

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 B6C3F₁ 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
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NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

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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).

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TELONE II®



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



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 B6C3F₁ 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 B6C3F₁ 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 B6C3F₁ 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.

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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.

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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 B6C3F₁ 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 B6C3F₁ 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®



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



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 nucleo-

philic 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^o 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^o or D-D^o 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[2-¹⁴C]propene was administered orally to Carworth Farm E rats, 80%-90% of the radio-label 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 [¹⁴C]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[¹⁴C]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 [¹⁴C]-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

I. INTRODUCTION

Pseudomonas sp. was responsible for this bio-transformation (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 ¹⁴C-*cis*-, *trans*-1,3-dichloropropene were administered to male F344 rats and 1 or 100 mg/kg to male B6C3F₁ 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 B6C3F₁ mice 2 hours following administration of a single oral dose of [¹⁴C]-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 LD₅₀ 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 LD₅₀ 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

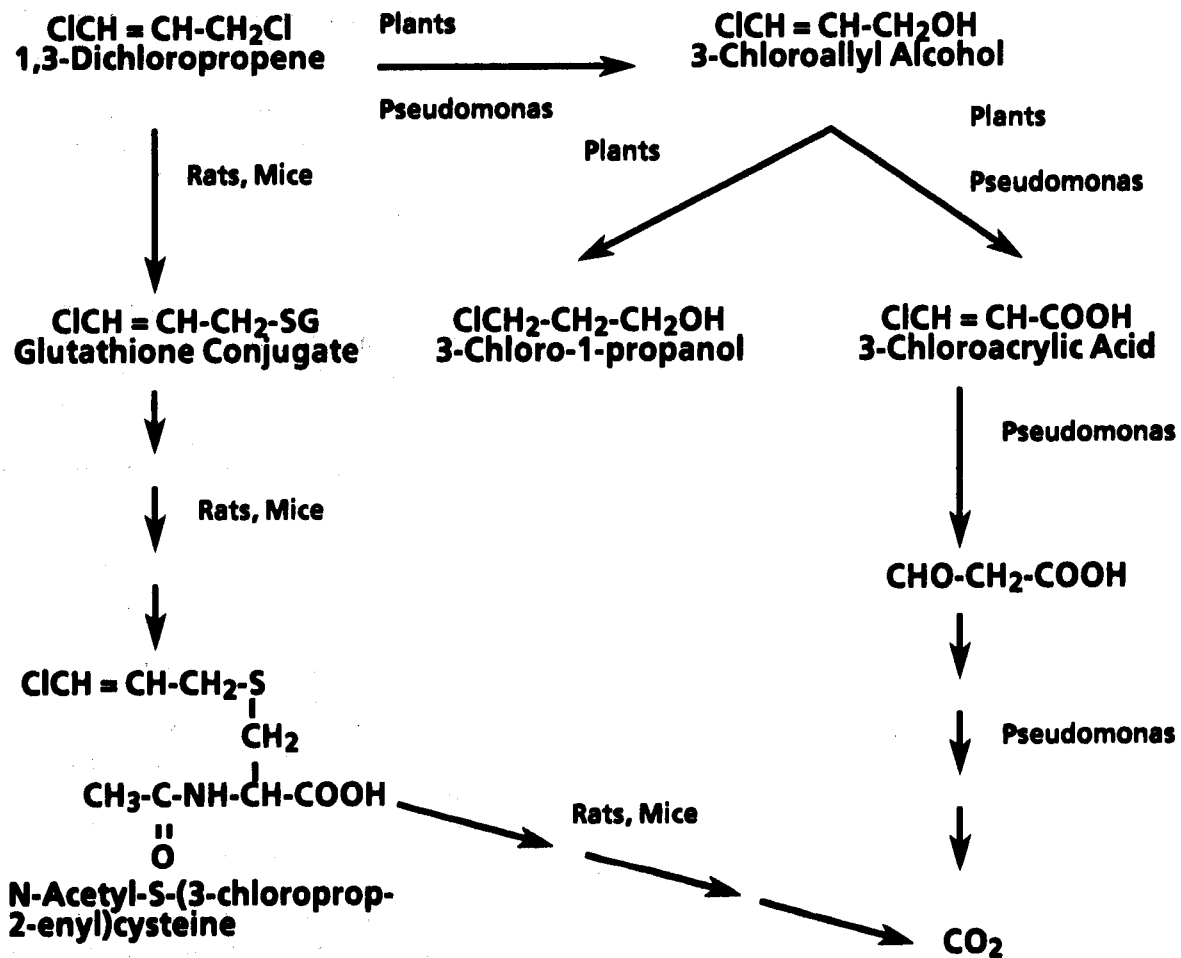


FIGURE 1. METABOLIC PATHWAY OF 1,3-DICHLOROPROPENE

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

I. INTRODUCTION

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^o in Animals (Parker et al., 1982)

D-D^o, 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^o 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^o and D-D^o 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

II. MATERIALS AND 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 ¹³C 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%
<i>cis</i> -isomer	41.6%
<i>trans</i> -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

II. MATERIALS AND METHODS

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 B6C3F₁ 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

Red blood cell
Hematocrit
Hemoglobin
Mean cell volume
Mean cell hemoglobin
Mean cell hemoglobin concentration
White blood cell
Differential-band neutrophils
Differential-segmented neutrophils
Differential lymphocytes
Differential monocytes
Differential eosinophils
Differential basophils
Absolute-band neutrophils
Absolute-segmented neutrophils
Absolute lymphocytes
Absolute monocytes
Absolute eosinophils

Clinical Chemistry

Calcium
Inorganic phosphate
Calcium/inorganic phosphate ratio
Total protein
Albumin
Albumin/(protein-albumin) ratio
Triglycerides
Cholesterol
Glucose
Lactic acid dehydrogenase
Creatinine phosphokinase
Hydroxybutyrate dehydrogenase
Phosphohexoisomerase
Leucine aminopeptidase
Cholinesterase
Blood urea nitrogen
Creatinine
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 B6C3F₁ (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.

II. MATERIALS AND METHODS

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 probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found

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.

II. MATERIALS AND METHODS

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

III. RESULTS: RATS

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	98	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	335	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	425	103.6	48	387	94.2	50
52	417	49	428	102.6	48	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	187	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.

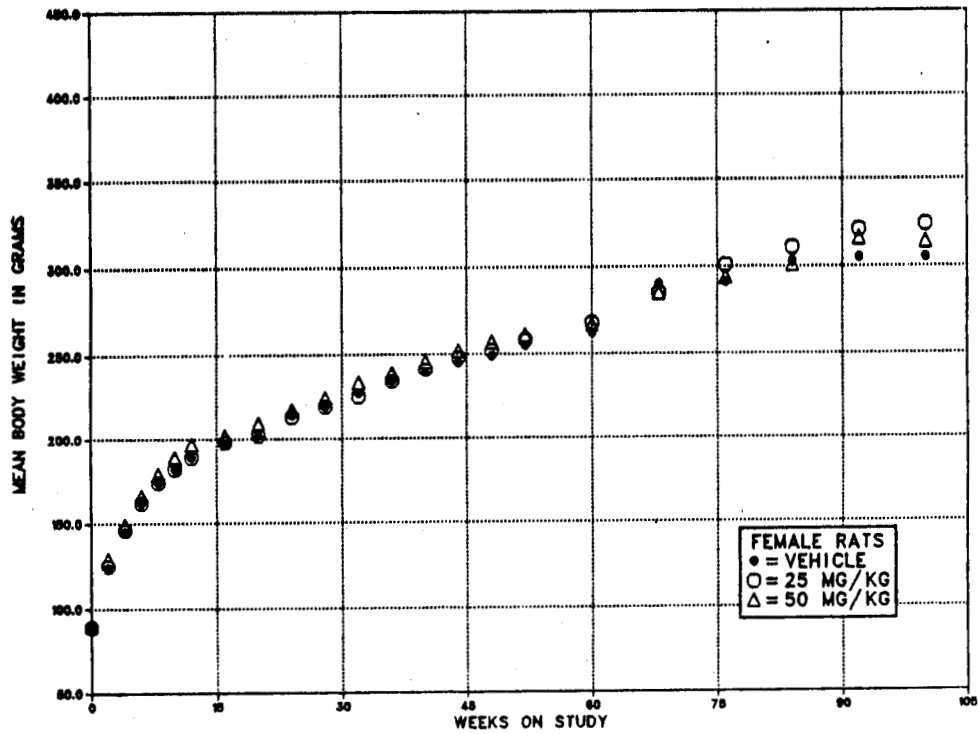
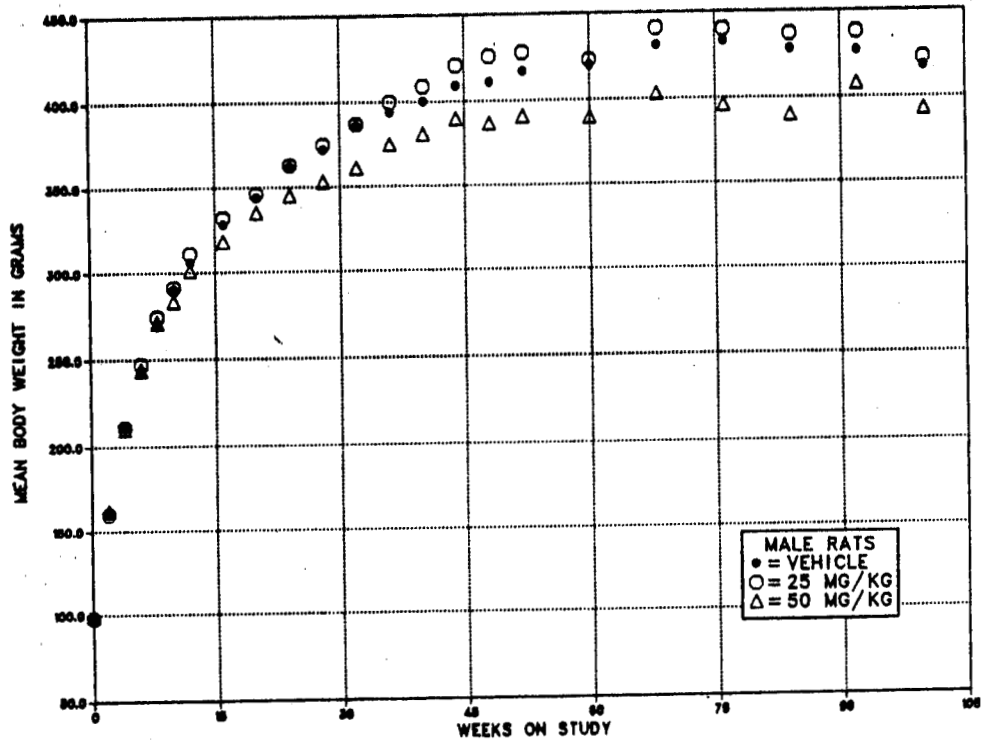


FIGURE 2. GROWTH CURVES FOR RATS ADMINISTERED TELONE II® IN CORN OIL BY GAVAGE FOR TWO YEARS

III. RESULTS: RATS

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.

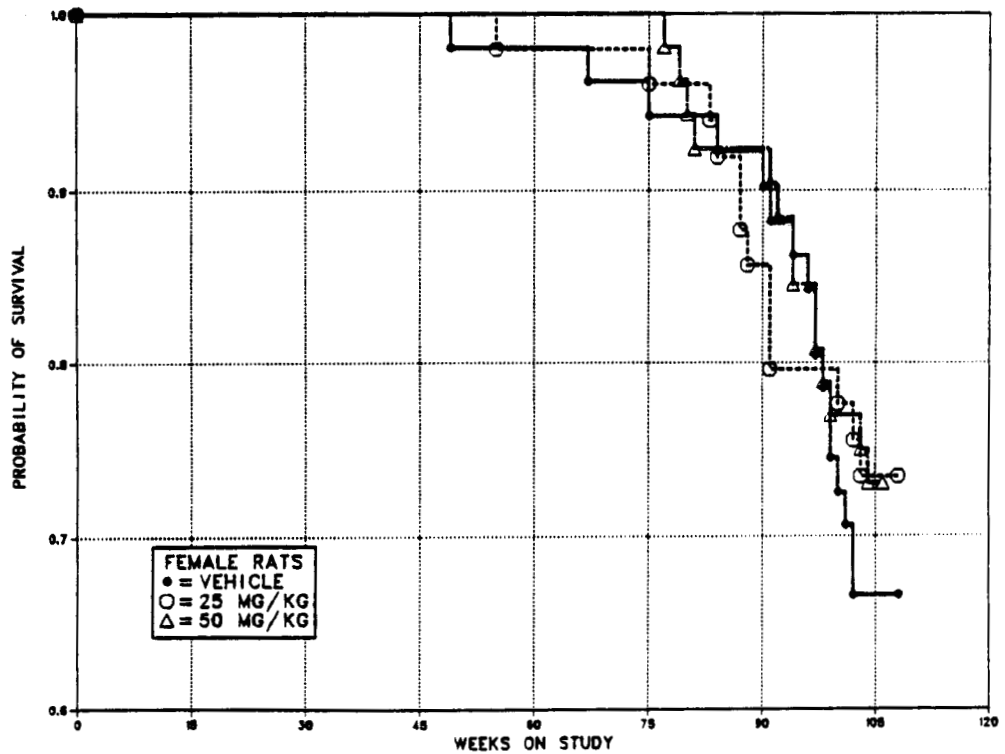
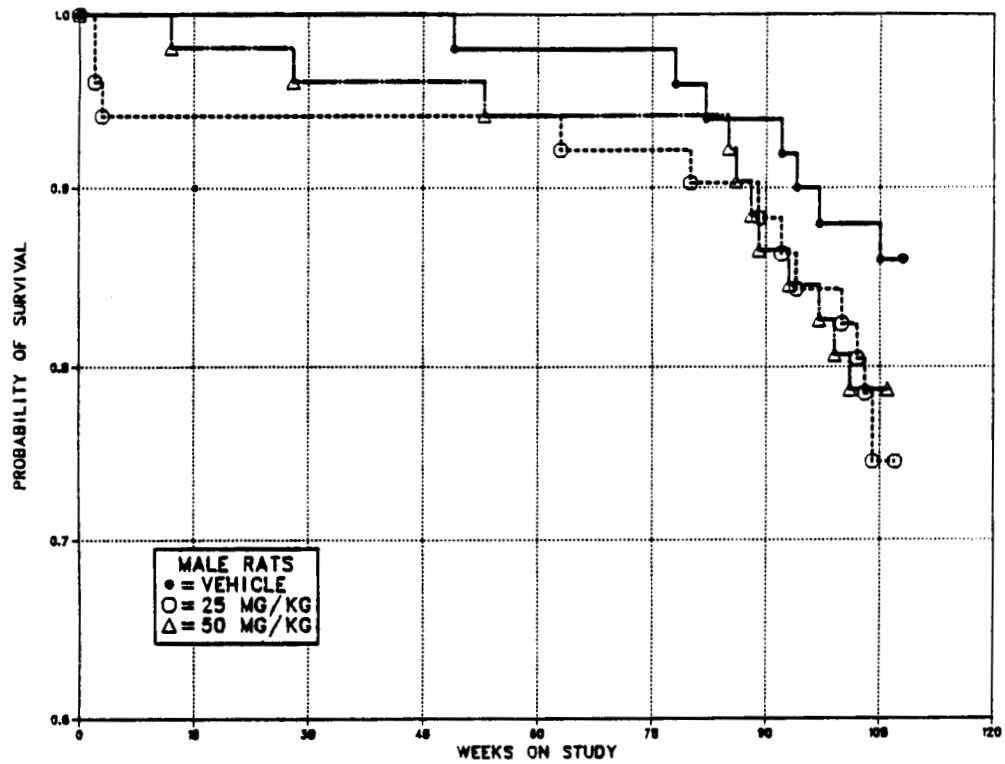


FIGURE 3. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED TELONE II® IN CORN OIL BY GAVAGE FOR TWO YEARS

III. RESULTS: RATS

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%)

III. RESULTS: RATS

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 a 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*

	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%

III. RESULTS: RATS

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*

	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*

	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

III. RESULTS: RATS

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*

	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	28	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	45
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

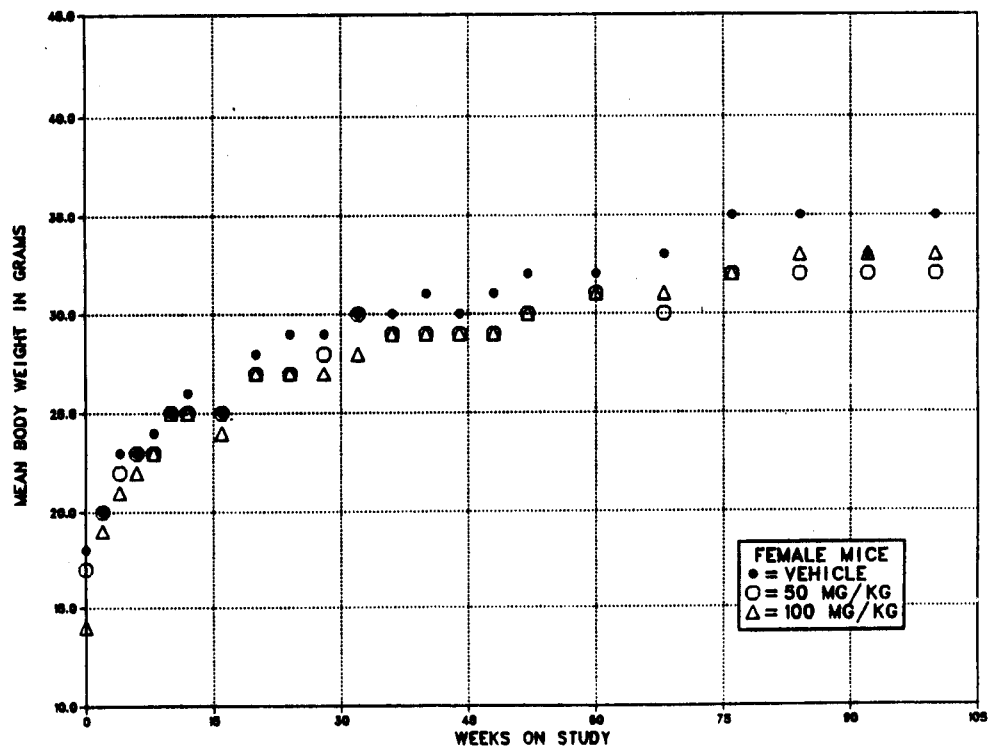
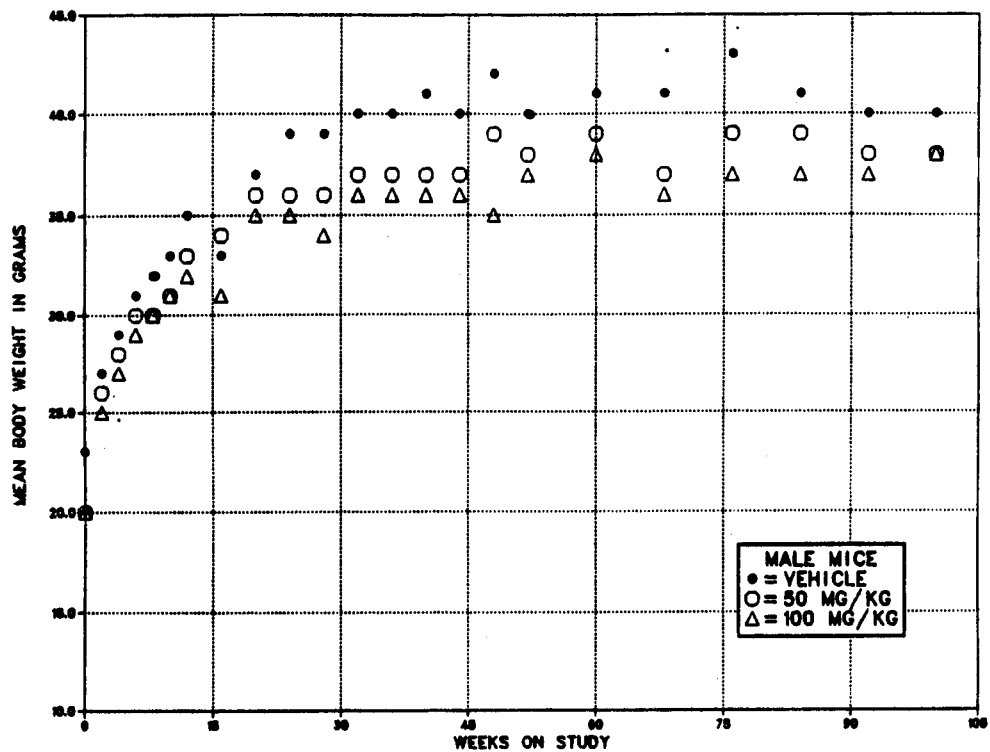


FIGURE 4. GROWTH CURVES FOR MICE ADMINISTERED TELONE II® IN CORN OIL BY GAVAGE FOR TWO YEARS

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.

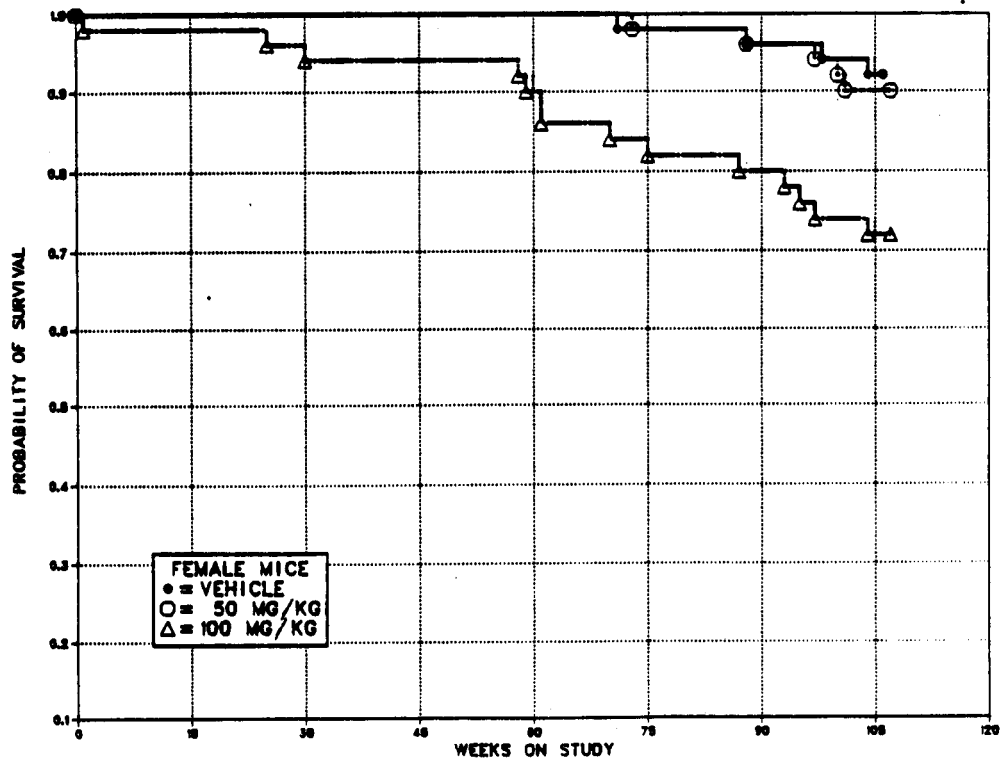
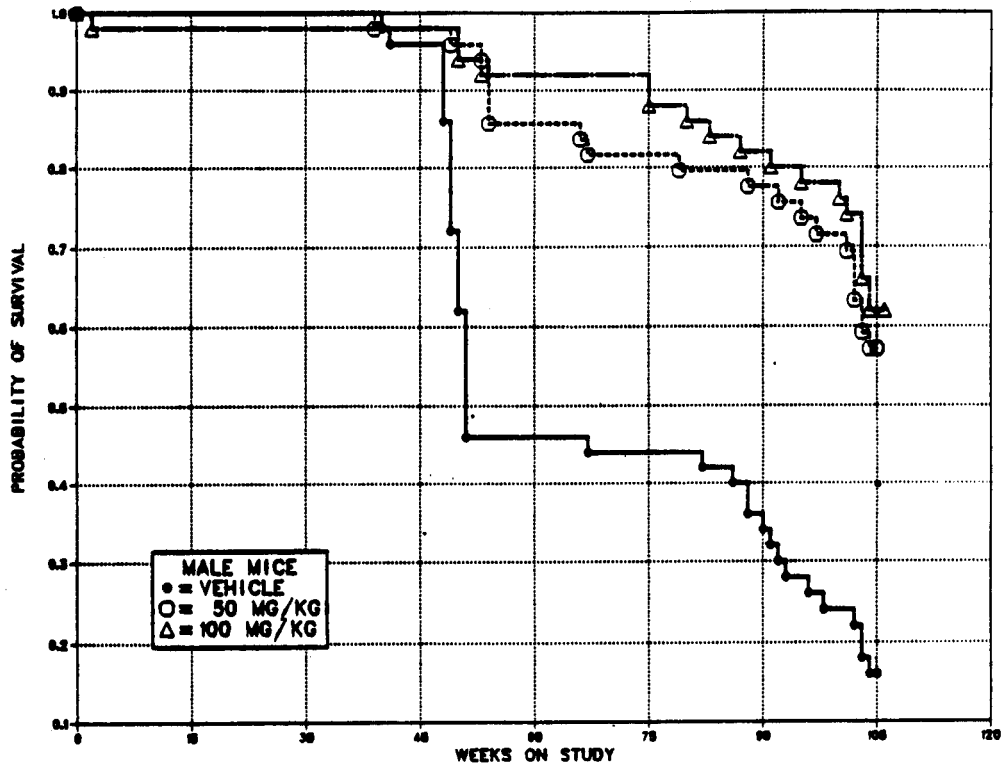


FIGURE 5. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED TELONE II® IN CORN OIL BY GAVAGE FOR TWO YEARS

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

III. RESULTS: MICE

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%

III. RESULTS: MICE

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.

III. RESULTS: MICE

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 B6C3F₁ 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.

IV. DISCUSSION AND CONCLUSIONS

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 B6C3F₁ 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 B6C3F₁ 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 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

IV. DISCUSSION AND CONCLUSIONS

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 B6C3F₁ 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

IV. DISCUSSION AND CONCLUSIONS

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.

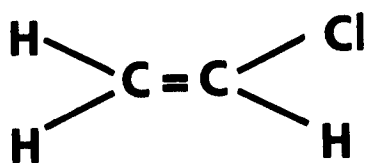
Mutagenicity

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

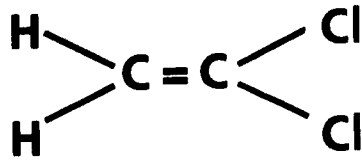
oxidation products of 1,3-dichloropropene were tentatively identified in one of the mixtures of polar impurities: these were epichlorohydrin and 1,3-dichloro-2-propanol--both of which are mutagenic in *Salmonella* (McCann et al., 1975; Stolzenberg and Hine, 1980). These results suggest that mutagenic 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

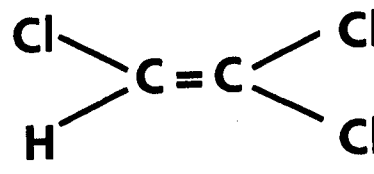
Chu and Milman (1981) have reviewed the carcinogenesis data on vinyl chloride (a structural analog of 1,3-dichloropropene), vinylidene chloride, trichloroethylene, 1,2-dichloroethane, 1,2-dibromoethane, tetrachloroethylene, and epichlorohydrin. These compounds have been shown to be carcinogenic in at 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.



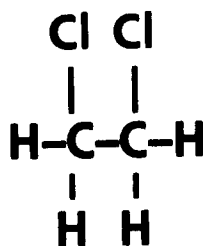
Vinyl Chloride



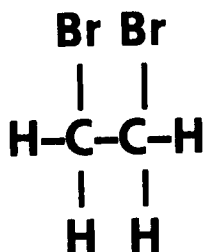
Vinylidene Chloride



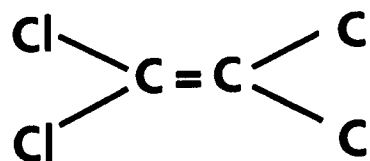
Trichloroethylene



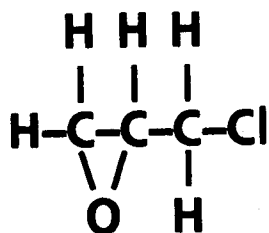
1,2-Dichloroethane



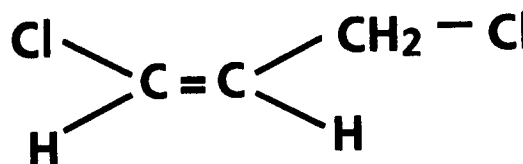
1,2-Dibromoethane (EDB)



Tetrachloroethylene



Epichlorohydrin



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

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

IV. DISCUSSION AND CONCLUSIONS

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 B6C3F₁ 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 B6C3F₁ 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.

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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%)		
MONOCYTTIC 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%)		1 (2%)
ADENOCARCINOMA, NOS	2 (4%)		24 (46%)
FIBROADENOMA	14 (27%)	20 (38%)	
*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	0				1				2				3				4				5														
	1	3	5	7	9	1	1	1	1	1	1	2	2	2	2	3	3	3	3	3	4	4	4	4	5	5	5	5	7	7	7	7	9	9	9
WEEKS ON STUDY	7	7	7	7	7	7	7	7	7	7	6	7	1	7	7	8	7	7	7	7	7	7	7	7	2	8	7	0	1	7	7	7	7	7	7
INTEGUMENTARY SYSTEM																																			
Skin	+																																		
Basal cell carcinoma	+																																		
Subcutaneous tissue	+																																		
Fibroma	+																																		
RESPIRATORY SYSTEM																																			
Lungs and bronchi	+																																		
Alveolar/bronchiolar adenoma	+																																		
Alveolar/bronchiolar carcinoma	+																																		
Trachea	+																																		
HEMATOPOIETIC SYSTEM																																			
Bone marrow	+																																		
Spleen	+																																		
Monocytic leukemia	+																																		
Lymph nodes	+																																		
Thymus	+																																		
CIRCULATORY SYSTEM																																			
Heart	+																																		
DIGESTIVE SYSTEM																																			
Salivary gland	+																																		
Liver	+																																		
Neoplastic nodule	+																																		
Bile duct	+																																		
Gallbladder & common bile duct	N																																		
Pancreas	+																																		
Acinar cell adenoma	+																																		
Esophagus	+																																		
Stomach	+																																		
Squamous cell papilloma	+																																		
Small intestine	+																																		
Large intestine	+																																		
URINARY SYSTEM																																			
Kidney	+																																		
Urinary bladder	+																																		
ENDOCRINE SYSTEM																																			
Pituitary	+																																		
Adenoma, NOS	+																																		
Chromophobe adenoma	+																																		
Adrenal	+																																		
Cortical adenoma	+																																		
Pheochromocytoma	+																																		
Thyroid	+																																		
C-cell adenoma	+																																		
C-cell carcinoma	+																																		
Parathyroid	+																																		
Adenoma, NOS	+																																		
Pancreatic islets	+																																		
Islet cell adenoma	+																																		
Islet cell carcinoma	+																																		
REPRODUCTIVE SYSTEM																																			
Mammary gland	+																																		
Fibroadenoma	+																																		
Testis	+																																		
Interstitial cell tumor	+																																		
Prostate	+																																		
Preputial/clitoral gland	+																																		
Carcinoma, NOS	+																																		
Adenocarcinoma, NOS	+																																		
NERVOUS SYSTEM																																			
Brain	+																																		
BODY CAVITIES																																			
Tunica vaginalis	+																																		
Mesothelioma, NOS	+																																		
Mesothelioma, malignant	+																																		
ALL OTHER SYSTEMS																																			
Multiple organs NOS	N																																		
Malignant melanoma, metastatic	+																																		
Monocytic leukemia	+																																		

+	: Tissue Examined Microscopically	:	: No Tissue Information Submitted
-	: Required Tissue Not Examined Microscopically	C	: Necropsy, No Histology Due To Protocol
X	: Tumor Incidence	A	: Autolysis
N	: Necropsy, No Autolysis, No Microscopic Examination	M	: Animal Missing
S	: Animal Missexed	B	: No Necropsy Performed

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

ANIMAL NUMBER	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
WEEKS ON STUDY	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	6	2	3	6	3	2	4	6	6	6	6	6	6	6	4	6	6	4	6	6	
INTEGUMENTARY SYSTEM																					
Skin	+																				
Squamous cell carcinoma																				X	
Trichoepithelioma																					
Subcutaneous tissue	+																				
Fibroma																				X	
Leiomyosarcoma																					
RESPIRATORY SYSTEM																					
Lungs and bronchi	+																				
Alveolar/bronchiolar adenoma											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																				X	
Neoplastic nodule																					
Bile duct	+																				
Gallbladder & common bile duct	N																				
Pancreas	+																				
Esophagus	+																				
Stomach	+																				
Squamous cell papilloma																					
Small intestine	+																				
Large intestine	+																				
URINARY SYSTEM																					
Kidney	+																				
Liposarcoma																					
Urinary bladder	+																				
ENDOCRINE SYSTEM																					
Pituitary	+																				
Chromophobe adenoma											X										
Acidophil adenoma																					
Adrenal	+																				
Cortical adenoma																					
Pheochromocytoma																X					
Thyroid	+																				
Follicular cell adenoma																			X		
Follicular cell carcinoma																			X		
C-cell carcinoma																					
Parathyroid	+																				
Pancreatic islets	+																				
Islet cell adenoma																					
Islet cell carcinoma																					
REPRODUCTIVE SYSTEM																					
Mammary gland	+																				
Fibroadenoma																					
Testis	+																				
Interstitial cell tumor	X																				
Prostate	+																				
NERVOUS SYSTEM																					
Brain	+																				
Glioma, NOS																					
Oligodendroglioma																					
BODY CAVITIES																					
Peritoneum	N																				
Fibrous histiocytoma, malignant																			X		
Rhabdomyosarcoma																					
Tunica vaginalis	+																				
Mesothelioma, NOS																					
ALL OTHER SYSTEMS																					
Multiple organs NOS	N																				
Fibrous histiocytoma, metastatic																			X		
Mesothelioma, malignant																					
Osteosarcoma, metastatic																X					
Monocytic leukemia						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	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3
	5	5	5	5	6	6	6	7	7	7	7	7	8	8	8	8	9	9	9	9	9	9	1	0	0
WEEKS ON STUDY	1	1	1	1	0	0	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0
	6	6	6	6	0	2	6	6	6	9	6	6	6	6	6	7	6	7	7	7	7	7	7	2	2
	TOTAL																								
	TISSUES TUMORS																								
INTEGUMENTARY SYSTEM																									
Skin	+																								*52
Squamous cell carcinoma																									1
Trichoepithelioma																									1
Subcutaneous tissue	+																								*52
Fibroma																									1
Leiomyosarcoma																									1
RESPIRATORY SYSTEM																									
Lungs and bronchi	+																								52
Alveolar/bronchiolar adenoma																									2
C-cell carcinoma, metastatic																									2
Trachea	+																								52
HEMATOPOIETIC SYSTEM																									
Bone marrow	+																								52
Spleen	+																								52
Lymph nodes	+																								52
C-cell carcinoma, metastatic																									1
Thymus	+																								52
CIRCULATORY SYSTEM																									
Heart	+																								52
DIGESTIVE SYSTEM																									
Salivary gland	+																								52
Liver	+																								52
Neoplastic nodule																									6
Bile duct	+																								52
Gallbladder & common bile duct	N																								*52
Pancreas	+																								52
Esophagus	+																								51
Stomach	+																								52
Squamous cell papilloma																									1
Small intestine	+																								52
Large intestine	+																								52
URINARY SYSTEM																									
Kidney	+																								52
Liposarcoma																									1
Urinary bladder	+																								52
ENDOCRINE SYSTEM																									
Pituitary	+																								50
Chromophobe adenoma																									13
Acidophil adenoma																									1
Adrenal	+																								52
Cortical adenoma																									1
Pheochromocytoma	X																								8
Thyroid	+																								51
Follicular cell adenoma																									2
Follicular cell carcinoma																									2
C-cell carcinoma																									4
Parathyroid	+																								32
Pancreatic islets	+																								52
Islet cell adenoma																									7
Islet cell carcinoma																									6
REPRODUCTIVE SYSTEM																									
Mammary gland	+																								*52
Fibroadenoma																									5
Testis	+																								52
Interstitial cell tumor	X																								46
Prostate	+																								52
NERVOUS SYSTEM																									
Brain	+																								52
Glioma, NOS																									1
Oligodendroglioma																									1
BODY CAVITIES																									
Peritoneum	N																								*52
Fibrous histiocytoma, malignant																									1
Rhabdomyosarcoma																									1
Tunica vaginalis	+																								*52
Mesothelioma, NOS																									1
ALL OTHER SYSTEMS																									
Multiple organs NOS	N																								*52
Fibrous histiocytoma, metastatic																									1
Mesothelioma, malignant																									1
Osteosarcoma, metastatic																									1
Monocytic leukemia	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	WEEKS ON STUDY																			
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
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																				
Spleen	+																			
Lymph nodes	+																			
Thymus	+																			
CIRCULATORY SYSTEM																				
Heart	+																			
DIGESTIVE SYSTEM																				
Oral cavity	N																			
Squamous cell papilloma	X																			
Salivary gland	+																			
Liver	+																			
Neoplastic nodule	X																			
Hepatocellular carcinoma	X																			
Sarcoma, NOS, metastatic																				
Fibrous histiocytoma, metastatic	X																			
Bile duct	+																			
Gallbladder & common bile duct	N																			
Pancreas	+																			
Acinar cell adenoma																				
Esophagus	+																			
Stomach	+																			
Squamous cell papilloma	X																			
Squamous cell carcinoma	X																			
Small intestine	+																			
Large intestine	+																			
URINARY SYSTEM																				
Kidney	+																			
Tubular cell adenocarcinoma																				
Urinary bladder	+																			
ENDOCRINE SYSTEM																				
Pituitary	+																			
Carcinoma, NOS																				
Chromophobe adenoma	X																			
Adrenal	+																			
Pheochromocytoma	X																			
Thyroid	+																			
Follicular cell carcinoma																				
C-cell adenoma	X																			
C-cell carcinoma																				
Parathyroid	-																			
Carcinoma, NOS																				
Pancreatic islets	+																			
Islet cell adenoma	X																			
REPRODUCTIVE SYSTEM																				
Mammary gland	+																			
Fibroadenoma	X																			
Testis	+																			
Interstitial cell tumor	X																			
Prostate	+																			
Preputial/clitoral gland	N																			
Adenoma, NOS	N																			
NERVOUS SYSTEM																				
Brain	+																			
MUSCULOSKELETAL SYSTEM																				
Bone	N																			
Osteosarcoma	X																			
BODY CAVITIES																				
Tunica vaginalis	+																			
Mesothelioma, NOS																				
Mesothelioma, malignant	X																			
ALL OTHER SYSTEMS																				
Multiple organs NOS	N																			
Adenocarcinoma, NOS, metastatic	X																			
Osteosarcoma, metastatic																				
Malignant lymphoma, NOS	X																			
Monocytic leukemia	X																			
Site unknown	X																			
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 A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF TELEONE II[®]: VEHICLE CONTROL

ANIMAL NUMBER	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20
WEEKS ON STUDY	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
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																			
Squamous cell carcinoma	N																			
Salivary gland	+																			
Liver	+																			
Neoplastic nodule	X																			
Bile duct	+																			
Gallbladder & common bile duct	N																			
Pancreas	+																			
Esophagus	+																			
Stomach	+																			
Small intestine	+																			
Large intestine	+																			
URINARY SYSTEM																				
Kidney	+																			
Urinary bladder	+																			
Transitional cell carcinoma	+																			
ENDOCRINE SYSTEM																				
Pituitary	+																			
Chromophobe adenoma	X																			
Chromophobe carcinoma	X																			
Adrenal	+																			
Cortical adenoma	X																			
Pheochromocytoma	+																			
Thyroid	+																			
C-cell adenoma	X																			
C-cell carcinoma	X																			
Parathyroid	+																			
Pancreatic islets	+																			
Islet cell adenoma	X																			
REPRODUCTIVE SYSTEM																				
Mammary gland	+																			
Adenoma, NOS	+																			
Adenocarcinoma, NOS	+																			
Fibroadenoma	X																			
Uterus	+																			
Leiomyoma	+																			
Endometrial stromal polyp	X																			
Endometrial stromal sarcoma	X																			
Ovary	+																			
NERVOUS SYSTEM																				
Brain	+																			
ALL OTHER SYSTEMS																				
Multiple organs NOS	N																			
Malignant lymphoma, NOS	N																			
Monocytic leukemia	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	0 5 2	0 5 4	0 5 6	0 5 8	0 6 2	0 6 4	0 6 6	0 6 8	0 7 0	0 7 2	0 7 4	0 7 6	0 7 8	0 8 0	0 8 2	0 8 4	0 8 6	0 8 8	0 9 0	0 9 2	0 9 4	0 9 6	0 9 8	0 10 0	0 10 2	0 10 4	0 10 6	0 10 8	0 11 0	0 11 2	0 11 4	0 11 6	0 11 8	0 12 0	0 12 2	0 12 4	TOTAL
WEEKS ON STUDY	11 8	11 8	11 2	11 8	11 4	11 8	11 8	11 8	11 0	11 0	11 0	11 0	11 0	11 0	11 0	11 0	11 0	11 0	11 0	11 0	11 0	11 0	11 0	11 0	11 0	11 0	11 0	11 0	11 0	11 0	11 0	11 0	11 0	11 0	11 0	11 0	TISSUES TUMORS
INTEGUMENTARY SYSTEM																													52								
Subcutaneous tissue																													1								
Rhabdomyosarcoma																													52								
RESPIRATORY SYSTEM																													52								
Lungs and bronchi																													1								
Alveolar/bronchiolar carcinoma																													52								
Trachea																													52								
HEMATOPOIETIC SYSTEM																													51								
Bone marrow																													52								
Spleen																													52								
Lymph nodes																													52								
Thymus																													52								
CIRCULATORY SYSTEM																													52								
Heart																													52								
DIGESTIVE SYSTEM																													52								
Oral cavity																													1								
Squamous cell carcinoma																													52								
Salivary gland																													52								
Liver																													6								
Neoplastic nodule																													52								
Bile duct																													52								
Gallbladder & common bile duct																													52								
Pancreas																													52								
Esophagus																													52								
Stomach																													52								
Small intestine																													52								
Large intestine																													50								
URINARY SYSTEM																													52								
Kidney																													52								
Urinary bladder																													1								
Transitional cell carcinoma																													52								
ENDOCRINE SYSTEM																													50								
Pituitary																													28								
Chromophobe adenoma																													2								
Chromophobe carcinoma																													52								
Adrenal																													2								
Cortical adenoma																													1								
Pheochromocytoma																													52								
Thyroid																													4								
C-cell adenoma																													2								
C-cell carcinoma																													46								
Parathyroid																													52								
Pancreatic islets																													3								
Islet cell adenoma																													52								
REPRODUCTIVE SYSTEM																													52								
Mammary gland																													1								
Adenoma, NOS																													2								
Adenocarcinoma, NOS																													14								
Fibroadenoma																													52								
Uterus																													1								
Leiomyoma																													16								
Endometrial stromal polyp																													2								
Endometrial stromal sarcoma																													52								
Ovary																													52								
NERVOUS SYSTEM																													52								
Brain																													52								
ALL OTHER SYSTEMS																													52								
Multiple organs NOS																													1								
Malignant lymphoma, NOS																													9								
Monocytic leukemia																													52								

* Animals Necropsied

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

ANIMAL NUMBER	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2			
WEEKS ON STUDY	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1			
WEEKS ON STUDY	2	4	6	8	0	2	4	6	8	0	2	4	6	8	0	2	4	6	8	0	2	4	6	8	0	2	4	6	8	0
INTEGUMENTARY SYSTEM																														
Subcutaneous tissue																														
Fibroma																														
RESPIRATORY SYSTEM																														
Lungs and bronchi																														
Alveolar/bronchiolar carcinoma																														
Trachea																														
HEMATOPOIETIC SYSTEM																														
Bone marrow																														
Spleen																														
Lymph nodes																														
Thymus																														
Thymoma																														
CIRCULATORY SYSTEM																														
Heart																														
DIGESTIVE SYSTEM																														
Salivary gland																														
Liver																														
Neoplastic nodule																														
Bile duct																														
Gallbladder & common bile duct																														
Pancreas																														
Esophagus																														
Stomach																														
Squamous cell papilloma																														
Small intestine																														
Large intestine																														
URINARY SYSTEM																														
Kidney																														
Urinary bladder																														
Adenomatous polyp, NOS																														
ENDOCRINE SYSTEM																														
Pituitary																														
Chromophobe adenoma																														
Chromophobe carcinoma																														
Adrenal																														
Cortical carcinoma																														
Pheochromocytoma																														
Thyroid																														
Follicular cell adenoma																														
Follicular cell carcinoma																														
C-cell adenoma																														
C-cell carcinoma																														
Parathyroid																														
Pancreatic islets																														
Islet cell adenoma																														
REPRODUCTIVE SYSTEM																														
Mammary gland																														
Fibroadenoma																														
Preputial/clitoral gland																														
Carcinoma, NOS																														
Adenoma, NOS																														
Uterus																														
Endometrial stromal polyp																														
Ovary																														
NERVOUS SYSTEM																														
Brain																														
ALL OTHER SYSTEMS																														
Multiple organs NOS																														
Monocytic leukemia																														
Leukemia, mononuclear cell																														

+ : Tissue Examined Microscopically
 - : Required Tissue Not Examined Microscopically
 X : Tumor Incidence
 N : Necropsy, No Autolysis, No Microscopic Examination
 S : Animal Missed
 : 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	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3							
WEEKSON STUDY	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1							
	7	5	0	1	0	1	7	7	1	0	1	0	7	4	7	1	1	0	7	7	0	2	4	6	8	0	2	4	6	8	0	2	4
	TOTAL																																
	TISSUES TUMORS																																
INTEGUMENTARY SYSTEM																																	
Subcutaneous tissue	+																																
Fibroma																																	
	X																																
	*52																																
	1																																
RESPIRATORY SYSTEM																																	
Lungs and bronchi	+																																
Alveolar/bronchiolar carcinoma																																	
Trachea	+																																
	52																																
	1																																
	52																																
HEMATOPOIETIC SYSTEM																																	
Bone marrow	+																																
Spleen	+																																
Lymph nodes	+																																
Thymus	+																																
Thymoma																																	
	X																																
	51																																
	51																																
	52																																
	52																																
	1																																
CIRCULATORY SYSTEM																																	
Heart	+																																
	52																																
DIGESTIVE SYSTEM																																	
Salivary gland	+																																
Liver	+																																
Neoplastic nodule																																	
Bile duct	X																																
Gallbladder & common bile duct	+																																
Pancreas	+																																
Esophagus	+																																
Stomach	+																																
Squamous cell papilloma																																	
Small intestine	+																																
Large intestine	+																																
	52																																
	52																																
	6																																
	*52																																
	52																																
	52																																
	2																																
	52																																
	48																																
URINARY SYSTEM																																	
Kidney	+																																
Urinary bladder	+																																
Adenomatous polyp, NOS																																	
	52																																
	52																																
	1																																
ENDOCRINE SYSTEM																																	
Pituitary	+																																
Chromophobe adenoma																																	
Chromophobe carcinoma																																	
Adrenal	+																																
Cortical carcinoma																																	
Phaeochromocytoma																																	
Thyroid	+																																
Follicular cell adenoma																																	
Follicular cell carcinoma																																	
C-cell adenoma																																	
C-cell carcinoma																																	
Parathyroid	+																																
Pancreatic islets	+																																
Islet cell adenoma																																	
	51																																
	26																																
	1																																
	52																																
	1																																
	2																																
	52																																
	1																																
	1																																
	6																																
	2																																
	39																																
	52																																
	1																																
REPRODUCTIVE SYSTEM																																	
Mammary gland	+																																
Fibroadenoma																																	
Preputial/vulvar gland	+																																
Carcinoma, NOS																																	
Adenoma, NOS																																	
Uterus	+																																
Endometrial stromal polyp																																	
Ovary	+																																
	*52																																
	20																																
	*52																																
	2																																
	1																																
	52																																
	10																																
	52																																
NERVOUS SYSTEM																																	
Brain	+																																
	52																																
ALL OTHER SYSTEMS																																	
Multiple organs NOS	N																																
Monocytic leukemia																																	
Leukemia, mononuclear cell																																	
	X																																
	X																																
	*52																																
	9																																
	1																																

* Animals Necropsied

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

ANIMAL NUMBER	4 5 2	4 5 4	4 5 8	4 5 8	4 6 2	4 6 4	4 6 6	4 6 8	4 7 2	4 7 4	4 7 6	4 7 8	4 8 2	4 8 4	4 8 6	4 8 8	4 9 2	4 9 4	4 9 6	4 9 8	5 0 0	5 0 2	5 0 4	TOTAL
WEEKSON STUDY	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	TISSUES TUMORS
INTEGUMENTARY SYSTEM																							*52	
Skin																							1	
Squamous cell carcinoma																								
Subcutaneous tissue																							*52	
Carcinoma																							1	
RESPIRATORY SYSTEM																							52	
Lungs and bronchi																							2	
Alveolar/bronchiolar adenoma																								
Alveolar/bronchiolar carcinoma																							1	
Granulosa cell carcinoma, metastatic																							1	
Trachea																							52	
HEMATOPOIETIC SYSTEM																							50	
Bone marrow																							52	
Spleen																							1	
Hemangiosarcoma																							52	
Lymph nodes																							1	
Carcinoma, invasive																							50	
Thymus																								
CIRCULATORY SYSTEM																							52	
Heart																								
DIGESTIVE SYSTEM																							52	
Salivary gland																							52	
Liver																							10	
Neoplastic nodule																							52	
Bile duct																							*52	
Gallbladder & common bile duct																							52	
Pancreas																							1	
Fibrosarcoma, metastatic																							52	
Esophagus																							52	
Stomach																							3	
Squamous cell papilloma																							52	
Small intestine																							3	
Large intestine																							52	
URINARY SYSTEM																							52	
Kidney																							52	
Urinary bladder																								
ENDOCRINE SYSTEM																							52	
Pituitary																							30	
Chromophobe adenoma																							1	
Chromophobe carcinoma																							52	
Adrenal																							1	
Cortical adenoma																							52	
Thyroid																							2	
Follicular cell adenoma																							2	
Follicular cell carcinoma																							2	
C-cell adenoma																							1	
C-cell carcinoma																							37	
Parathyroid																							52	
Pancreatic islets																							1	
Islet cell carcinoma																								
REPRODUCTIVE SYSTEM																							*52	
Mammary gland																							1	
Adenocarcinoma, NOS																							24	
Fibroadenoma																							*52	
Preputial/clitoral gland																							2	
Carcinoma, NOS																							52	
Uterus																							12	
Adenocarcinoma, NOS																							12	
Endometrial stromal polyp																							52	
Ovary																							1	
Granulosa cell carcinoma																							1	
Fibrosarcoma																							1	
NERVOUS SYSTEM																							52	
Brain																								
SPECIAL SENSE ORGANS																							*52	
Zymbal gland																							1	
Carcinoma, NOS																								
ALL OTHER SYSTEMS																							*52	
Multiple organs NOS																							1	
Leiomyosarcoma, metastatic																							5	
Monocytic leukemia																								
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 ADENOMA, NOS	(50)	(50)	(50) 1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS HEPATOCELLULAR CARCINOMA, METAST	(50)	(50)	(50) 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	WEEKS ON STUDY																			
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	3	5	7	9	1	3	5	7	9	1	3	5	7	9	1	3	5	7	9	1
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	
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
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	0 5 1	0 5 3	0 5 5	0 5 7	0 5 9	0 6 1	0 6 3	0 6 5	0 6 7	0 6 9	0 7 1	0 7 3	0 7 5	0 7 7	0 8 1	0 8 3	0 8 5	0 8 7	0 8 9	0 9 1	0 9 3	0 9 5	0 9 7	0 9 9	0 9 1	0 9 3	0 9 5	0 9 7	0 9 9	TOTAL
WEEKS ON STUDY	1 0 4	1 0 5	0 4 8	1 0 3	0 5 0	0 9 5	0 1 1	0 0 0	0 4 8	0 9 8	0 4 1	0 5 0	0 9 0	0 4 5	0 4 9	0 9 5	0 4 8	0 9 2	0 4 9	0 9 9	0 5 4	0 8 0	0 9 6	0 4 8	0 9 2	0 5 4	0 8 0	0 9 5	TISSUES TUMORS	
RESPIRATORY SYSTEM																														
Lungs and bronchi	+																												50	
Alveolar/bronchiolar adenoma	+																												1	
Trachea	+																												50	
HEMATOPOIETIC SYSTEM																														
Bone marrow	+																												49	
Spleen	+																												50	
Hemangiosarcoma	+																												1	
Lymph nodes	+																												50	
Thymus	+																												49	
CIRCULATORY SYSTEM																														
Heart	+																												50	
DIGESTIVE SYSTEM																														
Salivary gland	+																												50	
Liver	+																												50	
Hepatocellular adenoma	+																												1	
Hepatocellular carcinoma	+																												4	
Bile duct	+																												50	
Gallbladder & common bile duct	N																												*50	
Pancreas	+																												50	
Esophagus	+																												50	
Stomach	+																												50	
Small intestine	+																												50	
Large intestine	+																												50	
CRINARY 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	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
WEEKS ON STUDY	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1
	1	3	5	7	9	1	3	5	7	9	1	3	5	7	9	1	3	5	7	9	1
INTEGUMENTARY SYSTEM																					
Subcutaneous tissue	+																				
Leiomyosarcoma																					
RESPIRATORY SYSTEM																					
Lungs and bronchi	+																				
Hepatocellular carcinoma, metastatic																					
Alveolar/bronchiolar adenoma	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																					
Lymph nodes	+																				
Malignant lymphoma, NOS																					
Thymus	+																				
Hemangiosarcoma																					
CIRCULATORY SYSTEM																					
Heart	+																				
DIGESTIVE SYSTEM																					
Salivary gland	+																				
Liver	+																				
Hepatocellular adenoma																					
Hepatocellular carcinoma				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
Pancreas	+																				
Esophagus	+																				
Stomach	+																				
Squamous cell papilloma																					
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
Malignant lymphoma, NOS																				X	N

+ : Tissue Examined Microscopically C : No Tissue Information Submitted
 - : Required Tissue Not Examined Microscopically N : Necropsy, No Histology Due To Protocol
 X : Tumor Incidence A : Autolysis
 N : Necropsy, No Autolysis, No Microscopic Examination M : Animal Missing
 B : Animal Missed S : No Necropsy Performed

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

ANIMAL NUMBER	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1																			TOTAL	
	2 4 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5																				TISSUES TUMORS
WEEKS ON STUDY	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
INTEGUMENTARY SYSTEM																				*50 1	
Subcutaneous tissues	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Leiomyosarcoma							X														
RESPIRATORY SYSTEM																				50 1 11 2 80	
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Hepatocellular carcinoma, metastatic																			X		
Alveolar/bronchiolar adenoma			X							X											
Alveolar/bronchiolar carcinoma																					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
HEMATOPOIETIC SYSTEM																				48 1 48 3 2 2 50 1 48 1	
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Hemangiosarcoma			X																		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Hemangioma				X																	
Hemangiosarcoma			X																		
Malignant lymphoma, NOS								X													
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Malignant lymphoma, NOS																					
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+		
Hemangiosarcoma																			X		
CIRCULATORY SYSTEM																				50	
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
DIGESTIVE SYSTEM																				50 50 1 6 50 *50 50 50 50 2 50 50	
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Hepatocellular adenoma				X																	
Hepatocellular carcinoma																			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		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Squamous cell papilloma																					
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
URINARY SYSTEM																				50 50	
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
ENDOCRINE SYSTEM																				48 1 50 49 27	
Pituitary	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Chromophobe adenoma				X																	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Parathyroid	-	+	-	+	+	-	-	-	-	+	+	-	-	+	+	-	+	-	+		
REPRODUCTIVE SYSTEM																				*50 50 50	
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
NERVOUS SYSTEM																				50	
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
ALL OTHER SYSTEMS																				*50 2	
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		
Malignant lymphoma, NOS																			X		

* Animals Necropsied

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

ANIMAL NUMBER	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
WEEKS ON STUDY	0	1	1	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0
	9	5	4	2	0	0	7	5	5	5	5	5	5	3	4	5	1	5	5	5	3	5	5	3	5	5	5	5	5	5	5	5	5	5	5	5	7	5
RESPIRATORY SYSTEM																																						
Lungs and bronchi	+																																					
Adenocarcinoma, NOS unc prim/metastatic																																						
Hepatocellular carcinoma, metastatic																																						
Alveolar/bronchiolar adenoma																																						
Alveolar/bronchiolar carcinoma																																						
Trachea	+																																					
HEMATOPOIETIC SYSTEM																																						
Bone marrow	+																																					
Spleen	+																																					
Hemangiosarcoma																																						
Malignant lymphoma, NOS																																						
Lymph nodes	+																																					
Thymus	-																																					
CIRCULATORY SYSTEM																																						
Heart	+																																					
DIGESTIVE SYSTEM																																						
Salivary gland	+																																					
Liver	+																																					
Hepatocellular adenoma																																						
Hepatocellular carcinoma																																						
Bile duct	+																																					
Gallbladder & common bile duct	N																																					
Pancreas	+																																					
Esophagus	+																																					
Stomach	+																																					
Squamous cell papilloma																																						
Small intestine	+																																					
Large intestine	+																																					
URINARY SYSTEM																																						
Kidney	+																																					
Urinary bladder	+																																					
Transitional cell carcinoma																																						
ENDOCRINE SYSTEM																																						
Pituitary	+																																					
Adrenal	+																																					
Cortical adenoma																																						
Thyroid	+																																					
Parathyroid	-																																					
REPRODUCTIVE SYSTEM																																						
Mammary gland	+																																					
Testis	+																																					
Prostate	+																																					
NERVOUS SYSTEM																																						
Brain	+																																					
SPECIAL SENSE ORGANS																																						
Lacrimal gland	N																																					
Adenoma, NOS	N																																					
ALL OTHER SYSTEMS																																						
Multiple organs NOS	N																																					
Hepatocellular carcinoma, metastatic																																						
Malignant lymphoma, NOS																																						

+ : 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 IN THE TWO-YEAR GAVAGE STUDY OF TELONE II®: VEHICLE CONTROL

ANIMAL NUMBER	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
	2	4	6	8	0	2	4	6	8	0	2	4	6	8	0	2	4	6	8	0	2	4	6	8	0	2	4	6	8	0
WEEKS ON STUDY	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	
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																														
Thymus	+																													
	X																													
	X																													
CIRCULATORY SYSTEM																														
Heart	+																													
DIGESTIVE SYSTEM																														
Salivary gland	+																													
Liver	+																													
Hepatocellular carcinoma																														
Hemangiosarcoma																														
Osteosarcoma, metastatic																														
Malign. lymphoma, lymphocytic type																														
Bile duct	+																													
Gallbladder & common bile duct	N																													
Pancreas	+																													
Esophagus	+																													
Stomach	+																													
Small intestine	+																													
Large intestine	+																													
URINARY SYSTEM																														
Kidney	+																													
Urinary bladder	+																													
ENDOCRINE SYSTEM																														
Pituitary	+																													
Chromophobe adenoma																														
Adrenal	+																													
Pheochromocytoma																														
Thyroid	+																													
Parathyroid	-																													
REPRODUCTIVE SYSTEM																														
Mammary gland	+																													
Adenocarcinoma, NOS																														
Uterus	+																													
Ovary	+																													
NERVOUS SYSTEM																														
Brain	+																													
ALL OTHER SYSTEMS																														
Multiple organs NOS	N																													
Malign. lymphoma, histiocytic type	N																													

+	: Tissue Examined Microscopically	:	No Tissue Information Submitted
-	: Required Tissue Not Examined Microscopically	C	: Necropsy, No Histology Due To Protocol
X	: Tumor Incidence	A	: Autolysis
N	: Necropsy, No Autolysis, No Microscopic Examination	M	: Animal Missing
S	: Animal Missexed	B	: No Necropsy Performed

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

ANIMAL NUMBER	0 1																				TOTAL
	5 5 5 5 6 6 6 7 7 7 7 8 8 8 8 8 9 9 9 9 0																				
WEEKS ON STUDY	2 4 6 8 0 2 4 6 8 0 2 4 6 8 0 2 4 6 8 0 0																				TISSUES TUMORS
	1 1 1 1 0 1 1 1 1 1 1 1 0 1 1 1 1 1 1 1 1																				
INTEGUMENTARY SYSTEM																					
Subcutaneous tissue	+																				*50
Osteosarcoma																					1
RESPIRATORY SYSTEM																					
Lungs and bronchi	+																				50
Alveolar/bronchiolar carcinoma																					2
Trachea	+																				50
HEMATOPOIETIC SYSTEM																					
Bone marrow	+																				50
Spleen	+																				50
Hemangiosarcoma	+																				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	+																				2
Osteosarcoma, metastatic	+																				1
Malig. lymphoma, lymphocytic type	+																				1
Bile duct	+																				50
Gallbladder & common bile duct	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	+																				4
Adrenal	+																				50
Pheochromocytoma	+																				1
Thyroid	+																				50
Parathyroid	+																				29
REPRODUCTIVE SYSTEM																					
Mammary gland	+																				*50
Adenocarcinoma, NOS	+																				2
Uterus	+																				50
Ovary	+																				50
NERVOUS SYSTEM																					
Brain	+																				50
ALL OTHER SYSTEMS																					
Multiple organs NOS	N																				*50
Malig. lymphoma, histiocytic type	+																				2

* Animals Necropsied

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

ANIMAL NUMBER	WEEKS ON STUDY																				TOTAL	TISSUES TUMORS		
	1/2	1/4	1/5	1/6	1/7	1/8	1/9	1/10	1/11	1/12	1/13	1/14	1/15	1/16	1/17	1/18	1/19	1/20	1/21	1/22				
RESPIRATORY SYSTEM																								
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic																							X	
Alveolar/bronchiolar adenoma																								
Alveolar/bronchiolar carcinoma																								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																								
Malignant lymphoma, NOS																								
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic																								
Malignant lymphoma, NOS																								
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
CIRCULATORY SYSTEM																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																								
Hepatocellular carcinoma																								
Hemangiosarcoma																								
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																								
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic																								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma	X	X																						
ENDOCRINE SYSTEM																								
Pituitary	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chromophobe adenoma																								
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																								
Pheochromocytoma																								
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																								
Fibroadenoma																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																								
Hemangioma																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																								
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
Malignant lymphoma, NOS																								

* 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	107	107	107	107	107	107	107	107	107	107
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic																									
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																									
Sarcoma, NOS, metastatic												X													
Hemangiosarcoma			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													
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	2152 548	2155 549	2158 552	2161 555	2164 558	2167 561	2170 564	2173 567	2176 570	2179 573	2182 576	2185 579	2188 582	2191 585	2194 588	2197 591	2200 594	2203 597	2206 600	2209 603	2212 606	2215 609	2218 612	2221 615	2224 618	2227 621	2230 624	2233 627	2236 630	2239 633	2242 636	2245 639	2248 642	2251 645	2254 648	2257 651	2260 654	2263 657	2266 660	2269 663	2272 666	2275 669	2278 672	2281 675	2284 678	2287 681	2290 684	2293 687	2296 690	2299 693	2302 696	2305 699	2308 702	2311 705	2314 708	2317 711	2320 714	2323 717	2326 720	2329 723	2332 726	2335 729	2338 732	2341 735	2344 738	2347 741	2350 744	2353 747	2356 750	2359 753	2362 756	2365 759	2368 762	2371 765	2374 768	2377 771	2380 774	2383 777	2386 780	2389 783	2392 786	2395 789	2398 792	2401 795	2404 798	2407 801	2410 804	2413 807	2416 810	2419 813	2422 816	2425 819	2428 822	2431 825	2434 828	2437 831	2440 834	2443 837	2446 840	2449 843	2452 846	2455 849	2458 852	2461 855	2464 858	2467 861	2470 864	2473 867	2476 870	2479 873	2482 876	2485 879	2488 882	2491 885	2494 888	2497 891	2500 894	2503 897	2506 900	2509 903	2512 906	2515 909	2518 912	2521 915	2524 918	2527 921	2530 924	2533 927	2536 930	2539 933	2542 936	2545 939	2548 942	2551 945	2554 948	2557 951	2560 954	2563 957	2566 960	2569 963	2572 966	2575 969	2578 972	2581 975	2584 978	2587 981	2590 984	2593 987	2596 990	2599 993	2602 996	2605 999	2608 1002	2611 1005	2614 1008	2617 1011	2620 1014	2623 1017	2626 1020	2629 1023	2632 1026	2635 1029	2638 1032	2641 1035	2644 1038	2647 1041	2650 1044	2653 1047	2656 1050	2659 1053	2662 1056	2665 1059	2668 1062	2671 1065	2674 1068	2677 1071	2680 1074	2683 1077	2686 1080	2689 1083	2692 1086	2695 1089	2698 1092	2701 1095	2704 1098	2707 1101	2710 1104	2713 1107	2716 1110	2719 1113	2722 1116	2725 1119	2728 1122	2731 1125	2734 1128	2737 1131	2740 1134	2743 1137	2746 1140	2749 1143	2752 1146	2755 1149	2758 1152	2761 1155	2764 1158	2767 1161	2770 1164	2773 1167	2776 1170	2779 1173	2782 1176	2785 1179	2788 1182	2791 1185	2794 1188	2797 1191	2800 1194	2803 1197	2806 1200	2809 1203	2812 1206	2815 1209	2818 1212	2821 1215	2824 1218	2827 1221	2830 1224	2833 1227	2836 1230	2839 1233	2842 1236	2845 1239	2848 1242	2851 1245	2854 1248	2857 1251	2860 1254	2863 1257	2866 1260	2869 1263	2872 1266	2875 1269	2878 1272	2881 1275	2884 1278	2887 1281	2890 1284	2893 1287	2896 1290	2899 1293	2902 1296	2905 1299	2908 1302	2911 1305	2914 1308	2917 1311	2920 1314	2923 1317	2926 1320	2929 1323	2932 1326	2935 1329	2938 1332	2941 1335	2944 1338	2947 1341	2950 1344	2953 1347	2956 1350	2959 1353	2962 1356	2965 1359	2968 1362	2971 1365	2974 1368	2977 1371	2980 1374	2983 1377	2986 1380	2989 1383	2992 1386	2995 1389	2998 1392	3001 1395	3004 1398	3007 1401	3010 1404	3013 1407	3016 1410	3019 1413	3022 1416	3025 1419	3028 1422	3031 1425	3034 1428	3037 1431	3040 1434	3043 1437	3046 1440	3049 1443	3052 1446	3055 1449	3058 1452	3061 1455	3064 1458	3067 1461	3070 1464	3073 1467	3076 1470	3079 1473	3082 1476	3085 1479	3088 1482	3091 1485	3094 1488	3097 1491	3100 1494	3103 1497	3106 1500	3109 1503	3112 1506	3115 1509	3118 1512	3121 1515	3124 1518	3127 1521	3130 1524	3133 1527	3136 1530	3139 1533	3142 1536	3145 1539	3148 1542	3151 1545	3154 1548	3157 1551	3160 1554	3163 1557	3166 1560	3169 1563	3172 1566	3175 1569	3178 1572	3181 1575	3184 1578	3187 1581	3190 1584	3193 1587	3196 1590	3199 1593	3202 1596	3205 1599	3208 1602	3211 1605	3214 1608	3217 1611	3220 1614	3223 1617	3226 1620	3229 1623	3232 1626	3235 1629	3238 1632	3241 1635	3244 1638	3247 1641	3250 1644	3253 1647	3256 1650	3259 1653	3262 1656	3265 1659	3268 1662	3271 1665	3274 1668	3277 1671	3280 1674	3283 1677	3286 1680	3289 1683	3292 1686	3295 1689	3298 1692	3301 1695	3304 1698	3307 1701	3310 1704	3313 1707	3316 1710	3319 1713	3322 1716	3325 1719	3328 1722	3331 1725	3334 1728	3337 1731	3340 1734	3343 1737	3346 1740	3349 1743	3352 1746	3355 1749	3358 1752	3361 1755	3364 1758	3367 1761	3370 1764	3373 1767	3376 1770	3379 1773	3382 1776	3385 1779	3388 1782	3391 1785	3394 1788	3397 1791	3400 1794	3403 1797	3406 1800	3409 1803	3412 1806	3415 1809	3418 1812	3421 1815	3424 1818	3427 1821	3430 1824	3433 1827	3436 1830	3439 1833	3442 1836	3445 1839	3448 1842	3451 1845	3454 1848	3457 1851	3460 1854	3463 1857	3466 1860	3469 1863	3472 1866	3475 1869	3478 1872	3481 1875	3484 1878	3487 1881	3490 1884	3493 1887	3496 1890	3499 1893	3502 1896	3505 1899	3508 1902	3511 1905	3514 1908	3517 1911	3520 1914	3523 1917	3526 1920	3529 1923	3532 1926	3535 1929	3538 1932	3541 1935	3544 1938	3547 1941	3550 1944	3553 1947	3556 1950	3559 1953	3562 1956	3565 1959	3568 1962	3571 1965	3574 1968	3577 1971	3580 1974	3583 1977	3586 1980	3589 1983	3592 1986	3595 1989	3598 1992	3601 1995	3604 1998	3607 2001	3610 2004	3613 2007	3616 2010	3619 2013	3622 2016	3625 2019	3628 2022	3631 2025	3634 2028	3637 2031	3640 2034	3643 2037	3646 2040	3649 2043	3652 2046	3655 2049	3658 2052	3661 2055	3664 2058	3667 2061	3670 2064	3673 2067	3676 2070	3679 2073	3682 2076	3685 2079	3688 2082	3691 2085	3694 2088	3697 2091	3700 2094	3703 2097	3706 2100	3709 2103	3712 2106	3715 2109	3718 2112	3721 2115	3724 2118	3727 2121	3730 2124	3733 2127	3736 2130	3739 2133	3742 2136	3745 2139	3748 2142	3751 2145	3754 2148	3757 2151	3760 2154	3763 2157	3766 2160	3769 2163	3772 2166	3775 2169	3778 2172	3781 2175	3784 2178	3787 2181	3790 2184	3793 2187	3796 2190	3799 2193	3802 2196	3805 2199	3808 2202	3811 2205	3814 2208	3817 2211	3820 2214	3823 2217	3826 2220	3829 2223	3832 2226	3835 2229	3838 2232	3841 2235	3844 2238	3847 2241	3850 2244	3853 2247	3856 2250	3859 2253	3862 2256	3865 2259	3868 2262	3871 2265	3874 2268	3877 2271	3880 2274	3883 2277	3886 2280	3889 2283	3892 2286	3895 2289	3898 2292	3901 2295	3904 2298	3907 2301	3910 2304	3913 2307	3916 2310	3919 2313	3922 2316	3925 2319	3928 2322	3931 2325	3934 2328	3937 2331	3940 2334	3943 2337	3946 2340	3949 2343	3952 2346	3955 2349	3958 2352	3961 2355	3964 2358	3967 2361	3970 2364	3973 2367	3976 2370	3979 2373	3982 2376	3985 2379	3988 2382	3991 2385	3994 2388	3997 2391	4000 2394	4003 2397	4006 2400	4009 2403	4012 2406	4015 2409	4018 2412	4021 2415	4024 2418	4027 2421	4030 2424	4033 2427	4036 2430	4039 2433	4042 2436	4045 2439	4048 2442	4051 2445	4054 2448	4057 2451	4060 2454	4063 2457	4066 2460	4069 2463	4072 2466	4075 2469	4078 2472	4081 2475	4084 2478	4087 2481	4090 2484	4093 2487	4096 2490	4099 2493	4102 2496	4105 2499	4108 2502	4111 2505	4114 2508	4117 2511	4120 2514	4123 2517	4126 2520	4129 2523	4132 2526	4135 2529	4138 2532	4141 2535	4144 2538	4147 2541	4150 2544	4153 2547	4156 2550	4159 2553	4162 2556	4165 2559	4168 2562	4171 2565	4174 2568	4177 2571	4180 2574	4183 2577	4186 2580	4189 2583	4192 2586	4195 2589	4198 2592	4201 2595	4204 2598	4207 2601	4210 2604	4213 2607	4216 2610	4219 2613	4222 2616	4225 2619	4228 2622	4231 2625	4234 2628	4237 2631	4240 2634	4243 2637	4246 2640	4249 2643	4252 2646	4255 2649	4258 2652	4261 2655	4264 2658	4267 2661	4270 2664	4273 2667	4276 2670	4279 2673	4282 2676	4285 2679	4288 2682	4291 2685	4294 2688	4297 2691	4300 2694	4303 2697	4306 2700	4309 2703	4312 2706	4315 2709	4318 2712	4321 2715	4324 2718	4327 2721	4330 2724	4333 2727	4336 2730	4339 2733	4342 2736	4345 2739	4348 2742	4351 2745	4354 2748	4357 2751	4360 2754	4363 2757	4366 2760	4369 2763	4372 2766	4375 2769	4378 2772	4381 2775	4384 2778	4387 2781	4390 2784	4393 2787	4396 2790	4399 2793	4402 2796	4405 2799	4408 2802	4411 2805	4414 2808	4417 2811	4420 2814	4423 2817	4426 2820	4429 2823	4432 2826	4435 2829	4438 2832	4441 2835	4444 2838	4447 2841	4450 2844	4453 2847	4456 2850	4459 2853	4462 2856	4465 2859	4468 2862	4471 2865	4474 2868	4477 2871	448
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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)
ABSCCESS, 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 INFLAMMATION, SUPPURATIVE	(52)	(52)	(52) 1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*THORACIC CAVITY ABSCCESS, CHRONIC	(52)	(52) 1 (2%)	(52)
*MEDIASTINUM INFLAMMATION, SUPPURATIVE ABSCCESS, NOS	(52) 1 (2%)	(52) 1 (2%)	(52)
*PERITONEUM INFLAMMATION, NOS INFLAMMATION, FOCAL	(52) 1 (2%)	(52) 1 (2%)	(52)
*EPICARDIUM INFLAMMATION, CHRONIC SUPPURATIVE	(52) 1 (2%)	(52)	(52)
*MESENTERY INFLAMMATION, GRANULOMATOUS NECROSIS, FAT	(52) 3 (6%)	(52) 3 (6%)	(52) 2 (4%) 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)
ABCESS, 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%)
ABCESS, 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)
ABCESS, 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%)		1 (2%)
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%)	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 FIBROSIS	1 (2%)		1 (2%)
NECROSIS, NOS			1 (2%)
INFARCT, HEALED		2 (4%)	5 (10%)
METAPLASIA, OSSEOUS			1 (2%)
#KIDNEY/PELVIS	(50)	(50)	(50)
INFLAMMATION, NECROTIZING INFECTION, BACTERIAL		1 (2%)	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
Hemorrhage	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)

	<u>Months on Study</u>					<u>Months on Study</u>					<u>Months on Study</u>				
	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)															
(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
Hemorrhage	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)

	<u>Months on Study</u>					<u>Months on Study</u>					<u>Months on Study</u>				
	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%		15.1%		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

(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).

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 B6C3F₁ 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 B6C3F₁ 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 B6C3F₁ 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 B6C3F₁ 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 B6C3F₁ 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 B6C3F₁ 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 B6C3F₁ 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 B6C3F₁ 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 B6C3F₁ 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®

APPENDIX H. CHEMICAL CHARACTERIZATION

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

A. Physical Properties

1. Boiling Point:	<u>Determined</u>	<u>Literature Values</u>
	109° C	108° C (tech) 104° C (<i>trans</i>) 112° C (<i>cis</i>) (Merck, 1968)
2. Appearance:	Colorless liquid	

B. Spectral Data

1. Infrared	<u>Determined</u>	<u>Literature Values</u>
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	<i>cis</i> -1,3-Dichloropropene: 3030, 2940, 1640, 1450, 1330, 1300, 1280, 1270, 1240, 1160, 1080, 940, 930, 860, 820, 780, 680 cm ⁻¹ <i>trans</i> -1,3-Dichloropropene: 3030, 2940, 1640, 1450, 1270, 1240, 1080, 940, 860, 780, 690 cm ⁻¹ (Graselli and Ritchy, 1975)
2. Ultraviolet/Visible	<u>Determined</u>	<u>Literature Values</u>
a. Instrument:	Cary 17 dual beam	
b. Solvent:	Hexane	
c. Results:	$\lambda_{\max} = 209 \text{ nm}$ $\epsilon_{\max} = 3395$	No reference found

APPENDIX H. CHEMICAL CHARACTERIZATION

3. Nuclear Magnetic Resonance

	<u>Determined</u>	<u>Literature Values</u>
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 $\delta = 129.1, 127.3, \text{ and } 122.3$ each have one directly bonded proton. The ^{13}C spectrum indicates a mixture of <i>cis</i> - and <i>trans</i> -isomers	<i>trans</i> - (E) - 1,3-Dichloro- propene $\delta^{13}\text{C}$, ppm values are given as 41.8, 129.0, and 122.7 with 10% deuterated chloroform as internal reference (Chukovskaya et al., 1976)

APPENDIX H. CHEMICAL CHARACTERIZATION

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

<u>Peak</u>	<u>Retention Time (min)</u>	<u>Area (percent of total)</u>
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

<u>Peak</u>	<u>Retention Time (min)</u>	<u>Area (percent of total)</u>
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

APPENDIX H. CHEMICAL CHARACTERIZATION

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.

<u>Peak</u>	<u>Computer Retention Time (min)</u>	<u>Identity</u>
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 (41.8%)	<i>cis</i> -1,3-Dichloropropene
10	9.80	Not identified
11	10.73 (45.9%)	<i>trans</i> -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.

APPENDIX H. CHEMICAL CHARACTERIZATION

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

APPENDIX I

CHEMICAL CHARACTERIZATION AND ANALYSIS OF DOSE MIXTURES: METHODS AND DATA

APPENDIX I. ANALYSIS: 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:** ⁶³Ni 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 II

TABLE II. 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 ($\mu\text{g}/\text{plate}$)	Revertants/plate (a)		
		-S9	+ S9 (rat)	+ S9 (hamster)
TA100	0	155 \pm 1.3	165 \pm 5.2	154 \pm 9.6
	3	165 \pm 12.3	--	--
	10	223 \pm 24.7	--	--
	33	510 \pm 6.7	197 \pm 12.5	203 \pm 7.1
	100	1,672 \pm 42.3	321 \pm 19.1	249 \pm 6.7
	333	2,327 \pm 171.6	740 \pm 18.2	484 \pm 22.7
	1,000	--	46 \pm 46.3	155 \pm 79.3
	3,333	--	Toxic	Toxic
TA1535	0	58 \pm 3.5	47 \pm 5.1	47 \pm 1.7
	3	56 \pm 5.4	--	--
	10	83 \pm 4.9	--	--
	33	136 \pm 23.1	60 \pm 3.7	63 \pm 5.6
	100	586 \pm 54.3	74 \pm 7.0	77 \pm 6.1
	333	745 \pm 26.4	163 \pm 19.5	135 \pm 7.0
	1,000	--	126 \pm 30.4	Toxic
	3,333	--	Toxic	Toxic
TA1537	0	5 \pm 1.8	9 \pm 1.7	6 \pm 1.5
	3	5 \pm 0.9	--	--
	10	7 \pm 0.7	--	--
	33	6 \pm 1.5	9 \pm 0.9	6 \pm 0.7
	100	6 \pm 1.5	10 \pm 1.2	4 \pm 0.7
	333	5 \pm 1.5	6 \pm 1.2	7 \pm 0.6
	1,000	--	5 \pm 2.7	11 \pm 3.3
	3,333	--	Toxic	Toxic
TA98	0	27 \pm 0.6	35 \pm 8.8	29 \pm 4.5
	3	35 \pm 1.8	--	--
	10	31 \pm 6.1	--	--
	33	46 \pm 5.0	32 \pm 2.7	28 \pm 0.9
	100	61 \pm 7.8	28 \pm 2.3	35 \pm 4.3
	333	19 \pm 11.3	31 \pm 3.8	34 \pm 5.9
	1,000	--	24 \pm 1.5	42 \pm 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	1/1,200	0/1,171	4/3,571
		3/1,159	0/1,119	1/1,069	4/3,347
					8/6,918 (0.12)
	5,750	7/1,343	2/836	5/1,106	14/3,285
		3/1,373	3/1,088	0/838	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. F₁ heterozygous females were crossed to their siblings and placed in individual vials. F₁ 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 suggested 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)					Total No. of Tests	Total No. of Translocations	Total Translocations (percent)
		1	2	3	4	5			
Injection	5,750	0	1	0	0	0	6,965	1	0.01
		1,401	1,267	1,478	1,414	1,405			
Historical Control	0	0	0	0	0	0	19,637	0	0.00
		4,563	4,335	4,373	3,623	2,743			

(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 F₁ males were backcrossed to *bw; st* females, and the F₂ 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 ≤ 0.05 as compared with the vehicle control group

(c) Significant (t-test) changes at P ≤ 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 B6C3F₁ 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 non-target 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

APPENDIX M. DATA AUDIT SUMMARY

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 B6C3F₁ mice.