069	0071	0073	0075	0077	0079	0081	0083	0085	0087	0089	0091	0093	0095	0097	0099	TOTAL
WEEKS ON STUDY	1004	1005	0048	1003	0050	1005	0091	0050	0048	0088	0044	0051	0050	1005	0049	0045	0048	0092	0049	0098	0045	0098	0048	0086	1002	1005	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X																									1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma						X																				1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Hepatocellular carcinoma																	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid	−	−	+	+	−	+	−	+	+	+	+	+	+	+	+	+	−	−	+	−	+	+	+	+	+	33
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

* Animals Necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TELONE II®: LOW DOSE

ANIMAL NUMBER	1 0 1	1 0 3	1 0 5	1 0 7	1 0 9	1 1 1	1 1 3	1 1 5	1 1 7	1 1 9	1 2 1	1 2 3	1 2 5	1 2 7	1 2 9	1 3 1	1 3 3	1 3 5	1 3 7	1 3 9	1 4 1	1 4 3	1 4 5	1 4 7	1 4 9
WEEKS ON STUDY	0 6 7	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 4	1 0 5	1 0 5	1 0 5	0 5 3	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 3	1 0 5	0 7 9	1 0 5	1 0 5	1 0 1	1 0 5
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																									
Alveolar/bronchiolar adenoma		X	X				X					X				X		X		X	X				X
Alveolar/bronchiolar carcinoma					X								X												
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma		X																X							
Hemangiosarcoma						X																			
Malignant lymphoma, NOS										X															
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS																			X						
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma				X								X						X		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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																			X	X					
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chromophobe adenoma																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	+	–	+	+	–	–	–	–	+	–	+	+	+	+	+	+	–	–	–	–	+	+	+	–
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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, NOS																								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 B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	151	153	155	157	159	161	163	165	167	169	171	173	175	177	179	181	183	185	187	189	191	193	195	197	199	TOTAL
WEEKS ON STUDY	102	084	103	103	105	092	097	084	103	095	095	084	102	088	086	049	105	102	102	054	105	093	095	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Leiomyosarcoma								X																		1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																					X					1
Alveolar/bronchiolar adenoma				X										X												11
Alveolar/bronchiolar carcinoma																										2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	48
Hemangiosarcoma			X																							1
Spleen	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma					X																					3
Hemangiosarcoma			X																							2
Malignant lymphoma, NOS											X															2
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, NOS																										1
Thymus	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																			X							1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma					X																					1
Hepatocellular carcinoma																					X					6
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
Squamous cell papilloma																										2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Chromophobe adenoma					X																					1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid	–	+	–	–	+	+	–	+	–	–	–	+	–	+	+	–	+	–	+	–	+	+	–	+	+	27
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL C MS																										
Multi	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
Mall a, NOS																								X		2

* Animals Necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TELONE II®: HIGH DOSE

ANIMAL NUMBER	201	203	205	207	209	211	213	215	217	219	221	223	225	227	229	231	233	235	237	239	241	243	245	247	249
WEEKS ON STUDY	095	105	104	092	050	080	087	095	105	105	105	105	105	103	104	105	101	105	105	105	103	105	105	105	075
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoca, NOS unc prim/metastatic																									
Hepatocellular carcinoma, metastatic																									
Alveolar/bronchiolar adenoma															X	X		X			X				
Alveolar/bronchiolar carcinoma							X		X								X								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X											
Malignant lymphoma, NOS																	X								
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma							X											X							
Hepatocellular carcinoma										X			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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma						X														X					
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma									X																
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–
Adrenal	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma												X								X					
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	–	+	–	–	+	+	+	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Adenoma, 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
Hepatocellular carcinoma, metastatic										X															
Malignant lymphoma, NOS									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 B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	251	253	255	257	259	261	263	265	267	269	271	273	275	277	279	281	283	285	287	289	291	293	295	297	299	TOTAL
WEEKS ON STUDY	050	105	105	103	105	105	093	075	100	053	105	105	083	105	091	106	106	106	105	106	106	106	106	106	106	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoca, NOS unc prim/metastatic													X													1
Hepatocellular carcinoma, metastatic												X														1
Alveolar/bronchiolar adenoma		X					X					X	X									X				9
Alveolar/bronchiolar carcinoma																										3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Malignant lymphoma, NOS																	X									2
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma															X											3
Hepatocellular carcinoma									X		X					X	X			X	X				X	10
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
Squamous cell papilloma	X																									3
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell carcinoma													X													2
ENDOCRINE SYSTEM																										
Pituitary	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+		45
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Cortical adenoma																										2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Parathyroid	+	+	+	+	–	+	+	+	–	–	–	–	–	–	+	–	–	–	+	–	+	–	–	+	–	28
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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
Adenoma, 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
Hepatocellular carcinoma, metastatic																										1
Malignant lymphoma, NOS																										2

*Animals Necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TELONE II®: VEHICLE CONTROL

ANIMAL NUMBER	0002	0004	0006	0008	0010	0012	0014	0016	0018	0020	0022	0024	0026	0028	0030	0032	0034	0036	0038	0040	0042	0044	0046	0048	0050
WEEKS ON STUDY	1006	1006	1006	1006	1006	1006	1006	1006	1006	1006	1006	1006	1006	1006	1006	1006	1006	1006	1004	1006	0711	1006	1006	1006	1006
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																					X				
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS																X				X					
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma														X											
Hemangiosarcoma																			X						
Osteosarcoma, metastatic																					X				
Malig. lymphoma, lymphocytic type														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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chromophobe adenoma																									X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	–	+	–	+	–	+	–	–	+	–	–	+	+	+	+	–	+	+	–	–	+	–	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Malig. lymphoma, histiocytic type																									

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

ANIMAL NUMBER	052	054	056	058	060	062	064	066	068	070	072	074	076	078	080	082	084	086	088	090	092	094	096	098	100	TOTAL
WEEKS ON STUDY	106	106	106	106	098	106	106	106	106	106	106	106	106	106	106	083	106	106	106	106	106	106	106	106	106	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Osteosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma															X		X									2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma									X																	1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, NOS																										2
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Hemangiosarcoma	X																									2
Osteosarcoma, metastatic																										1
Malig. lymphoma, lymphocytic type																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	48
Chromophobe adenoma	X									X									X							4
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma																						X				1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid	–	+	–	+	+	+	+	+	+	+	–	–	+	+	–	+	+	+	+	–	–	+	–	–	–	29
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS				X																				X		2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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
Malig. lymphoma, histiocytic type					X					X																2

* Animals Necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TELONE II®: LOW DOSE

ANIMAL NUMBER	1 0 2	1 0 4	1 0 6	1 0 8	1 1 0	1 1 2	1 1 4	1 1 6	1 1 8	1 2 0	1 2 2	1 2 4	1 2 8	1 2 8	1 3 0	1 3 2	1 3 4	1 3 6	1 3 8	1 4 0	1 4 2	1 4 4	1 4 6	1 4 8	1 5 0
WEEKS ON STUDY	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	0 9 7	1 0 6	1 0 6	1 0 6	1 0 0	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 1	1 0 7	1 0 7	1 0 8	1 0 6	0 7 3	1 0 6	1 0 6
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic																									
Alveolar/bronchiolar adenoma	X																					X			
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma					X																				
Malignant lymphoma, NOS																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic																									
Malignant lymphoma, NOS					X																				
Thymus	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma											X	X										X			
Hepatocellular carcinoma									X																
Hemangiosarcoma																	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								X																	
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma																		X					X	X	
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Chromophobe adenoma				X																					
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	+	–	+	–	+	–	+	–	+	–	–	–	–	–	–	+	–	+	–	–	–	–	+	–
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Fibroadenoma				X							X														
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Hemangioma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																			X						
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS											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 B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	1 5 2	1 5 4	1 5 6	1 5 8	1 6 0	1 6 2	1 6 4	1 6 6	1 6 8	1 7 0	1 7 2	1 7 4	1 7 6	1 7 8	1 8 0	1 8 2	1 8 4	1 8 6	1 8 8	1 9 0	1 9 2	1 9 4	1 9 6	1 9 8	2 0 0	TOTAL
WEEKS ON STUDY	1 0 7	1 0 7	0 8 8	1 0 7	1 0 7	1 0 7	1 0 7	1 0 6	1 0 6	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 6	1 0 7	1 0 7	TISSUES TUMORS
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																						X			1
Alveolar/bronchiolar adenoma									X																3
Alveolar/bronchiolar carcinoma															X										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																									1
Malignant lymphoma, NOS				X																					1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma, metastatic			X																						1
Malignant lymphoma, NOS																									1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	47
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																						X		X	5
Hepatocellular carcinoma									X					X											3
Hemangiosarcoma																									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
Squamous cell papilloma																									1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																						X			1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell carcinoma	X	X								X					X				X						8
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Chromophobe adenoma					X										X				X			X	X		6
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma													X												1
Pheochromocytoma							X																		1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid	+	+	+	+	–	+	–	–	+	+	–	–	+	+	–	–	–	–	+	–	–	+	–	–	21
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																						X			1
Fibroadenoma																									2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma			X																						1
Hemangioma																		X							1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																									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	*50
Malignant lymphoma, NOS			X			X					X	X						X					X		8

* Animals Necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TELONE II®: HIGH DOSE

ANIMAL NUMBER	202	204	206	208	210	212	214	216	218	220	222	224	226	228	230	232	234	236	238	240	242	244	246	248	250
WEEKS ON STUDY	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	028	107	107	107	107	107	107	107	087	107
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic														X											
Alveolar/bronchiolar adenoma				X			X				X						X								X
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma			X																						
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma												X													
Sarcoma, NOS, metastatic																								X	
Hemangiosarcoma			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				X							X														
Squamous cell carcinoma		X																							
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma		X			X	X		X		X	X	X	X		X		X			X					X
ENDOCRINE SYSTEM																									
Pituitary	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
Chromophobe adenoma													X		X										
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma												X													
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	-	-	+	+	+	-	+	+	+	-	+	+	+	+	+	-	+	-	+	+	+	+	-	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS														X											
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																								X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS										X															
Teratoma, NOS																X									
Hemangioma																									
Hemangiosarcoma																									
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, NOS	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 B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	252	254	256	258	260	262	264	266	268	270	272	274	276	278	280	282	284	286	288	290	292	294	296	298	300	TOTAL
WEEKS ON STUDY	070	107	107	107	107	001	004	107	093	059	107	061	071	095	107	107	107	098	085	030	107	107	107	075	061	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																										1
Alveolar/bronchiolar adenoma	X	X																					X			8
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma				X																						2
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																							X	X		3
Sarcoma, NOS, metastatic																										1
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										2
Squamous cell carcinoma									X																	2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Transitional cell carcinoma		X	X					X			X			X	X			X				X			X	21
ENDOCRINE SYSTEM																										
Pituitary	–	+	+	+	+	–	+	+	+	–	+	+	–	–	+	+	+	+	+	–	+	+	+	+	+	41
Chromophobe adenoma																										2
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma																										1
Thyroid	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	48
Parathyroid	–	–	+	+	–	–	–	+	–	+	–	–	+	+	+	+	–	–	–	+	+	–	+	+	+	31
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, NOS																										1
Ovary	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma, NOS																										1
Teratoma, NOS																										1
Hemangioma														X												1
Hemangiosarcoma																	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, NOS							X	X						X												9

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF TELONE II®

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TELONE II®

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	52	52	52
ANIMALS NECROPSIED	52	52	52
ANIMALS EXAMINED HISTOPATHOLOGICALLY	52	52	52
INTEGUMENTARY SYSTEM			
*SKIN	(52)	(52)	(52)
EPIDERMAL INCLUSION CYST	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)		
*SUBCUT TISSUE	(52)	(52)	(52)
CYST, NOS	2 (4%)		
ABSCESS, NOS	1 (2%)		
RESPIRATORY SYSTEM			
*LARYNX	(52)	(52)	(52)
ABSCESS, NOS		1 (2%)	
#TRACHEAL SUBMUCOSA	(52)	(52)	(52)
ABSCESS, NOS		1 (2%)	
#LUNG	(52)	(52)	(52)
CONGESTION, NOS	1 (2%)		
HEMORRHAGE	1 (2%)		
INFLAMMATION, INTERSTITIAL			1 (2%)
INFLAMMATION, SUPPURATIVE	1 (2%)		
BRONCHOPNEUMONIA, ACUTE	1 (2%)	1 (2%)	
ABSCESS, NOS		1 (2%)	
PNEUMONIA INTERSTITIAL CHRONIC	3 (6%)	1 (2%)	1 (2%)
BRONCHOPNEUMONIA, CHRONIC			1 (2%)
GRANULOMA, NOS	2 (4%)		
INFLAMMATION, FOCAL GRANULOMATOUS	1 (2%)		
GRANULOMA, FOREIGN BODY			1 (2%)
HYPERPLASIA, ADENOMATOUS	1 (2%)	3 (6%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(52)	(52)	(52)
HYPOPLASIA, NOS	1 (2%)		
#SPLEEN	(52)	(52)	(52)
INFARCT, NOS	3 (6%)		
INFARCT, HEALED			1 (2%)
HEMOSIDEROSIS	2 (4%)	2 (4%)	2 (4%)
#LYMPH NODE	(52)	(52)	(52)
HYPERPLASIA, LYMPHOID	1 (2%)		
#SUBMANDIBULAR L.NODE	(52)	(52)	(52)
HYPERPLASIA, LYMPHOID	5 (10%)		
#MANDIBULAR L. NODE	(52)	(52)	(52)
HYPERPLASIA, LYMPHOID	1 (2%)		
#MEDIASTINAL L.NODE	(52)	(52)	(52)
HYPERPLASIA, LYMPHOID	1 (2%)		
#THYMUS	(49)	(52)	(52)
ABSCESS, CHRONIC		1 (2%)	
CIRCULATORY SYSTEM			
#LUNG	(52)	(52)	(52)
PERIARTERITIS			1 (2%)
#HEART	(52)	(52)	(52)
INFLAMMATION, CHRONIC	43 (83%)	40 (77%)	39 (75%)
INFLAMMATION WITH FIBROSIS	2 (4%)		
FIBROSIS	43 (83%)	36 (69%)	31 (60%)
#HEART/ATRIUM	(52)	(52)	(52)
THROMBUS, ORGANIZED			1 (2%)
#ENDOCARDIUM	(52)	(52)	(52)
INFLAMMATION, CHRONIC		1 (2%)	

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TELONE II® (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM (Continued)			
*VEIN	(52)	(52)	(52)
THROMBOSIS, NOS		1 (2%)	
#LIVER	(52)	(52)	(52)
THROMBUS, ORGANIZED		1 (2%)	
#PANCREAS	(52)	(52)	(52)
PERIARTERITIS	1 (2%)	9 (17%)	8 (15%)
#KIDNEY	(52)	(52)	(52)
PERIARTERITIS	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(52)	(52)	(52)
HEPATITIS, TOXIC			1 (2%)
NECROSIS, FOCAL	1 (2%)	1 (2%)	1 (2%)
NECROSIS, CENTRAL	2 (4%)		
METAMORPHOSIS FATTY	4 (8%)		
FOCAL CELLULAR CHANGE	38 (73%)	39 (75%)	34 (65%)
ANGIECTASIS	1 (2%)		
REGENERATION, NOS			1 (2%)
#BILE DUCT	(52)	(52)	(52)
HYPERPLASIA, NOS	3 (6%)		2 (4%)
#PANCREAS	(52)	(52)	(52)
INFLAMMATION, CHRONIC	1 (2%)		
#PANCREATIC ACINUS	(52)	(52)	(52)
ATROPHY, NOS	24 (46%)	20 (38%)	21 (40%)
#STOMACH	(52)	(52)	(52)
ULCER, NOS	1 (2%)	1 (2%)	1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)		1 (2%)
HYPERPLASIA, FOCAL			1 (2%)
HYPERPLASIA, BASAL CELL	1 (2%)	3 (6%)	9 (17%)
#GASTRIC MUCOSA	(52)	(52)	(52)
ULCER, FOCAL		1 (2%)	
#GASTRIC SUBMUCOSA	(52)	(52)	(52)
INFLAMMATION, CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
#FORESTOMACH	(52)	(52)	(52)
HYPERPLASIA, BASAL CELL		2 (4%)	3 (6%)
URINARY SYSTEM			
#KIDNEY	(52)	(52)	(52)
CYST, NOS			1 (2%)
NEPHROPATHY	38 (73%)	35 (67%)	42 (81%)
#U.BLADDER/SUBMUCOSA	(52)	(52)	(52)
EDEMA, NOS			9 (17%)
ENDOCRINE SYSTEM			
#PITUITARY	(52)	(50)	(50)
CYST, NOS	1 (2%)		1 (2%)
MULTIPLE CYSTS	1 (2%)		
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)	1 (2%)
#ADRENAL CORTEX	(52)	(52)	(52)
DEGENERATION, LIPOID			1 (2%)
HYPERPLASIA, NOS	1 (2%)	3 (6%)	1 (2%)
HYPERPLASIA, FOCAL	7 (13%)	6 (12%)	2 (4%)
#ADRENAL MEDULLA	(52)	(52)	(52)
HYPERPLASIA, NOS	1 (2%)	1 (2%)	
HYPERPLASIA, FOCAL	3 (6%)	2 (4%)	
#THYROID	(52)	(51)	(51)
CYSTIC FOLLICLES			1 (2%)
FOLLICULAR CYST, NOS	2 (4%)		
INFLAMMATION, GRANULOMATOUS	1 (2%)		
HYPERPLASIA, C-CELL	3 (6%)		
#PANCREATIC ISLETS	(52)	(52)	(52)
HYPERPLASIA, NOS		2 (4%)	5 (10%)
HYPERPLASIA, FOCAL	3 (6%)	2 (4%)	

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TELONE II® (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(52)	(52)	(52)
DILATATION/DUCTS		2 (4%)	1 (2%)
#PROSTATE	(52)	(52)	(51)
INFLAMMATION, SUPPURATIVE	2 (4%)		
INFLAMMATION, CHRONIC	1 (2%)		
HYPERPLASIA, FOCAL	4 (8%)	2 (4%)	7 (14%)
#TESTIS	(52)	(52)	(52)
INFLAMMATION, GRANULOMATOUS	1 (2%)		
*EPIDIDYMIS	(52)	(52)	(52)
INFLAMMATION, GRANULOMATOUS	1 (2%)		
GRANULOMA, SPERMATIC	1 (2%)		
NERVOUS SYSTEM			
#BRAIN	(52)	(52)	(52)
HYDROCEPHALUS, INTERNAL	1 (2%)	1 (2%)	
SPECIAL SENSE ORGANS			
*EYE	(52)	(52)	(52)
INFLAMMATION, CHRONIC	1 (2%)		
ATROPHY, NOS	1 (2%)		
*EYE ANTERIOR CHAMBER	(52)	(52)	(52)
INFLAMMATION, SUPPURATIVE			1 (2%)
ABSCESS, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*MUSCLE OF NECK	(52)	(52)	(52)
GRANULOMA, PYOGENIC	1 (2%)		
BODY CAVITIES			
*PLEURA	(52)	(52)	(52)
INFLAMMATION, NOS			1 (2%)
ABSCESS, NOS			1 (2%)
*EPICARDIUM	(52)	(52)	(52)
INFLAMMATION, NOS			1 (2%)
ABSCESS, NOS			1 (2%)
*MESENTERY	(52)	(52)	(52)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
GRANULOMA, NOS		1 (2%)	
NECROSIS, FAT		4 (8%)	4 (8%)
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
INFLAMMATION, GRANULOMATOUS	1		
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		1	

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

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TELONE II®

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	52	52	52
ANIMALS NECROPSIED	52	52	52
ANIMALS EXAMINED HISTOPATHOLOGICALLY	52	52	52
INTEGUMENTARY SYSTEM			
*SKIN	(52)	(52)	(52)
EPIDERMAL INCLUSION CYST			1 (2%)
*SUBCUT TISSUE	(52)	(52)	(52)
CYST, NOS	1 (2%)		
ABSCESS, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#TRACHEA	(52)	(52)	(52)
ASPIRATION, FOREIGN BODY		1 (2%)	
#LUNG	(52)	(52)	(52)
INFLAMMATION, INTERSTITIAL			1 (2%)
BRONCHOPNEUMONIA, ACUTE	1 (2%)	1 (2%)	2 (4%)
ABSCESS, NOS	1 (2%)	1 (2%)	2 (4%)
PNEUMONIA INTERSTITIAL CHRONIC	1 (2%)		
GRANULOMA, NOS		1 (2%)	
INFLAMMATION, FOCAL GRANULOMATOUS		1 (2%)	
HYPERPLASIA, ADENOMATOUS	3 (6%)	5 (10%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*BLOOD	(52)	(52)	(52)
LEUKOCYTOSIS, NEUTROPHILIC		1 (2%)	
#BONE MARROW	(51)	(51)	(50)
HYPERPLASIA, NOS	1 (2%)		
#SPLEEN	(52)	(51)	(52)
FIBROSIS, FOCAL			1 (2%)
HEMOSIDEROSIS	7 (13%)	7 (14%)	8 (15%)
#MEDIASTINAL L.NODE	(52)	(52)	(52)
GRANULOMA, PYOGENIC	1 (2%)		
#KIDNEY	(52)	(52)	(52)
HEMATOPOIESIS		1 (2%)	
CIRCULATORY SYSTEM			
#HEART	(52)	(52)	(52)
INFLAMMATION, CHRONIC	27 (52%)	31 (60%)	33 (63%)
FIBROSIS	23 (44%)	19 (37%)	12 (23%)
#HEART/ATRIUM	(52)	(52)	(52)
THROMBOSIS, NOS	1 (2%)		
THROMBUS, ORGANIZED	1 (2%)		
#PANCREAS	(52)	(52)	(52)
PERIARTERITIS		1 (2%)	
*MESENTERY	(52)	(52)	(52)
PERIARTERITIS		1 (2%)	
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(52)	(52)	(52)
ATROPHY, NOS		1 (2%)	1 (2%)
#LIVER	(52)	(52)	(52)
ABSCESS, NOS	1 (2%)		
FIBROSIS, FOCAL			1 (2%)
INFECTION, BACTERIAL		1 (2%)	
NECROSIS, FOCAL	2 (4%)	1 (2%)	
NECROSIS, CENTRAL	3 (6%)		
METAMORPHOSIS FATTY	4 (8%)	2 (4%)	1 (2%)
FOCAL CELLULAR CHANGE	35 (67%)	36 (69%)	40 (77%)
ANGIECTASIS		1 (2%)	
REGENERATION, NOS		1 (2%)	
#LIVER/CENTRILOBULAR	(52)	(52)	(52)
CONGESTION, NOS	1 (2%)		
#BILE DUCT	(52)	(52)	(52)
HYPERPLASIA, NOS		1 (2%)	

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TELONE II® (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#PANCREAS	(52)	(52)	(52)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
#PANCREATIC ACINUS	(52)	(52)	(52)
ATROPHY, NOS	15 (29%)	16 (31%)	21 (40%)
#STOMACH	(52)	(52)	(52)
EPIDERMAL INCLUSION CYST	1 (2%)		
EDEMA, NOS		1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)	1 (2%)	
ULCER, PERFORATED	1 (2%)	1 (2%)	1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)		4 (8%)
HYPERPLASIA, FOCAL	2 (4%)	1 (2%)	1 (2%)
HYPERPLASIA, BASAL CELL			12 (23%)
HYPERKERATOSIS		1 (2%)	
#GASTRIC SUBMUCOSA	(52)	(52)	(52)
EDEMA, NOS	1 (2%)		
INFLAMMATION, NOS	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(52)	(52)	(52)
ABSCESS, NOS	1 (2%)		
NEPHROPATHY	15 (29%)	24 (46%)	25 (48%)
INFARCT, HEALED		1 (2%)	
#U. BLADDER/SUBMUCOSA	(52)	(52)	(52)
EDEMA, NOS			3 (6%)
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(51)	(52)
CYST, NOS	4 (8%)	2 (4%)	1 (2%)
MULTIPLE CYSTS	1 (2%)		
HYPERPLASIA, FOCAL	1 (2%)		
#ADRENAL	(52)	(52)	(52)
CONGESTION, NOS		2 (4%)	
ANGIECTASIS		1 (2%)	
#ADRENAL CORTEX	(52)	(52)	(52)
DEGENERATION, LIPOID			1 (2%)
HYPERPLASIA, NOS		10 (19%)	9 (17%)
HYPERPLASIA, FOCAL	15 (29%)	7 (13%)	13 (25%)
#THYROID	(52)	(52)	(52)
FOLLICULAR CYST, NOS			1 (2%)
HYPERPLASIA, C-CELL	1 (2%)	1 (2%)	
HYPERPLASIA, FOLLICULAR-CELL			2 (4%)
#PARATHYROID	(45)	(39)	(37)
HYPERPLASIA, NOS			1 (3%)
#PANCREATIC ISLETS	(52)	(52)	(52)
HYPERPLASIA, NOS			2 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(52)	(52)	(52)
DILATATION/DUCTS	2 (4%)	1 (2%)	
*PREPUTIAL GLAND	(52)	(52)	(52)
HYPERPLASIA, NOS		1 (2%)	
#UTERUS	(52)	(52)	(52)
METAPLASIA, SQUAMOUS	1 (2%)		
#UTERUS/ENDOMETRIUM	(52)	(52)	(52)
EMPYEMA		1 (2%)	
HYPERPLASIA, CYSTIC	5 (10%)	1 (2%)	1 (2%)
#OVARY	(52)	(52)	(52)
FOLLICULAR CYST, NOS	1 (2%)	2 (4%)	
NERVOUS SYSTEM			
#BRAIN	(52)	(52)	(52)
HYDROCEPHALUS, INTERNAL		1 (2%)	
HEMORRHAGE	1 (2%)		
HEMOSIDEROSIS	1 (2%)		

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TELONE II® (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*EYE/CONJUNCTIVA	(52)	(52)	(52)
INFLAMMATION, SUPPURATIVE			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*THORACIC CAVITY	(52)	(52)	(52)
ABSCESS, CHRONIC		1 (2%)	
*MEDIASTINUM	(52)	(52)	(52)
INFLAMMATION, SUPPURATIVE		1 (2%)	
ABSCESS, NOS	1 (2%)		
*PERITONEUM	(52)	(52)	(52)
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, FOCAL	1 (2%)		
*EPICARDIUM	(52)	(52)	(52)
INFLAMMATION, CHRONIC SUPPURATIVE	1 (2%)		
*MESENTERY	(52)	(52)	(52)
INFLAMMATION, GRANULOMATOUS			2 (4%)
NECROSIS, FAT	3 (6%)	3 (6%)	2 (4%)
ALL OTHER SYSTEMS			
OMENTUM			
INFLAMMATION, GRANULOMATOUS	1		
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		1	

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF TELONE II®

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TELONE II®

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
ABSCESS, CHRONIC			1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
RESPIRATORY SYSTEM			
*NASAL CAVITY	(50)	(50)	(50)
HEMORRHAGE			1 (2%)
#LUNG	(50)	(50)	(50)
EDEMA, NOS		1 (2%)	
HEMORRHAGE	2 (4%)	2 (4%)	2 (4%)
INFLAMMATION, INTERSTITIAL	1 (2%)		1 (2%)
ABSCESS, NOS		1 (2%)	
HEMOSIDEROSIS			1 (2%)
HEMATOPOIETIC SYSTEM			
#LYMPH NODE	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	1 (2%)
HEMOSIDEROSIS			1 (2%)
HYPERPLASIA, LYMPHOID		2 (4%)	
#MESENTERIC L. NODE	(50)	(50)	(50)
HEMORRHAGE		2 (4%)	7 (14%)
#SMALL INTESTINE	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID		1 (2%)	
#THYMUS	(49)	(48)	(47)
HEMORRHAGE	2 (4%)	9 (19%)	2 (4%)
CIRCULATORY SYSTEM			
#LUNG	(50)	(50)	(50)
THROMBUS, ORGANIZED		1 (2%)	
#HEART	(50)	(50)	(50)
HEMORRHAGE	4 (8%)	7 (14%)	6 (12%)
INFLAMMATION, SUPPURATIVE	39 (78%)	13 (26%)	5 (10%)
INFLAMMATION ACTIVE CHRONIC			1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		1 (2%)
FIBROSIS	1 (2%)		
NECROSIS, NOS	21 (42%)	10 (20%)	6 (12%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
INFLAMMATION, CHRONIC	14 (28%)	28 (56%)	21 (42%)
#LIVER	(50)	(50)	(50)
DILATATION, NOS			1 (2%)
INFLAMMATION, SUPPURATIVE	1 (2%)		
NECROSIS, FOCAL	2 (4%)	1 (2%)	
NECROSIS, CENTRAL	22 (44%)	9 (18%)	5 (10%)
INFARCT, NOS		1 (2%)	
METAMORPHOSIS FATTY	1 (2%)		
FOCAL CELLULAR CHANGE		2 (4%)	3 (6%)
ANGIECTASIS	1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TELONE II® (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#BILE DUCT	(50)	(50)	(50)
CYST, NOS			3 (6%)
HYPERPLASIA, NOS			1 (2%)
#PANCREAS	(50)	(50)	(50)
DILATATION/DUCTS		1 (2%)	
INFLAMMATION, CHRONIC		2 (4%)	
#PANCREATIC ACINUS	(50)	(50)	(50)
ATROPHY, NOS			2 (4%)
#STOMACH	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL			4 (8%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
HYDRONEPHROSIS	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)	12 (24%)	3 (6%)
INFLAMMATION, CHRONIC FOCAL	2 (4%)		
INFARCT, HEALED			1 (2%)
#KIDNEY/PELVIS	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)
#URINARY BLADDER	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		2 (4%)
INFLAMMATION, CHRONIC			1 (2%)
HYPERPLASIA, EPITHELIAL		9 (18%)	18 (36%)
ENDOCRINE SYSTEM			
#ADRENAL CORTEX	(50)	(50)	(48)
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)	
#THYROID	(50)	(49)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
#PANCREATIC ISLETS	(50)	(50)	(50)
HYPERPLASIA, NOS	2 (4%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
DILATATION/DUCTS	1 (2%)		
#TESTIS	(50)	(50)	(50)
HEMORRHAGE	1 (2%)		
*EPIDIDYMIS	(50)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
GRANULOMA, SPERMATIC			1 (2%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
#BRAIN	(50)	(50)	(50)
MINERALIZATION	8 (16%)	21 (42%)	25 (50%)
HEMORRHAGE	11 (22%)	2 (4%)	1 (2%)
CHOLESTEROL DEPOSIT	1 (2%)		
*SPINAL CORD	(50)	(50)	(50)
HEMORRHAGE	1 (2%)	1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TELONE II® (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*THORACIC CAVITY	(50)	(50)	(50)
ABSCESS, NOS		1 (2%)	
*MEDIASTINUM	(50)	(50)	(50)
HEMORRHAGE	1 (2%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	1	1

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

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TELONE II®

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
#LUNG	(50)	(50)	(50)
HEMORRHAGE	1 (2%)	1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
PNEUMONIA INTERSTITIAL CHRONIC			3 (6%)
INFLAMMATION, CHRONIC FOCAL	2 (4%)		
ABSCESS, CHRONIC			1 (2%)
HYPERPLASIA, ADENOMATOUS	1 (2%)	2 (4%)	1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(50)	(50)	(50)
MYELOFIBROSIS	46 (92%)	48 (96%)	39 (78%)
#SPLEEN	(50)	(50)	(50)
HEMOSIDEROSIS	1 (2%)	1 (2%)	
HYPERPLASIA, LYMPHOID	1 (2%)	3 (6%)	3 (6%)
#SPLENIC FOLLICLES	(50)	(50)	(50)
HYPERPLASIA, FOCAL	1 (2%)		
HYPERPLASIA, LYMPHOID		1 (2%)	
#LYMPH NODE	(50)	(50)	(50)
HEMOSIDEROSIS		1 (2%)	1 (2%)
HYPERPLASIA, LYMPHOID		3 (6%)	
CIRCULATORY SYSTEM			
#HEART	(50)	(50)	(50)
ENDOCARDITIS, BACTERIAL		1 (2%)	
ABSCESS, NOS			1 (2%)
INFLAMMATION, CHRONIC	1 (2%)		
#UTERUS	(50)	(50)	(49)
THROMBOSIS, NOS	1 (2%)		
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(48)	(50)	(50)
INFLAMMATION, CHRONIC	31 (65%)	28 (56%)	28 (56%)
ATROPHY, FOCAL		1 (2%)	
#LIVER	(50)	(50)	(50)
HEMATOMA, NOS		1 (2%)	
HEMATOMA, ORGANIZED	1 (2%)		
INFLAMMATION, CHRONIC	3 (6%)	2 (4%)	3 (6%)
INFLAMMATION, CHRONIC FOCAL	3 (6%)		
NECROSIS, FOCAL	1 (2%)	3 (6%)	
NECROSIS, CENTRAL	1 (2%)		1 (2%)
FOCAL CELLULAR CHANGE	8 (16%)	11 (22%)	3 (6%)
#PANCREAS	(50)	(50)	(49)
INFLAMMATION, CHRONIC	3 (6%)	4 (8%)	
#PANCREATIC ACINUS	(50)	(50)	(49)
ATROPHY, NOS	4 (8%)	4 (8%)	1 (2%)
#PERIPANCREATIC TISSUE	(50)	(50)	(49)
GRANULOMA, NOS			1 (2%)
#STOMACH	(50)	(50)	(50)
RUPTURE			1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)	1 (2%)	21 (42%)
#SMALL INTESTINE	(50)	(50)	(50)
PERFORATION, INFLAMMATORY			1 (2%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TELONE II® (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
HYDRONEPHROSIS		2 (4%)	14 (28%)
INFLAMMATION, CHRONIC	16 (32%)	9 (18%)	13 (26%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
FIBROSIS			1 (2%)
NECROSIS, NOS			1 (2%)
INFARCT, HEALED		2 (4%)	5 (10%)
METAPLASIA, OSSEOUS			1 (2%)
#KIDNEY/PELVIS	(50)	(50)	(50)
INFLAMMATION, NECROTIZING			1 (2%)
INFECTION, BACTERIAL		1 (2%)	
#URINARY BLADDER	(50)	(50)	(48)
INFLAMMATION, SUPPURATIVE		1 (2%)	1 (2%)
INFLAMMATION ACTIVE CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC	15 (30%)	15 (30%)	1 (2%)
HYPERPLASIA, EPITHELIAL	2 (4%)	15 (30%)	19 (40%)
#U.BLADDER/SUBMUCOSA	(50)	(50)	(48)
INFLAMMATION WITH FIBROSIS	1 (2%)		
FIBROSIS		1 (2%)	
ENDOCRINE SYSTEM			
#ADRENAL	(50)	(50)	(50)
HEMORRHAGE			1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
#ADRENAL CORTEX	(50)	(50)	(50)
HYPERPLASIA, NOS		1 (2%)	
#THYROID	(50)	(50)	(48)
FOLLICULAR CYST, NOS		1 (2%)	1 (2%)
INFLAMMATION, CHRONIC FOCAL	2 (4%)		
HYPERPLASIA, C-CELL	1 (2%)		
HYPERPLASIA, FOLLICULAR-CELL			2 (4%)
#THYROID FOLLICLE	(50)	(50)	(48)
HYPERPLASIA, CYSTIC	1 (2%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL	1 (2%)		
#UTERUS	(50)	(50)	(49)
HYDROMETRA			1 (2%)
#UTERUS/ENDOMETRIUM	(50)	(50)	(49)
HEMORRHAGE	1 (2%)		
HYPERPLASIA, NOS	4 (8%)	3 (6%)	9 (18%)
HYPERPLASIA, CYSTIC	23 (46%)	28 (56%)	25 (51%)
#OVARY	(50)	(50)	(48)
FOLLICULAR CYST, NOS	5 (10%)	2 (4%)	6 (13%)
HEMATOMA, NOS	1 (2%)		
HEMOSIDEROSIS		1 (2%)	
#OVARY/FOLLICLE	(50)	(50)	(48)
HEMATOMA, NOS	1 (2%)	5 (10%)	2 (4%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
#BRAIN	(50)	(50)	(50)
MINERALIZATION	30 (60%)	18 (36%)	17 (34%)
HEMORRHAGE			1 (2%)
*SPINAL CORD	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
SPECIAL SENSE ORGANS			
NONE			

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TELONE II® (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(50)	(50)	(50)
INFLAMMATION WITH FIBROSIS	1 (2%)		
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
ABSCESS, NOS			1 (2%)
*PERITONEUM	(50)	(50)	(50)
INFLAMMATION, GRANULOMATOUS			1 (2%)
*MESENTERY	(50)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
NECROSIS, FAT		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
INFLAMMATION, CHRONIC	4 (8%)	3 (6%)	
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
SPECIAL MORPHOLOGY SUMMARY			
NONE			

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

APPENDIX E

SUMMARY OF THE INCIDENCE OF NEOPLASTIC AND NONNEOPLASTIC LESIONS IN RATS IN THE ANCILLARY GAVAGE STUDIES OF TELONE II®

TABLE E1. SUMMARY OF THE INCIDENCE OF NEOPLASTIC AND NONNEOPLASTIC LESIONS IN MALE RATS IN THE ANCILLARY GAVAGE STUDY OF TELONE II®

	Months on Study					Months on Study					Months on Study				
	9	16	21	24	27	9	16	21	24	27	9	16	21	24	27
	Vehicle Control (a)					25 mg/kg (a)					50 mg/kg (a)				
Liver															
(No. examined)	5	5	5	5	5	5	5	4	5	5	5	5	5	5	5
Neoplastic Nodule	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Monocytic Leukemia	0	0	0	2	0	0	0	0	1	0	0	0	0	0	1
Focal Cellular Change	0	3	5	4	5	0	4	4	5	2	0	3	4	5	4
Hyperplasia, Focal	0	0	0	3	0	0	0	0	0	0	0	2	0	0	0
Inflammation, Acute and Chronic	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Focal	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
Metamorphosis, Fatty	0	2	0	0	1	0	0	0	0	1	0	0	0	0	0
Necrosis, Focal	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
Liver/Bile Duct															
(No. Examined)	5	5	5	5	5	5	5	4	5	5	5	5	5	5	5
Hyperplasia, Focal	0	0	0	2	0	0	0	0	0	0	1	0	0	1	2
Kidney															
(No. examined)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Abcess, Chronic	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cyst, NOS	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
Inflammation, Chronic	1	1	0	0	0	1	2	0	0	0	0	1	0	0	0
Mineralization	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Nephropathy	0	1	5	5	5	0	0	4	5	5	1	0	4	5	5
Adrenal Cortex															
(No. examined)	5	5	5	5	5	5	5	5	5	5	5	4	5	5	5
Cortical Adenoma	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0
Hyperplasia, Focal	0	1	0	4	0	0	0	0	3	0	0	0	0	0	0
Adrenal/Medulla															
(No. examined)	5	5	5	5	5	5	5	5	5	5	5	4	5	5	5
Pheochromocytoma	0	0	1	0	1	0	1	1	1	3	0	1	1	1	1
Hyperplasia, Focal	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0
Urinary Bladder															
(No. examined)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	4
Inflammation, Chronic	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1
Urinary Bladder/Submucosa															
(No. examined)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	4
Edema, NOS	0	0	0	1	1	0	0	0	1	1	0	0	0	0	1
Forestomach															
(No. examined)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Squamous Cell Papilloma	0	0	0	0	0	0	0	0	0	0	0	0	0	2	2
Hyperplasia, Basal Cell	0	0	1	0	0	0	1	3	3	1	1	5	4	4	4
Inflammation, Acute	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Inflammation, Chronic	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1
Stomach															
(No. examined)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Hemorrage	0	0	2	0	0	0	0	1	0	1	0	1	1	0	0
Inflammation, Chronic	0	0	0	0	0	0	0	0	0	1	0	0	0	4	0

TABLE E1. SUMMARY OF THE INCIDENCE OF NEOPLASTIC AND NONNEOPLASTIC LESIONS IN MALE RATS IN THE ANCILLARY GAVAGE STUDY OF TELONE II® (Continued)

	Months on Study					Months on Study					Months on Study				
	9	16	21	24	27	9	16	21	24	27	9	16	21	24	27
	Vehicle Control (a)					25 mg/kg (a)					50 mg/kg (a)				
Thyroid															
(No. examined)	5	5	5	5	5	5	5	5	5	5	5	5	5	4	5
C-Cell Carcinoma	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
C-Cell Adenoma	0	0	1	1	1	0	0	1	1	0	0	0	0	0	1
Follicular Cell Adenoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Follicular Cyst, NOS	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1
Hyperplasia, C-Cell	0	0	0	1	1	0	0	0	0	1	0	0	0	0	1
Hyperplasia, Follicular Cell	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Mammary Gland															
(No. examined)	0	0	1	3	4	2	2	2	4	2	1	1	1	4	3
Fibroadenoma	0	0	0	0	1	0	0	0	0	0	0	0	0	1	1
Adenoma, NOS	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Dilatation/Ducts	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hyperplasia, NOS	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Fibroma	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Multiple Organs															
Malignant Lymphoma, Histiocytic Type	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
Monocytic Leukemia	0	0	0	1	0	0	0	1	0	0	0	0	0	0	1

(a) Scheduled kill

TABLE E2. SUMMARY OF THE INCIDENCE OF NEOPLASTIC AND NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE ANCILLARY GAVAGE STUDY OF TELONE II®

	Months on Study					Months on Study					Months on Study				
	9	16	21	24	27	9	16	21	24	27	9	16	21	24	27
	Vehicle Control (a)					25 mg/kg (a)					50 mg/kg (a)				
Liver															
(No. examined)	5	5	5	5	3	5	5	5	5	5	5	5	5	5	5
Neoplastic Nodule	0	0	0	0	0	0	0	0	2	0	0	0	0	0	2
Monocytic Leukemia	0	0	1	1	0	0	0	1	2	1	0	0	1	0	0
Focal Cellular Change	0	5	5	4	3	2	5	5	4	4	3	5	5	4	4
Hyperplasia, Focal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Acute and Chronic	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Focal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Metamorphosis, Fatty	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Necrosis, Focal	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0
Liver/Bile Duct															
(No. examined)	5	5	5	5	3	5	5	5	5	5	5	5	5	5	5
Hyperplasia, Focal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Kidney (No. examined)	5	5	5	5	3	5	5	5	5	5	5	5	5	5	5
Abcess, Chronic	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Cyst, NOS	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Chronic	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0
Mineralization	0	0	1	0	0	0	0	1	0	0	0	2	1	0	0
Nephropathy	0	0	2	2	3	0	0	1	4	5	0	0	2	5	5
Adrenal/Cortex															
(No. examined)	5	5	5	5	3	5	5	5	5	5	5	5	5	5	5
Cortical Adenoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hyperplasia, Focal	0	3	2	1	0	0	0	2	1	3	0	1	1	3	1
Hemorrhage	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Adrenal/Medulla															
(No. examined)	5	5	5	5	3	5	5	5	5	5	5	5	5	5	5
Pheochromocytoma	0	0	0	0	0	0	0	1	0	1	0	0	1	0	0
Hyperplasia, Focal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Urinary Bladder															
(No. examined)	5	5	4	5	3	5	5	5	5	5	4	5	5	5	5
Inflammation, Chronic	1	0	2	0	1	0	1	3	0	1	0	1	1	0	1
Urinary Bladder/Submucosa															
(No. examined)	5	5	4	5	3	5	5	5	5	5	4	5	5	5	5
Edema, NOS	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
Forestomach															
(No. examined)	5	5	5	5	3	5	5	5	5	5	5	5	5	5	5
Squamous Cell Papilloma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5
Hyperplasia, Basal Cell	0	0	0	0	0	0	2	2	1	0	0	5	5	4	5
Inflammation, Acute	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Chronic	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Stomach															
(No. examined)	5	5	5	5	3	5	5	5	5	5	5	5	5	5	5
Hemorrage	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Inflammation, Chronic	0	0	1	1	0	0	0	2	3	0	0	0	2	0	1

TABLE E2. SUMMARY OF THE INCIDENCE OF NEOPLASTIC AND NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE ANCILLARY GAVAGE STUDY OF TELONE II® (Continued)

	Months on Study					Months on Study					Months on Study				
	9	16	21	24	27	9	16	21	24	27	9	16	21	24	27
	Vehicle Control (a)					25 mg/kg (a)					50 mg/kg (a)				
Thyroid															
(No. examined)	5	5	5	5	3	5	5	5	5	5	5	5	5	5	5
C-Cell Carcinoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C-Cell Adenoma	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0
Follicular Cell Adenoma	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Follicular Cyst, NOS	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0
Hyperplasia, C-Cell	0	1	0	0	0	0	0	0	1	1	0	0	0	2	2
Hyperplasia, Follicular Cell	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0
Mammary Gland															
(No. examined)	0	1	3	5	3	0	0	2	5	4	0	2	3	4	3
Fibroadenoma	0	0	0	1	0	0	0	1	0	2	0	0	1	1	2
Adenoma, NOS	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Dilatation/Ducts	0	0	1	0	0	0	0	0	1	0	0	0	0	1	0
Hyperplasia, NOS	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Multiple Organs															
Malignant Lymphoma, Histiocytic Type	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Monocytic Leukemia	0	0	0	1	1	0	0	0	0	2	0	0	0	0	0

(a) Scheduled kill

APPENDIX F

ANALYSES OF PRIMARY TUMORS IN RATS AND MICE IN THE TWO-YEAR AND ANCILLARY GAVAGE STUDIES OF TELONE II®

TABLE F1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR AND ANCILLARY GAVAGE STUDIES OF TELONE II®

	Vehicle Control		25 mg/kg		50 mg/kg	
	2-Year Study	2-Year and Ancillary Studies (a)	2-Year Study	2-Year and Ancillary Studies (a)	2-Year Study	2-Year and Ancillary Studies (a)
Subcutaneous Tissue: Fibroma						
Overall Rates (b)	3/52 (6%)		1/52 (2%)		0/52 (0%)	
Adjusted Rates (c)	7.0%		2.3%		0.0%	
Terminal Rates (d)	3/43 (7%)		0/38 (0%)		0/40 (0%)	
Life Table Tests (e)	P=0.071N		P=0.342N		P=0.134N	
Incidental Tumor Tests (e)	P=0.055N		P=0.278N		P=0.134N	
Cochran-Armitage Trend Test (e)	P=0.060N					
Fisher Exact Tests			P=0.309N		P=0.121N	
Hematopoietic System: Mononuclear Cell Leukemia						
Overall Rates (b)	13/52 (25%)		12/52 (23%)		10/52 (19%)	
Adjusted Rates (c)	28.7%		30.7%		24.2%	
Terminal Rates (d)	11/43 (26%)		11/38 (29%)		9/40 (23%)	
Life Table Tests (e)	P=0.351N		P=0.545		P=0.387N	
Incidental Tumor Tests (e)	P=0.315N		P=0.550N		P=0.355N	
Cochran-Armitage Trend Test (e)	P=0.279N					
Fisher Exact Tests			P=0.500N		P=0.319N	
Liver: Neoplastic Nodule						
Overall Rates (b)	1/52 (2%)	1/77 (1%)	6/52 (12%)	6/76 (8%)	7/52 (13%)	8/77 (10%)
Adjusted Rates (c)	2.3%		15.8%		17.1%	
Terminal Rates (d)	1/43 (2%)		6/38 (16%)		7/40 (18%)	
Life Table Tests (e)	P=0.023	P=0.012	P=0.040	P=0.043	P=0.025	P=0.014
Incidental Tumor Tests (e)	P=0.023	P=0.012	P=0.040	P=0.043	P=0.025	P=0.014
Cochran-Armitage Trend Test (e)	P=0.030	P=0.017				
Fisher Exact Tests			P=0.056	P=0.056	P=0.030	P=0.017
Liver: Neoplastic Nodule or Carcinoma						
Overall Rates (b)	1/52 (2%)	1/77 (1%)	6/52 (12%)	6/76 (8%)	8/52 (15%)	9/77 (12%)
Adjusted Rates (c)	2.3%		15.8%		20.0%	
Terminal Rates (d)	1/43 (2%)		6/38 (16%)		8/40 (20%)	
Life Table Tests (e)	P=0.011	P=0.006	P=0.040	P=0.043	P=0.013	P=0.007
Incidental Tumor Tests (e)	P=0.011	P=0.006	P=0.040	P=0.043	P=0.013	P=0.007
Cochran-Armitage Trend Test (e)	P=0.015	P=0.009				
Fisher Exact Tests			P=0.056	P=0.056	P=0.016	P=0.009
Stomach: Squamous Cell Papilloma						
Overall Rates (b)	1/52 (2%)	1/77 (1%)	1/52 (2%)	1/77 (1%)	9/52 (17%)	13/77 (17%)
Adjusted Rates (c)	2.3%		2.4%		21.3%	
Terminal Rates (d)	1/43 (2%)		0/38 (0%)		7/40 (18%)	
Life Table Tests (e)	P=0.002	P<0.001	P=0.739	P=0.742	P=0.008	P<0.001
Incidental Tumor Tests (e)	P=0.002	P<0.001	P=0.702N	P=0.739N	P=0.011	P<0.001
Cochran-Armitage Trend Test (e)	P=0.002	P<0.001				
Fisher Exact Tests			P=0.752	P=0.752	P=0.008	P<0.001
Stomach: Squamous Cell Carcinoma						
Overall Rates (b)	0/52 (0%)	0/77 (0%)	0/52 (0%)	0/77 (0%)	4/52 (8%)	4/77 (5%)
Adjusted Rates (c)	0.0%		0.0%		10.0%	
Terminal Rates (d)	0/43 (0%)		0/38 (0%)		4/40 (10%)	
Life Table Tests (e)	P=0.014	P=0.014	(f)	(f)	P=0.054	P=0.056
Incidental Tumor Tests (e)	P=0.014	P=0.014	(f)	(f)	P=0.054	P=0.056
Cochran-Armitage Trend Test (e)	P=0.015	P=0.015				
Fisher Exact Tests			(f)	(f)	P=0.059	P=0.060

TABLE F1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR AND ANCILLARY GAVAGE STUDIES OF TELONE II® (Continued)

	Vehicle Control		25 mg/kg		50 mg/kg	
	2-Year Study	2-Year and Ancillary Studies (a)	2-Year Study	2-Year and Ancillary Studies (a)	2-Year Study	2-Year and Ancillary Studies (a)
Stomach: Squamous Cell Papilloma or Carcinoma						
Overall Rates (b)	1/52 (2%)	1/77 (1%)	1/52 (2%)	1/77 (1%)	13/52 (25%)	17/77 (22%)
Adjusted Rates (c)	2.3%		2.4%		30.8%	
Terminal Rates (d)	1/43 (2%)		0/38 (0%)		11/40 (28%)	
Life Table Tests (e)	P<0.001	P<0.001	P=0.739	P=0.742	P<0.001	P<0.001
Incidental Tumor Tests (e)	P<0.001	P<0.001	P=0.702N	P=0.739N	P<0.001	P<0.001
Cochran-Armitage Trend Test (e)	P<0.001	P<0.001				
Fisher Exact Tests			P=0.752	P=0.752	P<0.001	P<0.001
Pituitary: Chromophobe Adenoma						
Overall Rates (b)	23/52 (44%)		13/50 (26%)		16/50 (32%)	
Adjusted Rates (c)	48.7%		33.0%		37.6%	
Terminal Rates (d)	19/43 (44%)		11/37 (30%)		13/39 (33%)	
Life Table Tests (e)	P=0.159N		P=0.093N		P=0.196N	
Incidental Tumor Tests (e)	P=0.128N		P=0.074N		P=0.157N	
Cochran-Armitage Trend Test (e)	P=0.112N					
Fisher Exact Tests			P=0.042N		P=0.143N	
Pituitary: Adenoma						
Overall Rates (b)	24/52 (46%)		14/50 (28%)		16/50 (32%)	
Adjusted Rates (c)	50.8%		34.5%		37.6%	
Terminal Rates (d)	20/43 (47%)		11/37 (30%)		13/39 (33%)	
Life Table Tests (e)	P=0.121N		P=0.101N		P=0.150N	
Incidental Tumor Tests (e)	P=0.083N		P=0.069N		P=0.116N	
Cochran-Armitage Trend Test (e)	P=0.080N					
Fisher Exact Tests			P=0.045N		P=0.104N	
Pituitary: Adenoma or Carcinoma						
Overall Rates (b)	24/52 (46%)		14/50 (28%)		17/50 (34%)	
Adjusted Rates (c)	50.8%		34.5%		40.0%	
Terminal Rates (d)	20/43 (47%)		11/37 (30%)		14/39 (36%)	
Life Table Tests (e)	P=0.168N		P=0.101N		P=0.203N	
Incidental Tumor Tests (e)	P=0.123N		P=0.069N		P=0.164N	
Cochran-Armitage Trend Test (e)	P=0.117N					
Fisher Exact Tests			P=0.045N		P=0.147N	
Adrenal: Pheochromocytoma						
Overall Rates (b)	2/52 (4%)		8/52 (15%)		6/52 (12%)	
Adjusted Rates (c)	4.7%		21.1%		13.6%	
Terminal Rates (d)	2/43 (5%)		8/38 (21%)		3/40 (7%)	
Life Table Tests (e)	P=0.110		P=0.029		P=0.123	
Incidental Tumor Tests (e)	P=0.141		P=0.029		P=0.192	
Cochran-Armitage Trend Test (e)	P=0.127					
Fisher Exact Tests			P=0.046		P=0.135	
Thyroid: Follicular Cell Adenoma or Carcinoma						
Overall Rates (b)	0/52 (0%)		4/51 (8%)		1/51 (2%)	
Adjusted Rates (c)	0.0%		10.1%		2.4%	
Terminal Rates (d)	0/43 (0%)		3/38 (8%)		0/40 (0%)	
Life Table Tests (e)	P=0.361		P=0.052		P=0.486	
Incidental Tumor Tests (e)	P=0.435		P=0.067		P=0.602	
Cochran-Armitage Trend Test (e)	P=0.379					
Fisher Exact Tests			P=0.057		P=0.495	

TABLE F1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR AND ANCILLARY GAVAGE STUDIES OF TELONE II® (Continued)

	Vehicle Control		25 mg/kg		50 mg/kg	
	2-Year Study	2-Year and Ancillary Studies (a)	2-Year Study	2-Year and Ancillary Studies (a)	2-Year Study	2-Year and Ancillary Studies (a)
Thyroid: C-Cell Adenoma						
Overall Rates (b)	3/52 (6%)		0/51 (0%)		2/51 (4%)	
Adjusted Rates (c)	7.0%		0.0%		5.0%	
Terminal Rates (d)	3/43 (7%)		0/38 (0%)		2/40 (5%)	
Life Table Tests (e)	P=0.418N		P=0.144N		P=0.533	
Incidental Tumor Tests (e)	P=0.418N		P=0.144N		P=0.533N	
Cochran-Armitage Trend Test (e)	P=0.397N					
Fisher Exact Tests			P=0.125N		P=0.509N	
Thyroid: C-Cell Carcinoma						
Overall Rates (b)	3/52 (6%)		4/51 (8%)		2/51 (4%)	
Adjusted Rates (c)	7.0%		10.5%		5.0%	
Terminal Rates (d)	3/43 (7%)		4/38 (11%)		2/40 (5%)	
Life Table Tests (e)	P=0.454N		P=0.432		P=0.533N	
Incidental Tumor Tests (e)	P=0.454N		P=0.432		P=0.533N	
Cochran-Armitage Trend Test (e)	P=0.426N					
Fisher Exact Tests			P=0.489		P=0.509N	
Thyroid: C-Cell Adenoma or Carcinoma						
Overall Rates (b)	6/52 (12%)		4/51 (8%)		4/51 (8%)	
Adjusted Rates (c)	14.0%		10.5%		10.0%	
Terminal Rates (d)	6/43 (14%)		4/38 (11%)		4/40 (10%)	
Life Table Tests (e)	P=0.347N		P=0.449N		P=0.415N	
Incidental Tumor Tests (e)	P=0.347N		P=0.449N		P=0.415N	
Cochran-Armitage Trend Test (e)	P=0.315N					
Fisher Exact Tests			P=0.383N		P=0.383N	
Pancreatic Islets: Islet Cell Adenoma						
Overall Rates (b)	10/52 (19%)		7/52 (13%)		9/52 (17%)	
Adjusted Rates (c)	22.6%		17.3%		21.9%	
Terminal Rates (d)	9/43 (21%)		5/38 (13%)		8/40 (20%)	
Life Table Tests (e)	P=0.513N		P=0.391N		P=0.566N	
Incidental Tumor Tests (e)	P=0.435N		P=0.298N		P=0.503N	
Cochran-Armitage Trend Test (e)	P=0.446N					
Fisher Exact Tests			P=0.299N		P=0.500N	
Pancreatic Islets: Islet Cell Carcinoma						
Overall Rates (b)	2/52 (4%)		6/52 (12%)		0/52 (0%)	
Adjusted Rates (c)	4.7%		15.3%		0.0%	
Terminal Rates (d)	2/43 (5%)		5/38 (13%)		0/40 (0%)	
Life Table Tests (e)	P=0.293N		P=0.101		P=0.254N	
Incidental Tumor Tests (e)	P=0.265N		P=0.126		P=0.254N	
Cochran-Armitage Trend Test (e)	P=0.259N					
Fisher Exact Tests			P=0.135		P=0.248N	
Pancreatic Islets: Islet Cell Adenoma or Carcinoma						
Overall Rates (b)	12/52 (23%)		13/52 (25%)		9/52 (17%)	
Adjusted Rates (c)	27.2%		31.6%		21.9%	
Terminal Rates (d)	11/43 (26%)		10/38 (26%)		8/40 (20%)	
Life Table Tests (e)	P=0.353N		P=0.374		P=0.378N	
Incidental Tumor Tests (e)	P=0.272N		P=0.491		P=0.321N	
Cochran-Armitage Trend Test (e)	P=0.278N					
Fisher Exact Tests			P=0.500		P=0.313N	

TABLE F1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR AND ANCILLARY GAVAGE STUDIES OF TELONE II® (Continued)

	Vehicle Control		25 mg/kg		50 mg/kg	
	2-Year Study	2-Year and Ancillary Studies (a)	2-Year Study	2-Year and Ancillary Studies (a)	2-Year Study	2-Year and Ancillary Studies (a)
Mammary Gland: Fibroadenoma						
Overall Rates (b)	1/52 (2%)		5/52 (10%)		1/52 (2%)	
Adjusted Rates (c)	2.3%		12.7%		2.5%	
Terminal Rates (d)	1/43 (2%)		4/38 (11%)		1/40 (3%)	
Life Table Tests (e)	P=0.554		P=0.081		P=0.746	
Incidental Tumor Tests (e)	P=0.587		P=0.105		P=0.746	
Cochran-Armitage Trend Test (e)	P=0.589					
Fisher Exact Tests			P=0.102		P=0.752N	
Testis: Interstitial Cell Tumor						
Overall Rates (b)	46/52 (88%)		46/52 (88%)		48/52 (92%)	
Adjusted Rates (c)	97.9%		100.0%		100.0%	
Terminal Rates (d)	42/43 (98%)		38/38 (100%)		40/40 (100%)	
Life Table Tests (e)	P=0.102		P=0.117		P=0.126	
Incidental Tumor Tests (e)	P=0.243		P=0.390		P=0.343	
Cochran-Armitage Trend Test (e)	P=0.316					
Fisher Exact Tests			P=0.620N		P=0.371	
Preputial Gland: Adenoma, Adenocarcinoma or Carcinoma						
Overall Rates (b)	3/52 (6%)		0/52 (0%)		1/52 (2%)	
Adjusted Rates (c)	7.0%		0.0%		2.5%	
Terminal Rates (d)	3/43 (7%)		0/38 (0%)		1/40 (3%)	
Life Table Tests (e)	P=0.196N		P=0.144N		P=0.331N	
Incidental Tumor Tests (e)	P=0.196N		P=0.144N		P=0.331N	
Cochran-Armitage Trend Test (e)	P=0.176N					
Fisher Exact Tests			P=0.121N		P=0.309N	
All Sites: Mesothelioma						
Overall Rates (b)	3/52 (6%)		2/52 (4%)		3/52 (6%)	
Adjusted Rates (c)	6.6%		5.3%		6.9%	
Terminal Rates (d)	2/43 (5%)		2/38 (5%)		2/40 (5%)	
Life Table Tests (e)	P=0.566		P=0.549N		P=0.643	
Incidental Tumor Tests (e)	P=0.536N		P=0.509N		P=0.582N	
Cochran-Armitage Trend Test (e)	P=0.588N					
Fisher Exact Tests			P=0.500N		P=0.661N	

(a) Pooled results of the 2-year study and the ancillary study in which five rats per dose per sex were killed at 9, 16, 21, 24, and 27 months. Tumors observed in the ancillary studies are regarded as incidental rather than fatal in both the life table and incidental tumor tests.
(b) Number of tumor-bearing animals/number of animals examined at the site
(c) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(d) Observed tumor incidence at terminal kill
(e) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the 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's exact test compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(f) No P value is presented because no tumors were observed in the 25 mg/kg and vehicle control groups.

TABLE F2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR AND ANCILLARY GAVAGE STUDIES OF TELONE II®

	Vehicle Control		25 mg/kg		50 mg/kg	
	2-Year Study	2-Year and Ancillary Studies (a)	2-Year Study	2-Year and Ancillary Studies (a)	2-Year Study	2-Year and Ancillary Studies (a)
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma						
Overall Rates (b)	1/52 (2%)		1/52 (2%)		3/52 (6%)	
Adjusted Rates (c)	2.9%		2.8%		7.9%	
Terminal Rates (d)	1/34 (3%)		1/36 (3%)		3/38 (8%)	
Life Table Tests (e)	P=0.231		P=0.749N		P=0.345	
Incidental Tumor Tests (e)	P=0.231		P=0.749N		P=0.345	
Cochran-Armitage Trend Test (e)	P=0.202					
Fisher Exact Tests			P=0.752		P=0.309	
Hematopoietic System: Mononuclear Cell Leukemia						
Overall Rates (b)	9/52 (17%)		10/52 (19%)		5/52 (10%)	
Adjusted Rates (c)	20.8%		25.1%		11.7%	
Terminal Rates (d)	3/34 (9%)		7/36 (19%)		2/38 (5%)	
Life Table Tests (e)	P=0.147N		P=0.500		P=0.171N	
Incidental Tumor Tests (e)	P=0.179N		P=0.602N		P=0.286N	
Cochran-Armitage Trend Test (e)	P=0.173N					
Fisher Exact Tests			P=0.500		P=0.195N	
Liver: Neoplastic Nodule						
Overall Rates (b)	6/52 (12%)	6/75 (8%)	6/52 (12%)	8/77 (10%)	10/52 (19%)	12/77 (16%)
Adjusted Rates (c)	16.7%		15.5%	26.3%		
Terminal Rates (d)	5/34 (15%)		4/36 (11%)		10/38 (26%)	
Life Table Tests (e)	P=0.220	P=0.134	P=0.597N	P=0.451	P=0.275	P=0.166
Incidental Tumor Tests (e)	P=0.204	P=0.111	P=0.571	P=0.319	P=0.259	P=0.157
Cochran-Armitage Trend Test (e)	P=0.162	P=0.089				
Fisher Exact Tests			P=0.620	P=0.410	P=0.208	P=0.116
Stomach: Squamous Cell Papilloma						
Overall Rates (b)	0/52 (0%)	0/75 (0%)	2/52 (4%)	2/77 (3%)	3/52 (6%)	8/77 (10%)
Adjusted Rates (c)	0.0%		4.9%		7.4%	
Terminal Rates (d)	0/34 (0%)		1/36 (3%)		2/38 (5%)	
Life Table Tests (e)	P=0.097	P=0.002	P=0.241	P=0.245	P=0.138	P=0.006
Incidental Tumor Tests (e)	P=0.093	P=0.002	P=0.350	P=0.309	P=0.116	P=0.005
Cochran-Armitage Trend Test (e)	P=0.082	P=0.002				
Fisher Exact Tests			P=0.248	P=0.255	P=0.121	P=0.004
Pituitary: Chromophobe Adenoma						
Overall Rates (b)	28/50 (56%)		26/51 (51%)		30/52 (58%)	
Adjusted Rates (c)	71.5%		61.4%		68.1%	
Terminal Rates (d)	23/34 (68%)		19/35 (54%)		24/38 (63%)	
Life Table Tests (e)	P=0.477N		P=0.394N		P=0.505N	
Incidental Tumor Tests (e)	P=0.485		P=0.510N		P=0.489	
Cochran-Armitage Trend Test (e)	P=0.468					
Fisher Exact Tests			P=0.380N		P=0.511	
Pituitary: Chromophobe Adenoma or Carcinoma						
Overall Rates (b)	30/50 (60%)		27/51 (53%)		31/52 (60%)	
Adjusted Rates (c)	72.9%		62.3%		68.8%	
Terminal Rates (d)	23/34 (68%)		19/35 (54%)		24/38 (63%)	
Life Table Tests (e)	P=0.404N		P=0.332N		P=0.427N	
Incidental Tumor Tests (e)	P=0.495N		P=0.396N		P=0.565N	
Cochran-Armitage Trend Test (e)	P=0.528N					
Fisher Exact Tests			P=0.304N		P=0.565N	

TABLE F2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR AND ANCILARY GAVAGE STUDIES OF TELONE II® (Continued)

	Vehicle Control		25 mg/kg		50 mg/kg	
	2-Year Study	2-Year and Ancillary Studies (a)	2-Year Study	2-Year and Ancillary Studies (a)	2-Year Study	2-Year and Ancillary Studies (a)
Thyroid: Follicular Cell Adenoma or Carcinoma						
Overall Rates (b)	0/52 (0%)		2/52 (4%)		4/52 (8%)	
Adjusted Rates (c)	0.0%		5.6%		10.1%	
Terminal Rates (d)	0/34 (0%)		2/36 (6%)		3/38 (8%)	
Life Table Tests (e)	P=0.047		P=0.251		P=0.077	
Incidental Tumor Tests (e)	P=0.043		P=0.251		P=0.064	
Cochran-Armitage Trend Test (e)	P=0.037					
Fisher Exact Tests			P=0.248		P=0.059	
Thyroid: C-Cell Adenoma						
Overall Rates (b)	4/52 (8%)		6/52 (12%)		2/52 (4%)	
Adjusted Rates (c)	11.4%		16.7%		4.6%	
Terminal Rates (d)	3/34 (9%)		6/36 (17%)		1/38 (3%)	
Life Table Tests (e)	P=0.244N		P=0.405		P=0.296N	
Incidental Tumor Tests (e)	P=0.251N		P=0.327		P=0.292N	
Cochran-Armitage Trend Test (e)	P=0.294N					
Fisher Exact Tests			P=0.370		P=0.339N	
Thyroid: C-Cell Adenoma or Carcinoma						
Overall Rates (b)	6/52 (12%)		8/52 (15%)		3/52 (6%)	
Adjusted Rates (c)	16.3%		22.2%		7.2%	
Terminal Rates (d)	4/34 (12%)		8/36 (22%)		2/38 (5%)	
Life Table Tests (e)	P=0.170N		P=0.425		P=0.204N	
Incidental Tumor Tests (e)	P=0.188N		P=0.296		P=0.216N	
Cochran-Armitage Trend Test (e)	P=0.219N					
Fisher Exact Tests			P=0.387		P=0.244N	
Pancreatic Islets: Islet Cell Adenoma						
Overall Rates (b)	3/52 (6%)		1/52 (2%)		0/52 (0%)	
Adjusted Rates (c)	8.5%		2.8%		0.0%	
Terminal Rates (d)	2/34 (6%)		1/36 (3%)		0/38 (0%)	
Life Table Tests (e)	P=0.051N		P=0.287N		P=0.104N	
Incidental Tumor Tests (e)	P=0.070N		P=0.393N		P=0.127N	
Cochran-Armitage Trend Test (e)	P=0.060N					
Fisher Exact Tests			P=0.309N		P=0.121N	
Pancreatic Islets: Islet Cell Adenoma or Carcinoma						
Overall Rates (b)	3/52 (6%)		1/52 (2%)		1/52 (2%)	
Adjusted Rates (c)	8.5%		2.8%		2.6%	
Terminal Rates (d)	2/34 (6%)		1/36 (3%)		1/38 (3%)	
Life Table Tests (e)	P=0.175N		P=0.287N		P=0.269N	
Incidental Tumor Tests (e)	P=0.207N		P=0.393N		P=0.304N	
Cochran-Armitage Trend Test (e)	P=0.202N					
Fisher Exact Tests			P=0.309N		P=0.309N	
Mammary Gland: Fibroadenoma						
Overall Rates (b)	14/52 (27%)		20/52 (38%)		24/52 (46%)	
Adjusted Rates (c)	36.1%		51.2%		56.5%	
Terminal Rates (d)	10/34 (29%)		17/36 (47%)		20/38 (53%)	
Life Table Tests (e)	P=0.066		P=0.189		P=0.078	
Incidental Tumor Tests (e)	P=0.040		P=0.054		P=0.054	
Cochran-Armitage Trend Test (e)	P=0.027					
Fisher Exact Tests			P=0.148		P=0.033	

TABLE F2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR AND ANCILLARY GAVAGE STUDIES OF TELONE II® (Continued)

	Vehicle Control		25 mg/kg		50 mg/kg	
	2-Year Study	2-Year and Ancillary Studies (a)	2-Year Study	2-Year and Ancillary Studies (a)	2-Year Study	2-Year and Ancillary Studies (a)
Mammary Gland: Adenoma or Fibroadenoma						
Overall Rates (b)	15/52 (29%)		20/52 (38%)		24/52 (46%)	
Adjusted Rates (c)	38.8%		51.2%		56.5%	
Terminal Rates (d)	11/34 (32%)		17/36 (47%)		20/38 (53%)	
Life Table Tests (e)	P=0.097		P=0.252		P=0.114	
Incidental Tumor Tests (e)	P=0.063		P=0.085		P=0.083	
Cochran-Armitage Trend Test (e)	P=0.043					
Fisher Exact Tests			P=0.203		P=0.052	
Preputial/Clitoral Gland: Adenoma or Carcinoma						
Overall Rates (b)	0/52 (0%)		3/52 (6%)		2/52 (4%)	
Adjusted Rates (c)	0.0%		8.3%		5.3%	
Terminal Rates (d)	0/34 (0%)		3/36 (8%)		2/38 (5%)	
Life Table Tests (e)	P=0.231		P=0.131		P=0.263	
Incidental Tumor Tests (e)	P=0.231		P=0.131		P=0.263	
Cochran-Armitage Trend Test (e)	P=0.202					
Fisher Exact Tests			P=0.121		P=0.248	
Uterus: Endometrial Stromal Polyp						
Overall Rates (b)	16/52 (31%)		10/52 (19%)		12/52 (23%)	
Adjusted Rates (c)	41.5%		25.7%		31.6%	
Terminal Rates (d)	12/34 (35%)		8/36 (22%)		12/38 (32%)	
Life Table Tests (e)	P=0.136N		P=0.113N		P=0.161N	
Incidental Tumor Tests (e)	P=0.140N		P=0.110N		P=0.177N	
Cochran-Armitage Trend Test (e)	P=0.210N					
Fisher Exact Tests			P=0.129N		P=0.254N	
Uterus: Endometrial Stromal Polyp or Sarcoma						
Overall Rates (b)	17/52 (33%)		10/52 (19%)		12/52 (23%)	
Adjusted Rates (c)	44.2%		25.7%		31.6%	
Terminal Rates (d)	13/34 (38%)		8/36 (22%)		12/38 (32%)	
Life Table Tests (e)	P=0.093N		P=0.077N		P=0.112N	
Incidental Tumor Tests (e)	P=0.094N		P=0.073N		P=0.124N	
Cochran-Armitage Trend Test (e)	P=0.152N					
Fisher Exact Tests			P=0.090N		P=0.191N	

(a) Pooled results of the 2-year study and the ancillary study in which five rats per dose per sex were killed at 9, 16, 21, 24, and 27 months. Tumors observed in the ancillary studies are regarded as incidental rather than fatal in both the life table and incidental tumor tests..
(b) 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
(d) Observed tumor incidence at terminal kill
(e) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the 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's exact test compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE F3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TELONE II®

	Vehicle Control	50 mg/kg	100 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	1/50 (2%)	11/50 (22%)	9/50 (18%)
Adjusted Rates (b)	11.1%	33.4%	27.0%
Terminal Rates (c)	0/8 (0%)	7/28 (25%)	7/31 (23%)
Life Table Tests (d)	P=0.419	P=0.147	P=0.312
Incidental Tumor Tests (d)	P=0.185	P=0.026	P=0.162
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	0.0%	7.1%	8.0%
Terminal Rates (c)	0/8 (0%)	2/28 (7%)	1/31 (3%)
Life Table Tests (d)	P=0.271	P=0.538	P=0.361
Incidental Tumor Tests (d)	P=0.165	P=0.538	P=0.165
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	1/50 (2%)	13/50 (26%)	12/50 (24%)
Adjusted Rates (b)	11.1%	39.8%	33.5%
Terminal Rates (c)	0/8 (0%)	9/28 (32%)	8/31 (26%)
Life Table Tests (d)	P=0.264	P=0.097	P=0.166
Incidental Tumor Tests (d)	P=0.072	P=0.015	P=0.040
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	0/50 (0%)	5/50 (10%)	4/50 (8%)
Adjusted Rates (b)	0.0%	14.6%	12.9%
Terminal Rates (c)	0/8 (0%)	2/28 (7%)	4/31 (13%)
Life Table Tests (d)	P=0.383	P=0.206	P=0.340
Incidental Tumor Tests (d)	P=0.294	P=0.160	P=0.340
Circulatory System: Hemangioma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	0.0%	10.7%	0.0%
Terminal Rates (c)	0/8 (0%)	3/28 (11%)	0/31 (0%)
Life Table Tests (d)	P=0.324N	P=0.406	(e)
Incidental Tumor Tests (d)	P=0.324N	P=0.406	(e)
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	12.5%	9.9%	2.7%
Terminal Rates (c)	1/8 (13%)	2/28 (7%)	0/31 (0%)
Life Table Tests (d)	P=0.225N	P=0.698N	P=0.455N
Incidental Tumor Tests (d)	P=0.333N	P=0.678	P=0.588N
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	1/50 (2%)	6/50 (12%)	1/50 (2%)
Adjusted Rates (b)	12.5%	20.3%	2.7%
Terminal Rates (c)	1/8 (13%)	5/28 (18%)	0/31 (0%)
Life Table Tests (d)	P=0.123N	P=0.464	P=0.455N
Incidental Tumor Tests (d)	P=0.188N	P=0.400	P=0.588N
Liver: Adenoma			
Overall Rates (a)	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	4.5%	3.6%	8.7%
Terminal Rates (c)	0/8 (0%)	1/28 (4%)	2/31 (6%)
Life Table Tests (d)	P=0.487	P=0.552N	P=0.689
Incidental Tumor Tests (d)	P=0.293	P=0.753N	P=0.415

TABLE F3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TELONE II® (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Liver: Carcinoma			
Overall Rates (a)	4/50 (8%)	6/50 (12%)	10/50 (20%)
Adjusted Rates (b)	25.8%	19.9%	28.3%
Terminal Rates (c)	1/8 (13%)	5/28 (18%)	7/31 (23%)
Life Table Tests (d)	P=0.539N	P=0.268N	P=0.462N
Incidental Tumor Tests (d)	P=0.255	P=0.620	P=0.352
Liver: Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	7/50 (14%)	13/50 (26%)
Adjusted Rates (b)	29.2%	23.4%	35.9%
Terminal Rates (c)	1/8 (13%)	6/28 (21%)	9/31 (29%)
Life Table Tests (d)	P=0.520	P=0.197N	P=0.483N
Incidental Tumor Tests (d)	P=0.142	P=0.638	P=0.211
Stomach: Squamous Cell Papilloma			
Overall Rates (a)	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	0.0%	6.7%	7.4%
Terminal Rates (c)	0/8 (0%)	1/28 (4%)	1/31 (3%)
Life Table Tests (d)	P=0.234	P=0.510	P=0.280
Incidental Tumor Tests (d)	P=0.051	P=0.403	P=0.037

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the 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. Because of the deaths of 25 vehicle controls during weeks 48-51, Cochran-Armitage and Fisher exact tests (which do not adjust for survival differences) were not carried out.
(e) No P value is presented because no tumors were observed in the 100 mg/kg and vehicle control groups.

TABLE F4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TELONE II®

	Vehicle Control	50 mg/kg	100 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	8/50 (16%)
Adjusted Rates (b)	0.0%	6.7%	21.3%
Terminal Rates (c)	0/46 (0%)	3/45 (7%)	7/36 (19%)
Life Table Tests (d)	P<0.001	P=0.118	P=0.002
Incidental Tumor Tests (d)	P=0.001	P=0.118	P=0.003
Cochran-Armitage Trend Test (d)	P=0.002		
Fisher Exact Tests		P=0.121	P=0.003
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	8/50 (16%)
Adjusted Rates (b)	4.3%	8.9%	21.3%
Terminal Rates (c)	2/46 (4%)	4/45 (9%)	7/36 (19%)
Life Table Tests (d)	P=0.011	P=0.327	P=0.020
Incidental Tumor Tests (d)	P=0.019	P=0.327	P=0.032
Cochran-Armitage Trend Test (d)	P=0.029		
Fisher Exact Tests		P=0.339	P=0.046
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	5/50 (10%)	10/50 (20%)	9/50 (18%)
Adjusted Rates (b)	10.6%	20.8%	23.6%
Terminal Rates (c)	4/46 (9%)	7/45 (16%)	7/36 (19%)
Life Table Tests (d)	P=0.074	P=0.132	P=0.092
Incidental Tumor Tests (d)	P=0.137	P=0.157	P=0.158
Cochran-Armitage Trend Test (d)	P=0.169		
Fisher Exact Tests		P=0.131	P=0.194
Circulatory System: Hemangioma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	0.0%	6.7%	2.6%
Terminal Rates (c)	0/46 (0%)	3/45 (7%)	0/36 (0%)
Life Table Tests (d)	P=0.305	P=0.118	P=0.459
Incidental Tumor Tests (d)	P=0.371	P=0.118	P=0.638
Cochran-Armitage Trend Test (d)	P=0.376		
Fisher Exact Tests		P=0.121	P=0.500
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	6.4%	2.2%	8.0%
Terminal Rates (c)	2/46 (4%)	1/45 (2%)	2/36 (6%)
Life Table Tests (d)	P=0.494	P=0.317N	P=0.546
Incidental Tumor Tests (d)	P=0.586N	P=0.277N	P=0.640N
Cochran-Armitage Trend Test (d)	P=0.593N		
Fisher Exact Tests		P=0.309N	P=0.661N
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	6.4%	8.9%	10.4%
Terminal Rates (c)	2/46 (4%)	4/45 (9%)	2/36 (6%)
Life Table Tests (d)	P=0.302	P=0.486	P=0.375
Incidental Tumor Tests (d)	P=0.427	P=0.521	P=0.587
Cochran-Armitage Trend Test (d)	P=0.424		
Fisher Exact Tests		P=0.500	P=0.500

TABLE F4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF TELONE II® (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Liver: Hepatocellular Adenoma			
Overall Rates (a)	0/50 (0%)	5/50 (10%)	3/50 (6%)
Adjusted Rates (b)	0.0%	10.8%	7.8%
Terminal Rates (c)	0/46 (0%)	4/45 (9%)	2/36 (6%)
Life Table Tests (d)	P=0.082	P=0.033	P=0.088
Incidental Tumor Tests (d)	P=0.164	P=0.040	P=0.164
Cochran-Armitage Trend Test (d)	P=0.132		
Fisher Exact Tests		P=0.028	P=0.121
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	2.2%	6.7%	0.0%
Terminal Rates (c)	1/46 (2%)	3/45 (7%)	0/36 (0%)
Life Table Tests (d)	P=0.457N	P=0.298	P=0.549N
Incidental Tumor Tests (d)	P=0.457N	P=0.298	P=0.549N
Cochran-Armitage Trend Test (d)	P=0.381N		
Fisher Exact Tests		P=0.309	P=0.500N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	1/50 (2%)	8/50 (16%)	3/50 (6%)
Adjusted Rates (b)	2.2%	17.4%	7.8%
Terminal Rates (c)	1/46 (2%)	7/45 (16%)	2/36 (6%)
Life Table Tests (d)	P=0.183	P=0.018	P=0.232
Incidental Tumor Tests (d)	P=0.291	P=0.021	P=0.361
Cochran-Armitage Trend Test (d)	P=0.287		
Fisher Exact Tests		P=0.015	P=0.309
Stomach: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	0/50 (0%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (b)	0.0%	2.2%	10.6%
Terminal Rates (c)	0/46 (0%)	1/45 (2%)	3/36 (8%)
Life Table Tests (d)	P=0.014	P=0.496	P=0.040
Incidental Tumor Tests (d)	P=0.021	P=0.496	P=0.059
Cochran-Armitage Trend Test (d)	P=0.026		
Fisher Exact Tests		P=0.500	P=0.059
Urinary Bladder: Transitional Cell Carcinoma			
Overall Rates (a)	0/50 (0%)	8/50 (16%)	21/48 (44%)
Adjusted Rates (b)	0.0%	17.4%	56.5%
Terminal Rates (c)	0/46 (0%)	7/45 (16%)	19/35 (54%)
Life Table Tests (d)	P<0.001	P=0.005	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.006	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Tests		P=0.003	P<0.001
Pituitary: Chromophobe Adenoma			
Overall Rates (a)	4/48 (8%)	6/48 (13%)	2/41 (5%)
Adjusted Rates (b)	9.1%	14.0%	6.3%
Terminal Rates (c)	4/44 (9%)	6/43 (14%)	2/32 (6%)
Life Table Tests (d)	P=0.456N	P=0.355	P=0.491N
Incidental Tumor Tests (d)	P=0.456N	P=0.355	P=0.491N
Cochran-Armitage Trend Test (d)	P=0.369N		
Fisher Exact Tests		P=0.370	P=0.417N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the 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's exact test compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

APPENDIX G

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

TABLE G1. HISTORICAL INCIDENCE OF ADRENAL GLAND TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Pheochromocytoma	Malignant Pheochromocytoma	All Pheochromocytomas
Historical Incidence at Frederick Cancer Research Center			
Telone II®	2/52	2/52	2/52
Overall Historical Incidence			
TOTAL	193/1,135 (17.0%)	10/1,135 (0.9%)	202/1,135 (17.8%)
SD (b)	10.20%	1.51%	10.13%
Range (c)			
High	19/49	3/48	19/49
Low	1/50	0/52	1/50

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

TABLE G2. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Neoplastic Nodule	Carcinoma	Neoplastic Nodule or Carcinoma
Historical Incidence at Frederick Cancer Research Center			
Telone II®	1/52	0/52	1/52
Overall Historical Incidence			
TOTAL	31/1,141 (2.7%)	9/1,141 (0.8%)	40/1,141 (3.5%)
SD (b)	3.36%	1.45%	3.66%
Range (c)			
High	7/50	2/50	7/50
Low	0/50	0/52	0/50

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

TABLE G3. HISTORICAL INCIDENCE OF THYROID GLAND FOLLICULAR CELL TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Frederick Cancer Research Center			
Telone II®	0/52	0/52	0/52
Overall Historical Incidence			
TOTAL	(b) 7/1,104 (0.6%)	5/1,104 (0.5%)	12/1,104 (1.1%)
SD (c)	1.46%	0.87%	1.51%
Range (d)			
High	3/48	1/46	3/48
Low	0/52	0/52	0/52

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Includes three cystadenomas, NOS and one papillary cystadenoma, NOS
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE G4. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Frederick Cancer Research Center			
Telone II®	1/50	4/50	5/50
Overall Historical Incidence			
TOTAL	133/1,084 (12.3%)	(b) 222/1,084 (20.5%)	340/1,084 (31.4%)
SD (c)	6.72%	7.90%	10.30%
Range (d)			
High	13/50	18/50	25/50
Low	0/50	4/50	5/50

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

TABLE G5. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Leukemia	Lymphoma	Leukemia or Lymphoma
Historical Incidence at Frederick Cancer Research Center			
Telone II®	0/50	0/50	0/50
Overall Historical Incidence			
TOTAL	6/1,090 (0.6%)	126/1,090 (11.6%)	132/1,090 (12.1%)
SD (b)	2.24%	5.63%	6.35%
Range (c)			
High	5/48	11/50	13/48
Low	0/50	0/50	0/50

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

TABLE G6. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Frederick Cancer Research Center			
Telone II®	0/50	1/50	1/50
Overall Historical Incidence			
TOTAL	47/1,176 (4.0%)	34/1,176 (2.9%)	80/1,176 (6.8%)
SD (b)	2.55%	2.18%	3.37%
Range (c)			
High	5/50	4/50	7/50
Low	0/50	0/50	1/50

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

TABLE G7. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Frederick Cancer Research Center			
Telone II®	1/50	0/50	1/50
Overall Historical Incidence			
TOTAL	99/1,082 (9.1%)	(b) 58/1,082 (5.4%)	(b) 155/1,082 (14.3%)
SD (c)	4.77%	4.13%	6.31%
Range (d)			
High	10/50	7/50	13/50
Low	0/47	0/50	1/50

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

TABLE G8. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Frederick Cancer Research Center			
Telone II®	0/50	2/50	2/50
Overall Historical Incidence			
TOTAL	36/1,103 (3.3%)	16/1,103 (1.5%)	52/1,103 (4.7%)
SD (b)	2.81%	1.61%	3.46%
Range (c)			
High	5/50	2/49	6/50
Low	0/50	0/50	0/50

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

TABLE G9. HISTORICAL INCIDENCE OF STOMACH TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	No. of Animals At Risk	No. of Tumors in Vehicle Controls	Site	Diagnosis
Historical Incidence at Frederick Cancer Research Center				
Telone II®	52	1	Stomach, NOS	Squamous cell papilloma
Overall Historical Incidence				
	1,114	2	Stomach, NOS	Squamous cell papilloma
		1	Stomach, NOS	Squamous cell carcinoma
		2	Forestomach	Squamous cell papilloma
		1	Cardiac stomach	Squamous cell papilloma

(a) Data as of March 16, 1983, for studies of at least 104 weeks

TABLE G10. HISTORICAL INCIDENCE OF STOMACH TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	No. of Animals At Risk	No. of Tumors in Vehicle Controls	Site	Diagnosis
Historical Incidence at Frederick Cancer Research Center				
Telone II®	52	0		
Overall Historical Incidence				
	1,125	2	Stomach, NOS	Squamous cell papilloma
		1	Stomach, NOS	Squamous cell carcinoma
		1	Gastric mucosa	Squamous cell papilloma
		1	Forestomach	Squamous cell papilloma

(a) Data as of March 16, 1983, for studies of at least 104 weeks

TABLE G11. HISTORICAL INCIDENCE OF STOMACH TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	No. of Animals At Risk	No. of Tumors in Vehicle Controls	Site	Diagnosis
Historical Incidence at Frederick Cancer Research Center				
Telone II®	50	0		
Overall Historical Incidence				
	1,055	1	Stomach, NOS	Papilloma, NOS
		2	Stomach, NOS	Squamous cell papilloma
		2	Stomach, NOS	Squamous cell carcinoma
		1	Forestomach	Papilloma, NOS
		1	Forestomach	Squamous cell carcinoma

(a) Data as of March 16, 1983, for studies of at least 104 weeks

TABLE G12. HISTORICAL INCIDENCE OF STOMACH TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	No. of Animals At Risk	No. of Tumors in Vehicle Controls	Site	Diagnosis
Historical Incidence at Frederick Cancer Research Center				
Telone II®	50	0		
Overall Historical Incidence				
	1,077	2	Stomach, NOS	Squamous cell papilloma
		1	Stomach, NOS	Adenocarcinoma, NOS
		1	Gastric mucosa	Squamous cell papilloma
		1	Gastric mucosa	Adenoma, NOS
		1	Gastric mucosa	Adenomatous polyp, NOS
		1	Forestomach	Squamous cell papilloma

(a) Data as of March 16, 1983, for studies of at least 104 weeks

TABLE G13. HISTORICAL INCIDENCE OF URINARY BLADDER TRANSITIONAL CELL TUMORS IN $B6C3F_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Male	Female
Historical Incidence at Frederick Cancer Research Center		
Telone II®	0/50	0/50
Overall Historical Incidence		
	0/1,033	0/1,025

(a) Data as of March 16, 1983, for studies of at least 104 weeks

APPENDIX H

CHEMICAL CHARACTERIZATION OF TELONE II®

I. Identity and Purity Determinations of Lot No. EXP-N-3993

A. Physical Properties

1. Boiling Point:	Determined	Literature Values
	109° C	108° C (tech) 104° C (*trans*) 112° C (*cis*) (Merck, 1968)

2. Appearance: Colorless liquid

B. Spectral Data

1. Infrared	Determined	Literature Values
a. Instrument:	Perkin-Elmer 467	
b. Cell:	Neat liquid film between sodium chloride plates	
c. Results:	3080, 3060, 2955, 1630, 1440, 1332, 1290, 1275, 1258, 1238, 1154, 1082, 1032, 938, 923, 855, 820, 760, 680 cm^{-1}	*cis*-1,3-Dichloropropene: 3030, 2940, 1640, 1450, 1330, 1300, 1280, 1270, 1240, 1160, 1080, 940, 930, 860, 820, 780, 680 cm^{-1} *trans*-1,3-Dichloropropene: 3030, 2940, 1640, 1450, 1270, 1240, 1080, 940, 860, 780, 690 cm^{-1} (Graselli and Ritchy, 1975)

2. Ultraviolet/Visible	Determined	Literature Values
a. Instrument:	Cary 17 dual beam	
b. Solvent:	Hexane	
c. Results:	λ_{max} = 209 nm ε_{max} = 3395	No reference found

3. Nuclear Magnetic Resonance

	Determined	Literature Values
Run 1: Proton spectrum		
a. Instrument:	Varian XL-100	
b. Solvent:	Deuterated chloroform with internal tetramethylsilane	
c. Results:	Unexplained resonances add up to approximately 16%-17% of total proton intensities	
Run 2: Carbon-13 spectrum		
a. Instrument:	Varian XL-100	
b. Solvent:	Deuterated chloroform with internal tetramethylsilane	
c. Results:	The ^{13}C spectrum for this 3-carbon compound showed six resonances. Off-resonance decoupling showed that the carbons resonating at $\delta = 42.0$ and 37.9 have two directly bonded protons, whereas the four olefinic carbons at $\delta = 129.1$, 127.3, and 122.3 each have one directly bonded proton. The ^{13}C spectrum indicates a mixture of *cis*- and *trans*-isomers	*trans*- (E) - 1,3-Dichloropropene δ ^{13}C, ppm values are given as 41.8, 129.0, and 122.7 with 10% deuterated chloroform as internal reference (Chukovskaya et al., 1976)

C. Gas-Liquid Chromatographic Analyses

Assay 1:

Instrument: Hewlett-Packard 5710A
Detector: Flame ionization
Column: 3% SP-2250 on 100-120 mesh Supelcoport, 6 ft × 2 mm ID glass column
Carrier gas: Nitrogen
Carrier flow rate: 25 ml/min
Column oven temperature program: 45°-80° C at 4° C/min
Results: Two major and nine minor peaks

Peak	Retention Time (min)	Area (percent of total)
1	3.64	3.1
2	3.92	0.7
3	4.27	0.9
4	4.87	43.5
5	5.22	4.1
6	5.96	44.9
7	6.48	0.7
8	6.95	0.3
9	7.38	1 3
10	7.88	0.2
11	9.28	0.2
		Total = 99.9

Assay 2:

Instrument: Hewlett-Packard 5710A
Detector: Flame ionization
Column: 10% Carbowax 20M on 100-120 mesh HP Chromosorb W, 6 ft × 2 mm ID, glass
Carrier gas: Nitrogen
Carrier flow rate: 20 ml/min
Column oven temperature program: 50°-100° C at 4° C/min and held at 100° C for 8 min
Results: Two major peaks and 11 minor peaks

Peak	Retention Time (min)	Area (percent of total)
1	2.22	1.2
2	3.34	0.9
3	4.67	2.5
4	6.18	4.5
5	6.88	0.6
6	8.11	0.4
7	8.92	0.1
8	10.28	41.6
9	11.35	0.1
10	11.98	0.4
11	12.37	0.3
12	13.33	45.9
13	14.97	1.5
		Total = 100

D. **Mass Spectrometry:**

Instrument: Finnigan 3300 EI/MS with 6000 Finnigan data system
Ionization mode: GLC/EI/MS
Chromatograph: Varian 1400 GLC
Column: 10% Carbowax 20M on 100-120 mesh HP Chromosorb W, 6 ft × 2 mm ID glass column
Carrier gas: Helium
Carrier flow rate: 25 ml/min
Column temperature program: 50°-100° C at 4° C/min
Results: Two major components plus 12 other components observed. Spectra were obtained on 12 of the 14 peaks . Five components were identified.

Peak	Computer Retention Time (min)	Identity
1	2.93	Not identified
2	3.33	Not identified
3	4.13	Not identified
4	4.87	Not identified
5	5.40	Not identified
6	5.80 (2.5%)	1,2-Dichloropropane
7	6.27	Not identified
8	6.87	Not identified
9	8.40 (41.6%)	*cis*-1,3-Dichloropropene
10	9.80	Not identified
11	10.73 (45.9%)	*trans*-1,3-Dichloropropene
12	11.93 (1.5%)	Trichloropropene isomer
13	14.00	Not identified
14	16.70	Trichloropropene isomer

Note: The percentages in parentheses next to the retention times were taken from the gas-liquid chromatographic purity assay number 2 above.

II. Test Chemical Stability Study of Lot No. EXP-N-3993

A. Analytical Method:

Instrument: Hewlett-Packard 5710A
Detector: Flame ionization
Column: 3% SP-2250 on 100-120 mesh Supelcoport, 6 ft × 2 mm ID glass column
Carrier gas: Nitrogen
Carrier flow rate: 20 ml/min
Column temperature program: Held at 45° C for 2 min; then increased to 100° C at 4° C/min and held at 100° C for 2 min

B. Results:

Date	Isomer	Percentage Run 1	Percentage Run 2	Percentage Run 3	*cis*- and *trans*-1,3-Dichloropropene Total Percentage
10/78	*cis*	43.0	43.2	--	
	trans	46.8	46.6	--	89.8
1/79	*cis*	42.0	42.0	43.2	
	trans	47.1	46.6	46.0	89.0
4/79	*cis*	43.6	43.9	--	
	trans	45.9	46.6	--	90.0
7/79	*cis*	43.7	43.5	--	
	trans	46.1	46.5	--	89.9

APPENDIX I

CHEMICAL CHARACTERIZATION AND ANALYSIS OF DOSE MIXTURES: METHODS AND DATA

Studies Conducted at the Analytical Chemistry Laboratory

I. **Homogeneity:** Telone II® in corn oil formed an isotropic solution of one phase. This conclusion was supported by the quality control program's data.

II. **Stability:** Telone II®/corn oil dose mixtures were prepared fresh daily and were used immediately after preparation.

III. **Quality Control Program Analysis:**

A. **Assay method:** Gas-liquid chromatography
B. **Instrument:** Hewlett-Packard 5710A
C. **Column:** 3% SP-2250 on 100-120 mesh Supelcoport, 6 ft × 2 mm ID glass column
D. **Detection:** ^{63}Ni electron capture
E. **Oven Temperature:** Isothermal at 50° C.
F. **Carrier gas:** Argon:methane (95:5)
G. **Flow rate:** 20 ml/min
H. **Results:** See Table I1

TABLE I1. ANALYSIS OF TELONE II®/CORN OIL MIXTURES IN THE TWO-YEAR GAVAGE STUDIES

Date Mixed	Concentration of Telone II® in Corn Oil for Target Concentrations (a)			
	Rats		Mice	
	5 mg/ml	10 mg /ml	10 mg/ml	20 mg/ml
8/10/77	4.9	10.6	--	--
9/12/77	5.3	10.4	--	--
10/25/77	(b) 4.0	9.0	--	--
11/23/77	5.2	10.0	--	--
12/7/77	(b) 5.7	9.9	--	--
1/9/78	(b) 5.8	9.2	--	--
3/1/78	5.1	9.9	--	--
4/25/78	4.3	9.1	--	--
5/29/78	4.1	9.5	--	--
7/1/78	4.8	9.1	--	--
8/19/78	4.7	9.0	(b) 8.8	19.6
9/5/78	4.8	(b) 8.8	(b) 8.9	19.6
10/10/78	4.9	10.1	9.1	19.1
11/8/78	(b) 4.1	9.1	9.3	18.8
12/15/78	4.9	9.1	9.5	21.0
1/17/79	4.8	9.3	9.5	18.6
2/5/79	5.0	9.5	--	--
3/26/79	4.8	9.1	--	--
4/13/79	4.4	(b) 8.8	--	--
5/25/79	--	--	(b) 11.1	21.1
6/25/79	--	--	(b) 11.2	21.8
7/9/79	--	--	10.2	19.4
8/29/79	--	--	9.8	(b) 23.7
9/7/79	--	--	(b) 13.1	(b) 25.5
10/4/79	--	--	10.5	21.6
12/12/79	--	--	9.4	(b) 23.0
5/23/80	--	--	9.1	(b) 17.8
6/24/80	--	--	(b) 12.5	22.0
Mean (mg/ml)	4.8	9.4	10.1	20.8
Standard deviation	0.50	0.54	1.31	2.14
Coefficient of variation (percent)	10.4	5.7	13.0	10.3
Range (mg/ml)	4.0-5.8	8.8-10.6	8.8-13.1	17.8-25.5
Number of samples	19	19	15	15

(a) The data presented are the results of duplicate analyses.
(b) Measured concentration differs from target concentration by more than 10%

APPENDIX J

MUTAGENICITY OF 95% 1,3-DICHLOROPROPENE IN SALMONELLA

TABLE J1. MUTAGENICITY OF 95% 1,3-DICHLOROPROPENE IN SALMONELLA

Strain	Dose (µg/plate)	Revertants/plate (a) -S9	+S9 (rat)	+S9 (hamster)
TA100	0	155 ± 1.3	165 ± 5.2	154 ± 9.6
	3	165 ± 12.3	--	--
	10	223 ± 24.7	--	--
	33	510 ± 6.7	197 ± 12.5	203 ± 7.1
	100	1,672 ± 42.3	321 ± 19.1	249 ± 6.7
	333	2,327 ± 171.6	740 ± 18.2	484 ± 22.7
	1,000	--	46 ± 46.3	155 ± 79.3
	3,333	--	Toxic	Toxic
TA1535	0	58 ± 3.5	47 ± 5.1	47 ± 1.7
	3	56 ± 5.4	--	--
	10	83 ± 4.9	--	--
	33	136 ± 23.1	60 ± 3.7	63 ± 5.6
	100	586 ± 54.3	74 ± 7.0	77 ± 6.1
	333	745 ± 26.4	163 ± 19.5	135 ± 7.0
	1,000	--	126 ± 30.4	Toxic
	3,333	--	Toxic	Toxic
TA1537	0	5 ± 1.8	9 ± 1.7	6 ± 1.5
	3	5 ± 0.9	--	--
	10	7 ± 0.7	--	--
	33	6 ± 1.5	9 ± 0.3	6 ± 0.7
	100	6 ± 1.5	10 ± 1.2	4 ± 0.7
	333	5 ± 1.5	6 ± 1.2	7 ± 0.6
	1,000	--	5 ± 2.7	11 ± 3.3
	3,333	--	Toxic	Toxic
TA98	0	27 ± 0.6	35 ± 8.8	29 ± 4.5
	3	35 ± 1.8	--	--
	10	31 ± 6.1	--	--
	33	46 ± 5.0	32 ± 2.7	28 ± 0.9
	100	81 ± 7.8	28 ± 2.3	35 ± 4.3
	333	19 ± 11.3	31 ± 3.8	34 ± 5.9
	1,000	--	24 ± 1.5	42 ± 4.9
	3,333	--	Toxic	Toxic

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

APPENDIX K

RESULTS OF TESTS IN DROSOPHILA

TABLE K1. INDUCTION OF SEX-LINKED RECESSIVE LETHAL MUTATIONS IN DROSOPHILA BY 1,3-DICHLOROPROPENE

Route of Exposure	Dose (ppm)	Number of Lethals/Number of X Chromosomes Tested (a) Mating 1	Mating 2	Mating 3	Total (percent)
Feeding	0	3/1,200 3/1,159	1/1,200 0/1,119	0/1,171 1/1,069	4/3,571 4/3,347 8/6,918 (0.12)
	5,750	7/1,343 3/1,373	2/836 3/1,088	5/1,106 0/838	14/3,285 6/3,299 20/6,584 (0.30)

(a) The sex-linked recessive lethal assay was performed essentially as described by Abrahamson and Lewis (1971). Exposure by feeding was done by allowing 24-hr-old Canton-S males to feed for 3 days on a solution of the test chemical dissolved in 5% sucrose. Exposed males were mated to 3 *Basc* females for 3 days and given fresh females at 2-day intervals to produce 3 broods of 3, 2, and 2 days, after which the parents were discarded. F_1 heterozygous females were crossed to their siblings and placed in individual vials. F_1 daughters from the same parental males were kept together to identify clusters; none were found. After 17 days, presumptive lethals were identified as vials containing no wild-type males; these were retested. Comparisons were made with concurrent controls using the normal approximation to the Poisson distribution sugggested by Margolin et al. (1983). The z value for the fed flies was 2.402, and it was significant at the 5% level of significance. Details on control frequencies of NTP-sponsored Drosophila studies can be found in Woodruff et al. (1984).

TABLE K2. INDUCTION OF RECIPROCAL TRANSLOCATIONS IN DROSOPHILA BY 1,3-DICHLOROPROPENE

Route of Exposure (a)	Dose (ppm)	Storages (Translocations/Tests) 1	2	3	4	5	Total No. of Tests	Total No. of Translocations	Total Translocations (percent)
Injection	5,750	0 1,401	1 1,267	0 1,478	0 1,414	0 1,405	6,965	1	0.01
Historical Control	0	0 4,563	0 4,335	0 4,373	0 3,623	0 2,743	19,637	0	0.00

(a) The reciprocal translocations assay was performed essentially as described by Abrahamson and Lewis (1971). Exposed males were mated to 3 *bw; st* females for 3 days and discarded. The females were transferred to fresh medium every 3-4 days to produce a total of five cultures, and then they were discarded. In this manner, successive cultures sample sperm that were stored for increasing lengths of time. Individual F_1 males were backcrossed to *bw; st* females, and the F_2 were screened for pseudolinkage. This procedure allows the recovery of translocations involving the Y, second, or third chromosomes in any combination. Presumptive translocations were retested. Results were not significant at the 5% level of significance (Kastenbaum and Bowman, 1970).

APPENDIX L

SUMMARY OF SERUM CHOLINESTERASE DATA IN THE ANCILLARY GAVAGE STUDIES OF TELONE II®

TABLE L1. SUMMARY OF SERUM CHOLINESTERASE DATA IN THE ANCILLARY GAVAGE STUDIES OF TELONE II® (a)

Weeks	Male Rats			Female Rats		
	Vehicle Control	25 mg/kg	50 mg/kg	Vehicle Control	25 mg/kg	50 mg/kg
+1	86.9 ± 11.8	80.4 ± 5.1	78.9 ± 9.7	167.9 ± 28.5	155.0 ± 28.8	(b) 145.9 ± 13.0
5	80.7 ± 9.0	76.3 ± 19.3	76.8 ± 22.0	264.2 ± 48.0	(c) 340.0 ± 45.5	225.0 ± 34.1
9	87.5 ± 8.6	(b) 78.4 ± 9.5	77.3 ± 12.7	343.7 ± 65.6	344.1 ± 87.7	302.2 ± 56.9
13	82.9 ± 8.3	85.8 ± 13.7	74.3 ± 12.1	358.5 ± 79.5	392.1 ± 39.5	(c) 279.3 ± 49.0
17	96.5 ± 18.8	84.3 ± 9.7	87.9 ± 12.5	393.8 ± 56.1	328.2 ± 105.7	(c) 301.1 ± 51.9
21	91.9 ± 11.9	94.3 ± 25.7	82.1 ± 11.0	443.8 ± 97.7	365.3 ± 110.0	(c) 328.1 ± 90.0
25	107.0 ± 12.5	(c) 89.5 ± 12.9	105.2 ± 12.8	548.3 ± 85.8	489.5 ± 28.1	(c) 341.8 ± 87.8
29	116.2 ± 23.7	102.2 ± 18.9	108.0 ± 12.5	485.3 ± 101.4	(c) 355.3 ± 87.3	(c) 274.0 ± 92.8
33	114.0 ± 8.8	103.3 ± 15.2	99.3 ± 16.7	442.3 ± 81.6	416.4 ± 77.8	(b) 343.7 ± 58.9
37	126.6 ± 22.7	108.8 ± 18.4	122.1 ± 14.8	507.1 ± 58.4	449.1 ± 94.7	(c) 298.5 ± 73.6
39	112.3 ± 10.6	95.2 ± 16.6	98.7 ± 11.3	496.7 ± 98.3	455.1 ± 97.8	392.5 ± 84.6
69	95.2 ± 11.6	96.2 ± 12.6	85.3 ± 4.7	357.5 ± 37.4	358.7 ± 41.9	(c) 244.5 ± 46.4

(a) Values represent mean ± standard deviation in milliunits per milliliter (N = 12).
(b) Significant (t-test) changes at $P \leq 0.05$ as compared with the vehicle control group
(c) Significant (t-test) changes at $P \leq 0.01$ as compared with the vehicle control group

APPENDIX M

DATA AUDIT SUMMARY

APPENDIX M. DATA AUDIT SUMMARY

The data from the 2-year toxicology and carcinogenesis studies of Telone II® in F344/N rats and B6C3F$_1$ mice and the ancillary studies in F344/N rats were audited by the following persons from the National Toxicology Program (NTP) and Dynamac Corporation on January 10-20, 1984 (2-year carcinogenesis studies) and April 10-12, 1984 (ancillary studies): NTP--Ms. C. Davies, Dr. S. Eustis, Ms. A. Grant, Mr. M. Pielmier, Dr. C. Whitmire, and Dr. R. Yang; Dynamac Corporation--Dr. H. Appleton, Mr. C. Dippel, Dr. F. Garner, Mr. C. Lunchick, Mr. J. Plantz, Dr. R. Schueler, and Ms. C. Sunier.

The in-life phase of the studies was conducted from February 1977 to July 1980. The work was conducted by Frederick Cancer Research Center (FCRC) under a contract with the National Cancer Institute. These studies were initiated before NTP required Good Laboratory Practices compliance in October 1980.

The full audit reports (carcinogenicity and ancillary studies) are on file at the NTP Archives, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. The audit consisted of examination of 10%-100% of the available toxicology, chemistry, and pathology data; this examination included the audit of 100% of clinical observation, mortality data, individual animal data records (IADR's), 100% of the slide/block matches of the high dose and vehicle control animals, and 10%-23% of the wet tissues.

One major problem unrelated to the audit was the early death in male mice, particularly in the vehicle control group. A technician's note implied gavage error; however, gross and microscopic examination did not uncover sufficient evidence to support the claim of gavage error. On the other hand, suppurative inflammation of the heart (myocarditis) was observed in all of these early deaths. The etiology of this lesion is not known. Because of the low survival rate of vehicle control male mice (8/50 alive at the termination of the study), the male mouse study was considered inadequate. The data indicated possible Telone II®-related neoplastic and nonneoplastic effects. Two lesser problems involved randomization of animals and body weight data. The rats were to have been randomized by body weight, and the body weights were indeed comparable among different groups at the start of the study; however, no record was available. In the mouse studies, three shipments of mice were received at 2-week intervals, and no record of randomization was available. The vehicle control male and female mice were from the first shipment, low dose males and females mostly from the second shipment, and the high dose groups mostly from the third shipment. Consequently, the body weights of the vehicle control mice groups were greater than those in the dosed groups. Any other discrepancies were generally related to poor recordkeeping (including loss of records) and undesirable laboratory practices. None of these problems was considered to have affected the final outcome of the study.

All chemical analyses were performed by the chemistry section of FCRC. The identity of the test material was confirmed, and the dose preparation was considered adequate. The chemical/vehicle analyses records were incomplete, but the available data provided sufficient information to suggest the accuracy of the dosing concentrations.

In the audit of IADR necropsy observations vs histopathology findings, discrepancies were found on the correlation of microscopic diagnoses with gross observations. Most of these were related to nontarget organs and are of minimal importance. The few items needing attention included some untrimmed lesions in the target organs (i.e., stomach and liver nodules or growths); these were subsequently recut, and microscopic examinations were carried out by the original pathologist. Subsequent diagnostic updates were made and incorporated into the Technical Report. An exception to the above was the stomach nodules observed in two low dose male mice and one high dose male mouse; they were not re-examined because (1) the male mouse study was considered inadequate and (2) if a conclusion were to be drawn from the incidence of forestomach neoplastic lesions in the male mice, the additional information from these three mice would not have changed the conclusion. Other

problems and discrepancies concerning pathology data were minor and not considered of sufficient magnitude to affect the findings.

The ancillary studies were conducted concurrently with the 2-year rat carcinogenesis studies. Therefore, much of the above audit summary applies to the ancillary studies as well. Discrepancies were found between the protocol-designated interim-kill dates and the actual kill dates. As much as a 39-day difference was found. This particular discrepancy was rectified by designating the originally scheduled 15-month kill as the 16-month kill. A restricted pathology quality assessment/audit was conducted by Experimental Pathology Laboratory, Inc. As requested by NTP, this review was limited to three target tissues (liver, forestomach, and thyroid gland). Differences of opinion were noted in the diagnoses of neoplastic nodules in the liver and diagnoses of basal cell hyperplasia in the forestomach. No change was made in the Technical Report.

In conclusion, problems and discrepancies of varying magnitude were found; however, none was considered to be serious enough to preclude drawing conclusions from the data regarding the toxicity and carcinogenicity of Telone II® to F344/N rats and B6C3F_1 mice.

GOVERNMENT PRINTING OFFICE: 1985 461 320 21106