NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 318

TOXICOLOGY AND CARCINOGENESIS STUDIES OF AMPICILLIN TRIHYDRATE

(CAS NO. 7177-48-2)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

NATIONAL TOXICOLOGY PROGRAM

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

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF AMPICILLIN TRIHYDRATE

(CAS NO. 7177-48-2)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

April 1987

NTP TR 318

NIH Publication No. 87-2574

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

NOTE TO THE READER

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

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

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

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

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

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

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

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

CONTENTS

TABLES

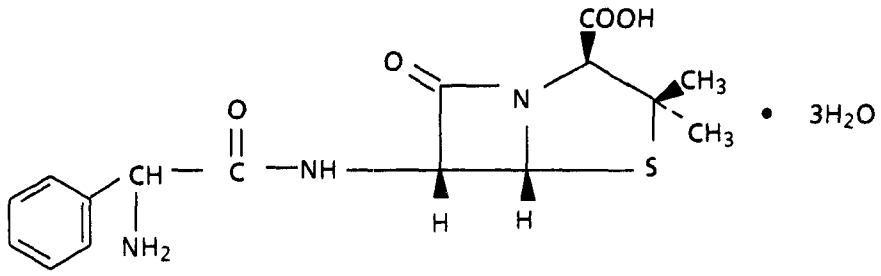
TABLES (Continued)

FIGURES

APPENDIXES

APPENDIXES (Continued)

APPENDIXES (Continued)



AMPICILLIN TRIHYDRATE
CAS No. 7177-48-2

Synonyms and trade names: Acillin, Amcap, Amcill, aminobenzylpencillin trihydrate, α-aminobenzylpencillin trihydrate, Amperil, Ampichel, Ampikel, Ampinova, Amplin, Cymbi, Divercillin, Liffampil, Morepen, Pen A, Pensyn, Polycillin, Princillin, Principen, Ro-ampen, Trafarbiot

Solubility: 1 g/150 ml water; insoluble in alcohol, acetone, chloroform, ether and oils

$C_{16}H_{19}N_3O_4S \cdot 3H_2O$ Molecular weight 403.46

ABSTRACT

Toxicology and carcinogenesis studies of ampicillin trihydrate (97%-99% pure) were conducted by administering the chemical in corn oil by gavage to groups of 50 F344/N rats and 50 $B6C3F_1$ mice of each sex, 5 days per week for 103 weeks. Male and female rats received doses of 0, 750, or 1,500 mg/kg, and male and female mice received doses of 0, 1,500, or 3,000 mg/kg. Doses selected for the 2-year studies were based on the lack of body weight effects and histopathologic effects at 2,400 mg/kg in the 14-day studies and 3,000 mg/kg in the 13-week studies. Clinical signs in the 13-week studies included diarrhea at 3,000 mg/kg in male and female rats and male mice. Corn oil suspensions containing more than 300 mg ampicillin trihydrate/ml were too viscous to be administered by gavage; therefore, a high dose of 1,500 mg/kg was selected for rats and a high dose of 3,000 mg/kg was selected for mice.

During the 2-year studies, mean body weights of male and female rats were similar to or slightly increased over those of the corresponding vehicle control groups. Mean body weights of low dose and high dose male mice were similar to those of the corresponding vehicle control group during year 1 of the study but were slightly below those of the vehicle control group during the last half of the study. Mean body weights of low dose and high dose female mice were greater than those of the vehicle controls throughout most of the study. No significant differences in survival were observed in groups of rats or mice of either sex. Clinical signs observed in dosed rats included diarrhea, excessive urination, and chromodacryorrhea and in dosed mice included increased salivation and decreased activity.

In male rats, administration of ampicillin trihydrate was associated with an increased incidence of mononuclear cell leukemia (vehicle control, 5/50; low dose, 14/50; high dose, 13/50). Malignant lymphomas were observed in one additional vehicle control male rat and two low dose male rats. Lymphocytic leukemia was seen in one high dose male rat. High dose male rats showed increased incidences of pheochromocytomas of the adrenal gland medulla (13/50; 12/50; 23/49). Malignant pheochromocytomas were observed in 1/50 vehicle control, 5/50 low dose, and 1/49 high dose male rats. The incidence of adrenal gland medullary hyperplasia was not increased in male rats (14/50; 10/50; 8/49). There were increased incidences of C-cell hyperplasia of the thyroid gland in low dose male and high dose female rats. High dose male rats showed increased incidences of hyperkeratosis and acanthosis of the forestomach.

In male and female mice, ampicillin trihydrate administration was associated with increased incidences of forestomach lesions, including ulcers, inflammation, hyperkeratosis, acanthosis, and evidence of fungal infection.

Ampicillin trihydrate was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 in the presence or absence of Aroclor 1254-induced male Syrian hamster or male Sprague-Dawley rat liver S9 when tested according to the preincubation protocol. Ampicillin trihydrate was not mutagenic in L5178Y mouse lymphoma cells with or without metabolic activation. Ampicillin trihydrate did not cause chromosomal aberrations or sister-chromatid exchanges in Chinese hamster ovary cells with or without metabolic activation.

An audit was conducted for these 2-year studies. Animal/carcass identification discrepancies were observed in rats and mice. The most common findings were the failure to clip some toes in rats and opened ear holes in mice. A review of the inlife data (including body weights, clinical observations, and dosing records) indicated that animals had not been interchanged among groups. The data are considered adequate to support the conclusions.

Under the conditions of these 2-year gavage studies, there was *equivocal evidence of carcinogenicity** of ampicillin trihydrate for male F344/N rats as shown by increased incidences of pheochromocytomas of the adrenal medulla and by marginally increased incidences of mononuclear cell leukemia. There was *no evidence of carcinogenicity* for female F344/N rats receiving 750 or 1,500 mg/kg or for male and female B6C3F$_1$ mice receiving 1,500 or 3,000 mg/kg per day. Nonneoplastic lesions of the forestomach were seen in male rats and male and female mice.

---

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 13-14.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Ampicillin Trihydrate is based on the 13-week studies that began in December 1979 and ended in March 1980 and on the 2-year studies that began in August 1980 and ended in September 1982 at Springborn Institute for Bioresearch, Inc.

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

June K. Dunnick, Ph.D., Chemical Manager

Gary A. Boorman, D.V.M., Ph.D.
Joseph K. Haseman, Ph.D.
James Huff, Ph.D.
C.W. Jameson, Ph.D.
E.E. McConnell, D.V.M.
G.N. Rao, D.V.M., Ph.D.
B.A. Schwetz, D.V.M., Ph.D.
Raymond W. Tennant, Ph.D.

NTP Pathology Working Group
(Evaluated Slides and Prepared Pathology Report on 12/29/83)

Robert Sauer, V.M.D. (Chair)
Clement Associates
Gary A. Boorman, D.V.M., Ph.D. (NTP)
Talmage Brown, D.V.M., Ph.D.
North Carolina State University
Scot L. Eustis, D.V.M., Ph.D. (NTP)
Bhola Gupta, B.V.Sc., Ph.D. (NTP)
A.W. Macklin, D.V.M., Ph.D.
Burroughs Wellcome Laboratories
Henk Solleveld, D.V.M., Ph.D. (NTP)
Katsuhiko Yoshitoma, D.V.M., Ph.D.
(NTP Observer)

Principal Contributors at Springborn Institute for Bioresearch, Inc.
(Conducted Studies and Evaluated Tissues)

Richard A. Hiles, Ph.D.
Principal Investigator
J. Boyce, D.V.M.
Pathologist (for mice)
Richard A. Hiles, Ph.D.
Chemist
C. Crisp, D.V.M.
Pathologist (for rats)

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

Melvin Hamlin, D.V.M.
J. Gauchat, Pathology Coordinator

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

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

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on ampicillin trihydrate on December 9, 1985, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee

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

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

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

Ad Hoc Subcommittee Panel of Experts

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

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

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

Richard J. Kociba, D.V.M., Ph.D.
(Principal Reviewer)
Dow Chemical USA
Midland, Michigan

David Kotelchuck, Ph.D.* (Principal Reviewer)
Environmental Health Science Program
Hunter School of Health Sciences
New York, New York

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

I.F.H. Purchase, Ph.D.
Central Toxicology Laboratory
Imperial Chemical Industries, PLC
Alderley Park, England

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

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

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

*Unable to attend

SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF AMPICILLIN TRIHYDRATE

On December 9, 1985, the draft Technical Report on the toxicology and carcinogenesis studies of ampicillin trihydrate received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. J. Dunnick, NTP, introduced the studies by reviewing the experimental design, results, and proposed conclusions (equivocal evidence of carcinogenicity in male rats; no evidence of carcinogenicity in female rats or in male and female mice).

Dr. Kociba, a principal reviewer, agreed with the conclusions as written for female rats and male and female mice. However, he said that the conclusion for male rats should be expressed as equivocal evidence of benign tumor induction, based on the increased incidence of adrenal gland pheochromocytomas. He thought that, within the range of historical control incidences, the increased incidence of mononuclear cell leukemia was not compound related. Dr. Kociba said that the design of both the 13-week and 2-year studies would have been made more useful by inclusion of clinical pathology, more detailed clinical observations, and ampicillin blood levels, possibly being correlated with pharmacologic effects. He requested deletion of the last sentence in the conclusions regarding nonneoplastic lesions.

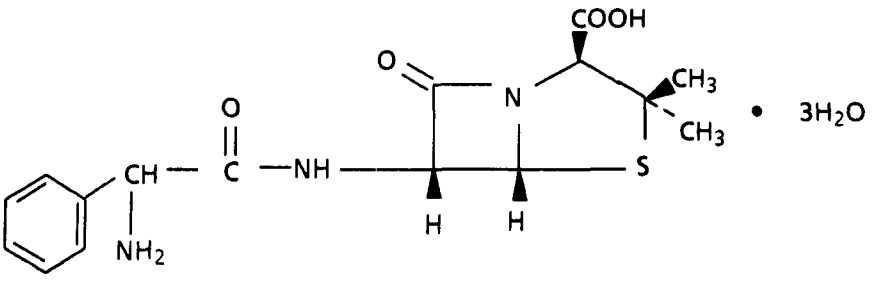
As second principal reviewer, Dr. Turnbull agreed with the conclusions for female rats and male and female mice. He said that the evidence for any increase in mononuclear cell leukemia was weak and should not be part of the conclusion for male rats. He asked that the report indicate whether original and quality assurance (QA) pathology examinations were performed in a "blind" fashion with respect to dose group or other diagnoses. Dr. S. Eustis, NIEHS, indicated that the Program did not routinely endorse pathology diagnoses without awareness of all relevant information. During the PWG, however, there is "blind" pathology in some select instances.

Most of the ensuing discussion dealt with the level of evidence of carcinogenicity in male rats and whether the increased incidences of adrenal medullary pheochromocytomas and mononuclear cell leukemia were related to administration of ampicillin trihydrate. Dr. Swenberg commented that the incidences of mononuclear cell leukemia in both low and high dose groups (28% and 26%, respectively) were almost double the historical control average (14%) and were at the top of the historical range. Thus, in his opinion, equivocal evidence of carcinogenicity was appropriate. Dr. Mirer argued that the positive trend test and statistical significance of increases in mononuclear cell leukemia by the life table test supported a designation of some evidence of carcinogenicity. Dr. Perera agreed. Dr. Eustis said that the highly variable incidence of mononuclear cell leukemia argued for the level chosen. In response to Dr. Perera, Dr. J. Huff, NIEHS, noted the decreased incidence of adrenal medullary hyperplasia, a precursor lesion to pheochromocytoma, in both dose groups. Dr. Turnbull questioned the appropriateness of the life table test for analysis in view of the numbers of rats with mononuclear cell leukemia surviving to the end of the studies. Dr. J. Haseman, NIEHS, replied that mononuclear cell leukemia is generally considered by the NTP to be a fatal tumor, although this determination is not clear-cut in this instance, since the leukemia incidences were similar in male rats dying before the end of the study and in the animals surviving 2 years.

Dr. Hooper moved that the conclusions in the Technical Report on ampicillin trihydrate be accepted as written for female rats and male and female mice, no evidence of carcinogenicity. Dr. Mirer seconded the motion, and it was approved unanimously with 11 affirmative votes. Dr. Kociba moved that the phrase "and marginally increased incidence of mononuclear cell leukemia" be deleted from the first sentence of the conclusion as supporting equivocal evidence of carcinogenicity in male rats. Dr. Swenberg seconded the motion, and it was defeated by six votes (Drs. Hooper, Mirer, Perera, Scala, Swenberg, and Tannenbaum) to five votes (Drs. Crowley, Jones, Kociba, Purchase, and Turnbull). Dr. Swenberg then moved that the conclusions as written for male rats, equivocal evidence of carcinogenicity, be accepted. Dr. Tannenbaum seconded the motion, and it was approved by six affirmative votes to one negative vote (Dr. Kociba) with four abstentions (Drs. Crowley, Jones, Purchase, and Turnbull).

I. INTRODUCTION

I. INTRODUCTION



AMPICILLIN TRIHYDRATE
CAS No. 7177-48-2

Synonyms and trade names: Acillin, Amcap, Amcill, aminobenzylpencillin trihydrate, α-aminobenzylpencillin trihydrate, Amperil, Ampichel, Ampikel, Ampinova, Amplin, Cymbi, Divercillin, Liffampil, Morepen, Pen A, Pensyn, Polycillin, Princillin, Principen, Ro-ampen, Trafarbiot

Solubility: 1 g/150 ml water; insoluble in alcohol, acetone, chloroform, ether and oils

$C_{16}H_{19}N_3O_4S \cdot 3H_2O$ Molecular weight 403.46

Ampicillin trihydrate is a broad-spectrum semisynthetic penicillin that is effective in the treatment of gram-positive and gram-negative bacterial infections produced by Streptococcus, *Bacillus anthracis, Haemophilus influenzae, Neisseria gonorrhoeae,* and *Escherichia coli.* This antibiotic is used in the treatment of upper respiratory tract infections, genital and urinary tract infections, and otitis media in children (PDR, 1984; Mandell and Sande, 1980).

The ampicillins, also known as 2-aminobenzylpenicillins, were first used in the early 1960's. This group of antibiotics is widely used because of its stability in acid, low toxicity, broad spectrum of action, and efficient absorption after oral administration. Ampicillin, like the other penicillins, consists of a thiazolidine ring connected to a *beta*-lactam ring and a unique side chain that differentiates this from the other antibiotics (e.g., a broad spectrum of activity against both gram-positive and gram-negative bacteria and acid stability) (Mandell and Sande, 1980; Frank et al., 1961; Kaufmann and Bauer, 1963; Johnson and Hardcastle, 1964; Johnson and Wolfe, 1964). *beta*-Lactam antibiotics may be inactivated by penicillinase that opens the *beta*-lactam ring or by amidases that break the side chain (Mandell and Sande, 1980). *beta*-Lactam antibiotics exert their bactericidal effects by inhibiting the cross-linking step (transpeptidation) of bacterial cell wall biosynthesis (Waxman and Strominger, 1983).

Production and Human Exposure

Ampicillin products are distributed by several drug companies in the United States, and an estimated 18.5 million prescriptions were written for ampicillin products in 1982, making this among the top 25 prescription drug chemicals (FDA, 1983). Humans are exposed systemically to ampicillin products through oral administration or by intramuscular or intravenous injection for the treatment of bacterial infections.

Doses of ampicillin trihydrate vary depending on the type of disease treated and age of the patient, but doses are normally between 50 and 200 mg/kg per day, usually given in four equally divided doses (PDR, 1984; McCracken, 1983). The most common side effects reported are hypersensitivity (anaphylactoid) reactions. Other side effects reported (incidence not specified) include gastrointestinal symptoms, such as nausea, vomiting, and diarrhea; skin rashes; elevated serum glutamic oxaloacetic transaminase; and reversible effects on the hemic and

lymphatic system, including anemia, thrombocytopenia, and leukopenia (PDR, 1984; Erffmeyer, 1981). Penicillin and structurally related antibiotics elicit antibodies of all the major classes (IgE, IgA, IgM, IgG, IgD). When a person has an allergy to one penicillin, it is assumed that he may be allergic to all penicillins (Erffmeyer, 1981).

Reproductive and Teratogenic Effects

The penicillins are probably the antibiotics prescribed most frequently during pregnancy (Ledger, 1977). Reproductive toxicity of ampicillin has not been reported to be a side effect of treatment in humans (PDR, 1984; Erffmeyer, 1981; Mandell and Sande, 1980). Ampicillin has been reported to cross the human placenta (Perry and Le Blanc, 1967; Adamkin et al., 1984; Stewart et al., 1973), although no congenital disorders have been associated with ampicillin treatment during pregnancy (Jick et al., 1981; Korzhova et al., 1981).

Effects in Animals

Ampicillin administered as a single oral or subcutaneous dose of up to 5 g/kg had no observable toxic effect in mice or rats. An intravenous dose of ampicillin (2 g/kg) to mice caused muscle tremors, slow respiration, and mild convulsions. No effects or biochemical, hematologic, or histologic abnormalities were seen in rats administered ampicillin orally at 100 or 500 mg/kg for 12 weeks (Brown and Acred, 1961). Ampicillin administered in the drinking water (25 mg/liter) to 4-week-old rats for up to 8 weeks resulted in an increase in body weight gain; no toxic effects were noted (King, 1975). The LD_{50} value (intraperitoneal injection) is 3,300 mg/kg for 1-day-old rats and 4,500 mg/kg for 83-day-old rats (Goldenthal, 1971). The oral LD_{50} value in rats is 10 g/kg and in mice is 15.2 g/kg (Khosid et al., 1975). Deaths occurred in 63%, 45%, and 100% of the rabbits receiving oral doses of 5, 15, or 50 mg/kg of ampicillin for 3 consecutive days (Milhaud et al., 1976).

Absorption, Distribution, and Metabolism

When ampicillin is administered orally to humans, peak serum levels are reached in about 2 hours; after intramuscular injection, peak serum levels are reached in about 1 hour (Wright and Wilkowske, 1983). Absorption in the duodenum is approximately 50% after oral administration (Loo et al., 1974). Ampicillin is excreted primarily in the urine, although biliary excretion also occurs (Jusko and Lewis, 1973). *alpha*-Aminobenzyl penicilloic acid was tentatively found to be the major metabolite in the urine (Masada et al., 1979, 1980). The plasma half-life of ampicillin is approximately 1.5 hours; 18% of the drug is bound to protein (Schumacher, 1982). The plasma half-life of ampicillin increases in the elderly, indicating decreased drug elimination (Triggs et al., 1980). Ampicillin is distributed to the major organ systems in rats, and the half-life of ampicillin in rats after intraperitoneal injection is estimated to be 27 minutes (Fabre et al., 1977).

Mutagenicity

The mutagenicity of ampicillin has been evaluated in both bacterial cells and mammalian cells in culture. Although ampicillin is an antimicrobial agent, *Salmonella typhimurium* can be used to assay its mutagenic activity because an end point other than cell death is monitored. The mutagenic activity of ampicillin can be measured at doses that do not produce extreme toxicity. Similar tests have been used to evaluate the mutagenic activity of other antimicrobials, including nitrofurantoin and streptomycin sulfate (Haworth et al., 1983). Ampicillin was not mutagenic in *S. typhimurim* strains TA1535, TA100, TA1530, TA98, TA1537, or TA97 with or without metabolic activation (De Flora et al., 1984). These results are consistent with those of NTP studies which indicated that ampicillin is not mutagenic in *S. typhimurium* strains TA1535, TA1537, TA98, or TA100 in the presence or absence of Aroclor 1254-induced male Sprague-Dawley rat or male Syrian hamster liver S9 when tested in a preincubation protocol (Appendix G, Table G1; Mortelmans et al., 1986). Ampicillin did not induce DNA damage in *Escherichia coli* in the absence of metabolic activation (Green and Tweats, 1981). It was also a weak inducer of lambda phage in *E. coli* (Elespuru and Pennington, 1981). Ampicillin trihydrate was not mutagenic in the mouse lymphoma L5178Y/$TK^{+/-}$ assay in the presence

or absence of Aroclor 1254-induced male F344 rat liver S9 (Tables G2 and G3).

Tests for cytogenetic effects in Chinese hamster ovary cells indicated that ampicillin trihydrate does not cause an increase in sister-chromatid exchanges or chromosomal aberrations in the presence or absence of S9 prepared from liver of Aroclor 1254-induced male Sprague-Dawley rats (Tables G4 and G5). No visible chromosomal breakage or structural alterations were found in cultures of human diploid fibroblasts incubated for 50 hours with 4 mg ampicillin per milliliter (Byarugaba et al., 1975). In human lymphocytes exposed in vitro to ampicillin at 28 μg/ml, a statistically significant ($P<0.05$) increase in the frequency of chromosomal aberrations was observed along with a slight depression (13.44%) of the mitotic index (Jaju et al., 1984). However, at 7 or 14 μg/ml (levels corresponding to those in plasma of adults given a 500-mg or 1-g intramuscular injection of the drug), no effects on the frequency of chromosomal aberrations or the mitotic index were observed. The frequency of sister-chromatid exchanges was not increased at any of these exposure levels. Jaju et al. (1984) discussed other studies in which ampicillin was shown to induce chromosomal damage in human lymphocytes. Crippa et al. (1976) had previously reported no significant increase in chromosomal abnormalities in lymphocytes of patients with rheumatism who had been treated with ampicillin and other drugs.

Study Rationale

Ampicillin trihydrate was selected for study as a representative of the ampicillin-type penicillins for which carcinogenicity data were not available. Ampicillin is one of the most frequently prescribed drugs in the United States (FDA, 1983), and exposure may occur throughout life. Ampicillin trihydrate was administered orally by gavage to mimic human intake of the drug and because it was found to be unstable in feed. Ampicillin trihydrate is only slightly soluble in water; therefore, corn oil was selected to improve suspendability in the gavage vehicle.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF AMPICILLIN TRIHYDRATE

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Study Design

Source and Specifications of Animals

Animal Maintenance

Clinical Examinations and Pathology

Statistical Methods

PROCUREMENT AND CHARACTERIZATION OF AMPICILLIN TRIHYDRATE

USP-grade ampicillin trihydrate was obtained in two lots (Table 1). The identity of the chemical was confirmed by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy (Appendix H). All spectroscopic data were consistent with the structure of ampicillin trihydrate. The chemical purity of both lots was determined to range from 98% to 99% (calculated on a dried basis) by elemental analysis, nonaqueous titration of amine and acidic functional groups, and thin-layer and high-performance liquid chromatography. Water content was determined to range from 13.2% to 14.3% by Karl Fischer analysis. High-performance liquid chromatography indicated that each lot contained 1.1%-2.2% total impurities; these impurities were not identified. Both lots of ampicillin trihydrate conformed to USP specifications.

An NTP stability study indicated that ampicillin trihydrate was stable when stored in the dark for 2 weeks at temperatures up to 60° C (Appendix H). Ampicillin trihydrate was stored at the study laboratory in the dark at 4° C. Reanalysis of the bulk chemical by infrared spectroscopy, titration, and high-performance liquid chromatography indicated no deterioration of ampicillin trihydrate over the course of the studies.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

Stability studies of ampicillin trihydrate mixed in NIH 07 Rat and Mouse Ration indicated that a 1% blend of ampicillin trihydrate was unstable when stored for 2 weeks at temperatures ranging from 5° C to 45° C (Appendix I). Ampicillin trihydrate is only slightly soluble in water. Corn oil enhanced the suspendability of ampicillin trihydrate and was therefore selected as the vehicle for gavage administration. Corn oil suspensions of ampicillin trihydrate were prepared relatively easily at concentrations up to 300 mg/ml. At higher concentrations, the dose mixtures were too viscous to be drawn through an 18-gauge gavage needle. Ampicillin trihydrate and corn oil were blended as described in Table 2. A 100 mg/ml suspension in corn oil was stable when stored at room temperature for 2 weeks (Appendix I). Ampicillin trihydrate/corn oil mixtures were stored at 4° C for no longer than 14 days. The dose mixtures were resuspended before being administered to the animals.

Periodic analyses for ampicillin trihydrate in corn oil were performed to determine if the dose mixtures contained the correct concentrations (Appendix J). Because 27/30 of the dose mixtures were within ±10% of the target concentrations, it is estimated that dose mixtures for the 2-year studies were formulated within specifications 90% of the time (Table 3; Appendix K, Table K2). The other samples were within ±20% of the target concentrations.

FOURTEEN-DAY STUDIES

Oral LD_{50} values for ampicillin in rats and mice had previously been reported in the literature (rats--10.0 g/kg; mice--15.2 g/kg; Khosid et al., 1975). For this reason, the studies of ampicillin

TABLE 1. IDENTITY AND SOURCE OF LOTS USED IN THE GAVAGE STUDIES OF AMPICILLIN TRIHYDRATE

	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Lot Numbers	61849K	61849K	61849K, 33564-550
Date of Initial Use	9/10/79	12/20/79	Lot 61849K--9/2/80 (rats), 8/25/80 (mice); lot 33564-550--week 72
Supplier	E.R. Squibb & Sons, Inc. (Princeton, NJ), manufactured by Ersana, Inc. (Humacao, Puerto Rico)	Same as 14-d studies	Ersana, Inc. (Humacao, Puerto Rico)

TABLE 2. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF AMPICILLIN TRIHYDRATE

	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation	Ampicillin trihydrate was mixed in a 250-ml beaker with part of the corn oil; premix then brought to volume with corn oil in a 100-ml volumetric flask, mixed, and then blended in a Waring blender.	Weighed ampicillin trihydrate mixed with corn oil in Waring blender, transferred to volumetric flask and brought to volume with corn oil, mixed in flask, then transferred to a beaker and mixed with a stirring bar and magna-stirrer	Ampicillin trihydrate initially prepared with corn oil as 30% or 15% (w/v) suspensions, mixed in Waring blender or Tekmer homogenizer. The suspension was divided into amounts needed daily.
Maximum Storage Time	1 d	2 wk	2 wk
Storage Conditions	4° C	4° C	4° C

TABLE 3. SUMMARY OF RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF AMPICILLIN TRIHYDRATE

	Concentration of Ampicillin Trihydrate in Corn Oil for Target Concentration (percent, w/v) (a)	
	15	30
Mean (percent, w/v)	15.0	29.3
Range (percent, w/v)	12.3-17.9	26.6-32.1
Standard deviation	1.14	1.31
Coefficient of variation (percent)	7.6	4.5
Number of samples	15	15

began with the 14-day studies. Ampicillin trihydrate/corn oil suspensions at concentrations above 300 mg/ml were too viscous to be easily administered by gavage. The NTP guidelines for gavage administration suggest that the volume not exceed 5 ml/kg for rats and 10 ml/kg for mice, corresponding to 1,500 and 3,000 mg/kg body weight, respectively.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 17 days before the studies began. Groups of five rats and five mice of each sex were administered 0, 200, 400, 800, 1,600, or 2,400 mg/kg ampicillin trihydrate in corn oil by gavage for 14 consecutive days with a high dose volume of 8 ml/kg body weight. An exception to the dose volume limitation was made for these studies in rats so that the effects of the compound at the same dose could be compared in rats and mice.

Animals were housed five per cage and received feed and water ad libitum. Further details of animal maintenance are presented in Table 4. The rats and mice were observed twice per day and weighed on days 0, 8, and 14. A necropsy was performed on all animals. A histologic examination was performed on three animals of each sex in the 2,400 mg/kg groups.

THIRTEEN-WEEK STUDIES

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

Five-week-old male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories, observed for 15 days, and assigned to cages according to a table of random

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

	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN			
Size of Study Groups	5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses	0, 200, 400, 800, 1,600, or 2,400 mg/kg ampicillin trihydrate in corn oil by gavage; dose vol--0.67-8 ml/kg	Rats--0, 180, 370, 750, 1,500, or 3,000 mg/kg ampicillin trihydrate in corn oil by gavage; dose vol--5 ml/kg (3,000 mg/kg group given 1,500 mg/kg 2 × d at least 5 h apart); mice--0, 250, 500, 1,000, 2,000, or 3,000 mg/kg ampicillin trihydrate in corn oil by gavage; dose vol--10 ml/kg	Rats--0, 750, or 1,500 mg/kg ampicillin trihydrate in corn oil by gavage; dose vol--5 ml/kg; mice--0, 1,500, or 3,000 mg/kg ampicillin trihydrate in corn oil by gavage; dose vol--10 ml/kg
Date of First Dose	9/10/79	12/20/79	Rats--9/2/80; mice--8/25/80
Date of Last Dose	9/23/79	3/19/80	Rats--8/23/82; mice--8/13/82
Duration of Dosing	14 consecutive d	5 d/wk for 13 wk	5 d/wk for 103 wk
Type and Frequency of Observation	Observed 2 × d; weighed on d 0, 8, and 14	Observed 2 × d; weighed 1 × wk	Observed 1 or 2 × d; weighed 1 × wk for 12 wk, then 1 × 4 wk; palpation of animals was performed 1 × mo from wk 41 to 101
Necropsy and Histologic Examination	Necropsy performed on all animals. Histologic exams performed on three per sex per species of the high dose group. Tissues examined: regional lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary glands, thigh muscle, sciatic nerve, bone marrow, costochondral junction (rib), thymus, larynx, trachea, lungs and bronchi, heart, thyroid gland, parathyroids, esophagus, stomach, duodenum, jejunum, ileum, colon, rectum, mesenteric lymph nodes, liver, pancreas, spleen, kidneys, adrenal glands, urinary bladder, seminal vesicles/prostate/testis or ovaries/uterus, nasal cavity, brain, pituitary gland, eyes, external and middle ear, spinal cord, and gallbladder (mice)	Necropsy performed on all animals. Histologic exams performed on vehicle control and high dose groups and on all animals dying during the study. Tissues examined: same as the 14-d studies	Necropsy and histologic exam performed on all animals; the following tissues were examined: gross lesions and tissue masses, blood smear, mandibular or mesenteric lymph nodes, salivary glands, sternebrae, femur, or vertebrae including marrow, thyroid gland, parathyroids, small intestine, large intestine, liver, prostate/testes/epididymis or ovaries/uterus, lungs with mainstem bronchi, skin, heart, esophagus, stomach, brain, thymus, trachea, pancreas, spleen, kidneys, adrenal glands, urinary bladder, pituitary gland, spinal cord (if neurologic signs present), eyes (if grossly abnormal), mammary glands and pharynx (if grossly abnormal)
ANIMALS AND ANIMAL MAINTENANCE			
Strain and Species	F344/N rats; B6C3F$_1$ mice	Same as 14-d studies	Same as 14-d studies
Animal Source	Charles River Breeding Laboratories (Portage, MI)	Same as 14-d studies	Same as 14-d studies
Study Laboratory	Springborn Institute for Bioresearch, Inc.	Same as 14-d studies	Same as 14-d studies

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

	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)			
Method of Animal Identification	Toe clip and ear punch	Same as 14-d studies	Same as 14-d studies
Time Held Before Study	17 d	15 d	18 d
Age When Placed on Study	52 d	7 wk	Rats and mice--7-8 wks
Age When Killed	66 d	20 wk	Rats and mice--111-112 wks
Necropsy Dates	9/24/79	3/20/80-3/21/80	Rats--8/30/82-9/2/82; mice--8/23/82-8/25/82
Method of Animal Distribution	According to tables of random numbers	Same as 14-d studies	Same as 14-d studies
Feed	NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners, PA); available ad libitum	Same as 14-d studies	Same as 14-d studies
Bedding	Anipads (Ancare Corp., L.I., NY)	Ancubes (Ancare Corp., L.I., NY)	Heat-treated hardwood chips (Ancare Corp., L.I., NY)
Water	City water in bottles; available ad libitum	Half deionized/half tap water; automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	City water from deep well passed through reverse osmosis unit to remove 90% of the dissolved salts (Osmonics, Inc., Hopkins, MN); rats and group housed mice--automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum; water in bottles for mice housed individually
Cages	Stainless steel wire mesh hanging cages (Shoreline, Kansas City, MO)	Polycarbonate (Lab Products, Inc., Rochelle Park, NJ)	Same as 13-wk studies
Cage Filters	None	100% polyester filter sheets (Snow Filtration, Cincinnati, OH)	Same as 13-wk studies; no filter sheets for mice housed individually
Animals per Cage	5	5	5 except for some aggressive and/or wounded male mice housed individually
Other Chemicals on Study in the Same Room	None	None	None
Animal Room Environment	Temp--71.2° ± 0.9° F; humidity--70% ± 6.2%; fluorescent light 12 h/d; 12 room air changes/h	Temp--70.6° ± 1.5° F; humidity--53% ± 7.4%; fluorescent light 12 h/d; 12 room air changes/h	Temp--66°-81° F; humidity--18%-100%; fluorescent light 12 h/d; 12 room air changes/h

numbers. The cages were then assigned to dosed and vehicle control groups according to a table of random numbers.

Groups of 10 rats of each sex were administered 0, 180, 370, 750, 1,500, or 3,000 mg/kg 5 days per week for 13 weeks. Rats in the highest dose group (3,000 mg/kg) were administered 1,500 mg/kg (5 ml/kg) twice daily at least 5 hours apart 5 days per week for 13 weeks. All other groups received one administration of 5 ml/kg. Groups of 10 mice of each sex were administered 0, 250, 500, 1,000, 2,000, or 3,000 mg/kg (dose volume, 10 ml/kg body weight) 5 days per week for 13 weeks.

Animals were checked twice per day; moribund animals were killed. Animal weights were recorded weekly. Further experimental details are summarized in Table 4.

At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 4.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats of each sex were administered 0, 750, or 1,500 mg/kg ampicillin trihydrate in corn oil by gavage, 5 days per week for 103 weeks (dose volume, 5 ml/kg body weight). Groups of 50 mice of each sex were administered 0, 1,500, or 3,000 mg/kg on the same schedule (dose volume, 10 ml/kg body weight).

Source and Specifications of Animals

The male and female F344/N rats and $B6C3F_1$ (C57BL/6N, female, × C3H/HeN MTV^-, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Animals were shipped to the study laboratory at 5-6 weeks of age. The animals were quarantined at the study facility for 18 days. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats and mice were placed on study at 7-8 weeks of age. The health of the animals was monitored during the course of the study according to the protocols of the NTP Sentinel Animal Program (Appendix L).

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

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

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

Animal Maintenance

All animals were housed five per cage and received feed and water ad libitum. Further details of animal maintenance are given in Table 4.

Clinical Examinations and Pathology

All animals were observed twice daily, and clinical signs were recorded once per week. Body

weights by cage were recorded once per week for the first 12 weeks of the study and once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals including those found dead, unless they were excessively autolyzed or cannibalized, missexed, or found missing. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study.

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

When the pathology evaluation was completed, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assessment pathologist. The quality assessment report and slides were submitted to the Pathology Working Group (PWG) Chairperson, who reviewed all target tissues and those about which there was a disagreement between the laboratory and quality assessment pathologists.

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

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

Statistical Methods

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

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found dead of other than natural causes or were found to be missing; animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) life table test for a dose-related trend. When significant survival differences were detected, additional analyses using these procedures were carried out to determine the time point at which significant differences in the survival curves were first detected. All reported P values for the survival analysis are two-sided.

Calculation of Incidence: The incidence of neoplastic or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators include only

those animals for which the site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) prior to histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the number of animals on which a necropsy was performed.

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

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

Life Table Analyses--The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and vehicle control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel method to obtain an overall P value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975). The underlying variable considered by this analysis is time to death due to tumor. If the tumor is rapidly lethal, then time to death due to tumor closely approximates time to tumor onset. In this case, the life table test also provides a comparison of the time-specific tumor incidences.

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

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

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

III. RESULTS

RATS

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

FOURTEEN-DAY STUDIES

All the rats survived to the end of the studies (Table 5). The final mean body weights of all dosed groups were lower than those of the vehicle controls. The final mean body weight of males that received 2,400 mg/kg was 14% lower than that of the vehicle controls; males receiving 200-1,600 mg/kg had final body weights 8%-12% lower than that of the vehicle controls. The reduction in final body weights in dosed females (3%-7%) was less pronounced than that for dosed males.

Dose-related clinical signs, including diarrhea and excessive salivation, were seen in all high dose rats immediately after dosing. No dose-related gross pathologic changes were observed. No histopathologic alterations attributable to the chemical were seen in high dose animals.

Doses for rats in the 13-week studies were set at 0, 180, 370, 750, 1,500, or 3,000 mg/kg. The highest dose of 3,000 mg/kg was selected because no dose-related deaths were seen at 2,400 mg/kg in the 14-day studies. This dose is the maximum one that was practical to administer to rats (administered as two 1,500 mg/kg doses with a dose volume of 5 ml/kg body weight).

TABLE 5. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FOURTEEN-DAY GAVAGE STUDIES OF AMPICILLIN TRIHYDRATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	98 ± 1	236 ± 9	+138 ± 9	--
200	5/5	99 ± 1	218 ± 3	+119 ± 3	92
400	5/5	98 ± 1	208 ± 7	+110 ± 6	88
800	5/5	99 ± 1	210 ± 6	+111 ± 5	89
1,600	5/5	99 ± 1	215 ± 7	+116 ± 7	91
2,400	5/5	98 ± 1	204 ± 10	+106 ± 10	86
FEMALE					
0	5/5	100 ± 1	146 ± 2	+46 ± 2	--
200	5/5	99 ± 1	141 ± 4	+42 ± 4	97
400	5/5	100 ± 1	142 ± 2	+42 ± 2	97
800	5/5	100 ± 1	139 ± 3	+39 ± 3	95
1,600	5/5	100 ± 1	136 ± 3	+36 ± 2	93
2,400	5/5	99 ± 1	137 ± 2	+38 ± 1	94

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean
(c) Mean body weight change of the group ± standard error of the mean

THIRTEEN-WEEK STUDIES

The 12 deaths observed in dosed and vehicle control rats were considered to be due to gavage error (Table 6). The final mean body weights of the female rats were not related to the dose levels. The final mean body weight of the males that received 3,000 mg/kg was 9% lower than that of the vehicle controls. Male and female rats that received 3,000 mg/kg ampicillin trihydrate had diarrhea. No compound-related gross or histopathologic effects were observed.

Dose Selection Rationale: No dose-related effects were seen in the 13-week studies at 1,500 or 3,000 mg/kg. Doses selected for rats for the 2-year studies were 0, 750, and 1,500 mg/kg ampicillin trihydrate in corn oil administered by gavage 5 days per week in a volume of 5 ml/kg body weight.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed male and female rats were similar or slightly increased over those of the corresponding vehicle control group throughout the studies (Table 7 and Figure 1). Diarrhea, chromodacryorrhea, and excessive urination were considered to be compound related.

TABLE 6. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF AMPICILLIN TRIHYDRATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	9/10	118 ± 3	349 ± 4	+230 ± 5	--
180	8/10	134 ± 3	328 ± 6	+195 ± 6	94
370	9/10	130 ± 3	334 ± 5	+203 ± 3	96
750	9/10	126 ± 4	334 ± 8	+211 ± 6	96
1,500	9/10	117 ± 2	326 ± 8	+209 ± 6	93
3,000	8/10	109 ± 2	317 ± 6	+210 ± 6	91
FEMALE					
0	10/10	103 ± 4	205 ± 6	+102 ± 3	--
180	10/10	110 ± 3	189 ± 3	+79 ± 1	92
370	9/10	109 ± 2	196 ± 2	+86 ± 2	96
750	10/10	108 ± 2	204 ± 8	+96 ± 7	100
1,500	10/10	103 ± 3	203 ± 7	+100 ± 5	99
3,000	7/10	106 ± 3	198 ± 11	+90 ± 8	97

(a) Number surviving/number initially in group. All deaths were judged related to gavage techniques.
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean

TABLE 7. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF AMPICILLIN TRIHYDRATE

Weeks on Study	Vehicle Control		750 mg/kg			1,500 mg/kg		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors
MALE								
0	141	50	143	101	50	146	104	50
1	166	50	164	99	50	167	101	50
2	188	50	194	103	50	200	106	50
3	212	50	220	104	50	220	104	50
4	225	50	239	106	50	234	104	50
5	244	50	255	105	50	251	103	50
6	254	50	268	106	50	266	105	50
7	263	50	282	107	50	275	105	50
8	283	50	296	105	50	290	102	50
9	300	50	311	104	50	306	102	50
10	316	50	323	102	50	319	101	50
11	325	50	331	102	50	328	101	50
12	336	50	336	100	50	341	101	50
16	366	50	376	103	50	374	102	50
20	392	48	399	102	50	399	102	50
24	384	47	381	99	50	388	101	50
28	427	47	425	100	50	427	100	50
32	427	47	429	100	50	431	101	50
36	413	47	436	106	50	406	98	49
40	430	47	430	100	49	427	99	49
44	440	46	446	101	48	431	98	49
48	461	46	451	98	48	449	97	48
52	472	46	465	99	48	463	98	46
56	469	46	462	99	48	463	99	46
60	476	46	474	100	46	462	97	46
64	474	46	474	100	46	459	97	43
68	476	46	473	99	45	465	98	43
72	477	44	478	100	44	500	105	42
76	482	43	477	99	43	475	99	42
80	477	42	481	101	41	469	98	42
84	469	40	468	100	39	471	100	40
90	468	34	462	99	38	462	99	39
94	457	32	464	102	35	450	98	32
98	455	32	462	102	33	456	100	27
102	449	32	457	102	28	462	103	27
FEMALE								
0	115	50	111	97	49	115	100	50
1	126	50	121	96	49	125	99	50
2	143	50	141	99	49	143	100	50
3	152	50	148	97	49	151	99	50
4	160	50	164	103	48	160	100	50
5	168	50	166	99	48	167	99	50
6	170	50	171	101	48	171	101	50
7	177	50	179	101	48	175	99	50
8	181	50	185	102	48	184	102	50
9	186	50	190	102	48	186	100	50
10	190	50	195	103	48	189	99	50
11	195	50	203	104	48	197	101	50
12	199	50	201	101	48	196	98	50
16	208	50	211	101	48	208	100	50
20	219	50	225	103	48	223	102	50
24	222	50	222	100	48	220	99	50
28	232	50	234	101	48	236	102	50
32	234	50	238	102	48	237	101	50
36	238	50	246	103	48	244	103	50
40	251	50	257	102	48	253	101	50
44	259	50	268	103	48	262	101	50
48	262	50	269	103	48	271	103	50
52	270	49	286	106	48	283	105	50
56	278	49	294	106	47	286	103	50
60	284	48	303	107	46	294	104	49
64	298	48	303	102	46	305	102	49
68	302	48	321	106	46	311	103	49
72	306	48	325	106	45	320	105	49
76	314	46	331	105	45	328	104	48
80	319	46	338	106	43	333	104	47
84	321	46	366	114	39	344	107	45
90	323	41	337	104	37	339	105	45
94	321	38	332	103	34	324	101	41
98	333	38	360	108	34	352	106	36
102	339	36	358	105	34	350	103	35

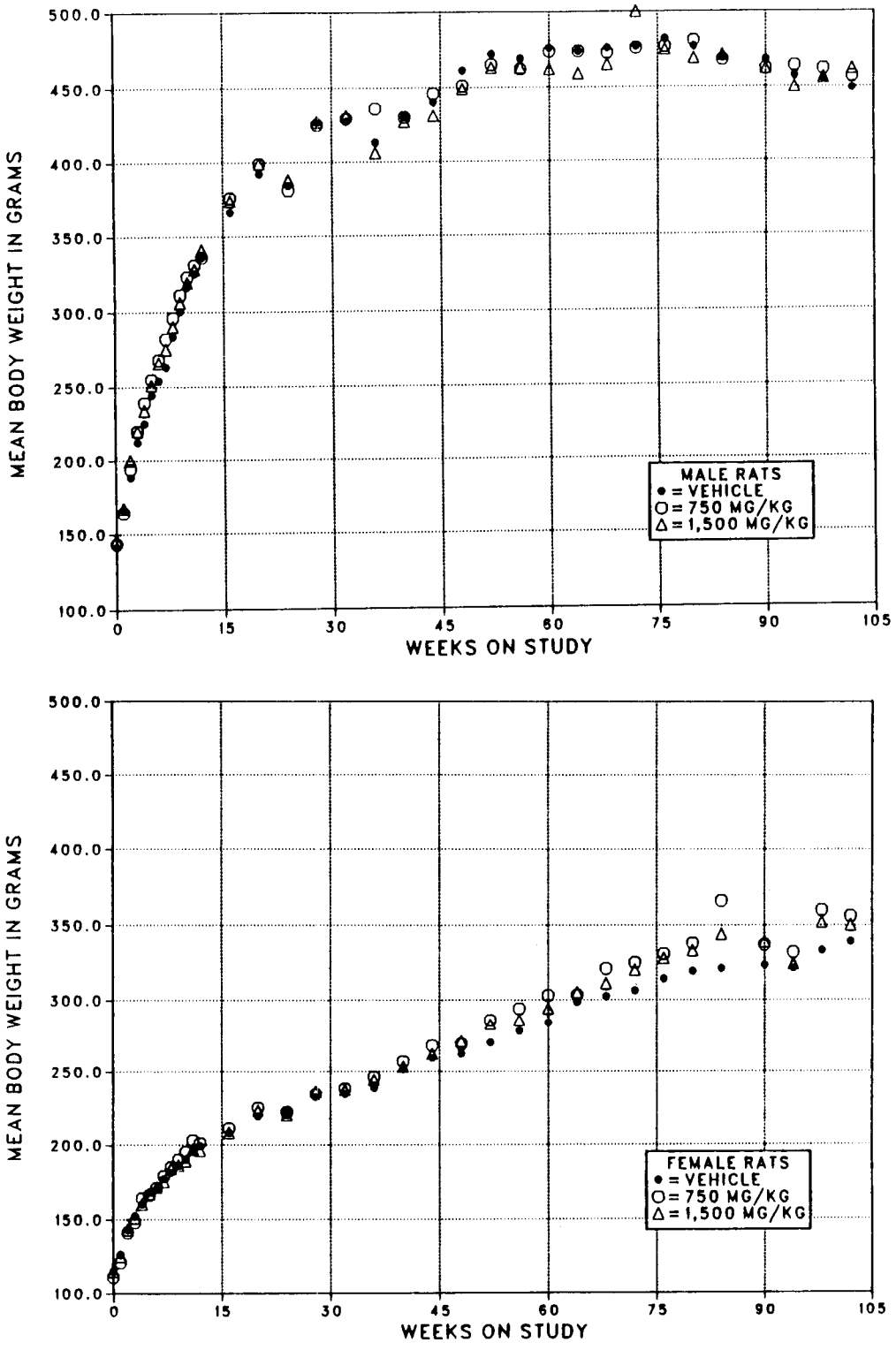


FIGURE 1. GROWTH CURVES FOR RATS ADMINISTERED AMPICILLIN TRIHYDRATE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats administered ampicillin trihydrate at the doses used in these studies and for vehicle controls are shown in the Kaplan and Meier curves in Figure 2. No significant differences in survival were observed between any groups of either sex (Table 8). All accidental deaths were due to gavage accidents.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the hematopoietic system, adrenal gland, mammary gland, thyroid gland, liver, forestomach, prostate, and eye. Histopathologic findings on neoplasms in rats are summarized in Appendix A (Tables A1 and A2); Appendix A (Tables A3 and A4) also gives the survival and tumor status for individual male and female rats. Findings on nonneoplastic lesions are summarized in Appendix C (Tables C1 and C2). Appendix E (Tables E1 and E2) 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 E (footnotes). Historical incidences of tumors in corn oil vehicle control animals are listed in Appendix F.

TABLE 8. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF AMPICILLIN TRIHYDRATE

	Vehicle Control	750 mg/kg	1,500 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	15	23	21
Accidentally killed	4	0	3
Killed at termination	31	27	26
Survival P values (c)	0.372	0.280	0.424
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	18	15	18
Accidentally killed	0	2	1
Killed at termination	32	31	31
Died during termination period	0	2	0
Survival P values (c)	1.000	0.880	0.966

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

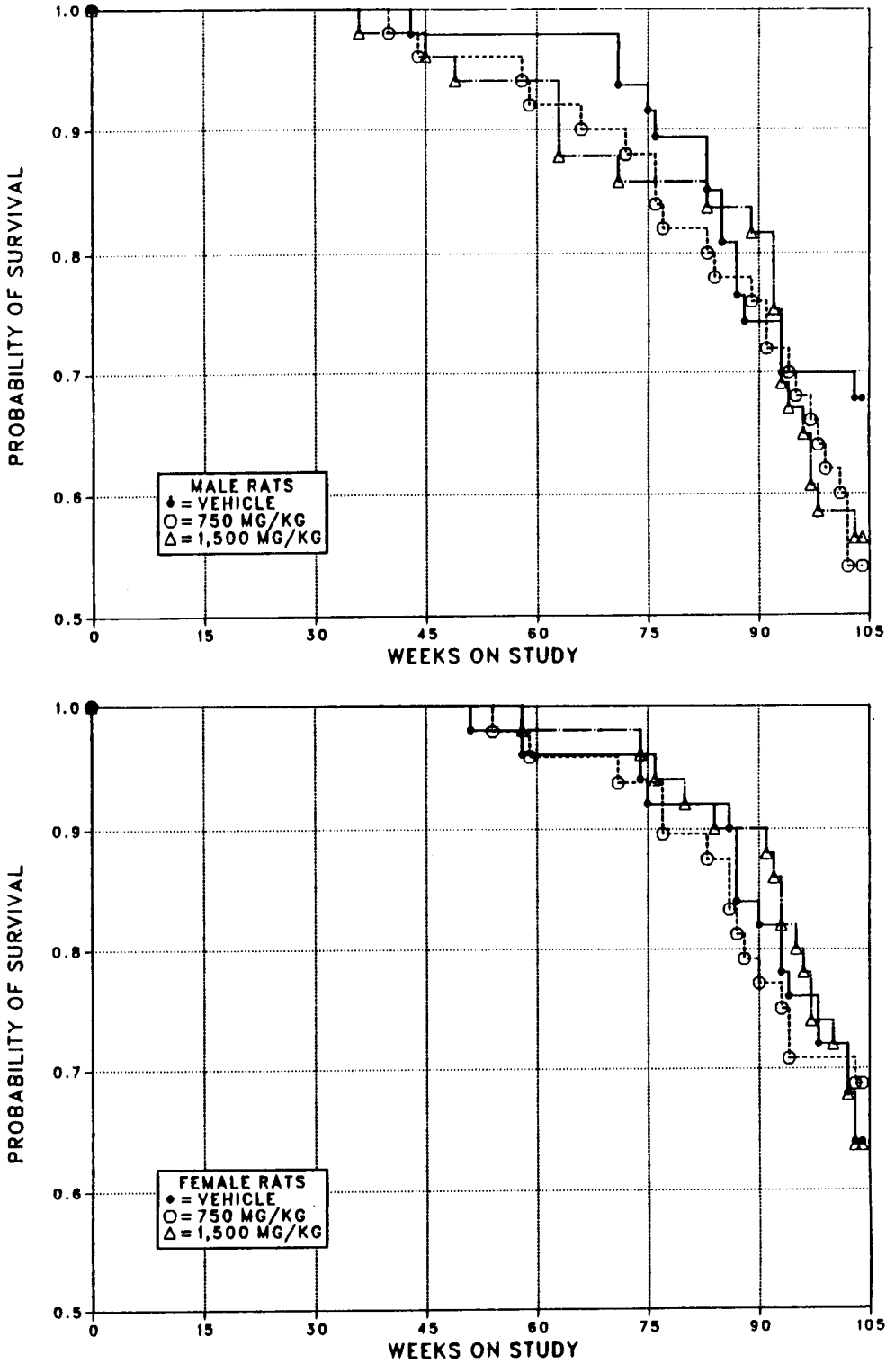


FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED AMPICILLIN TRIHYDRATE IN CORN OIL BY GAVAGE FOR TWO YEARS

Hematopoietic System: Mononuclear cell leukemia in male rats occurred with a significant positive trend, and the incidences in the dosed groups were greater than that in the vehicle controls (Table 9). The incidence of mononuclear cell leukemia was not increased in dosed female rats. Hematopoietic hyperplasia of the bone marrow was reported at increased incidences in dosed male (vehicle control, 7/50, 14%; low dose, 16/48, 33%; high dose, 17/50, 34%) and female rats (13/50, 26%; 22/49, 45%; 25/50, 50%). Hematopoietic hyperplasia was frequently present in rats with malignant neoplasms in a variety of organs. Necrosis and inflammation associated with neoplasia may have provided the physiologic stimulus or demand for increased blood leukocytes and hematopoietic hyperplasia.

TABLE 9. ANALYSIS OF HEMATOPOIETIC SYSTEM TUMORS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF AMPICILLIN TRIHYDRATE (a)

	Vehicle Control	750 mg/kg	1,500 mg/kg
MALE			
Mononuclear Cell Leukemia (b)			
Overall Rates	5/50 (10%)	14/50 (28%)	13/50 (26%)
Adjusted Rates	13.8%	41.7%	38.8%
Terminal Rates	2/31 (6%)	8/27 (30%)	7/26 (27%)
Week of First Observation	83	89	63
Life Table Tests	P=0.024	P=0.019	P=0.029
Incidental Tumor Tests	P=0.069	P=0.040	P=0.066
Lymphocytic Leukemia			
Overall Rates	0/50 (0%)	0/50 (0%)	1/50 (2%)
Malignant Lymphoma			
Overall Rates	1/50 (2%)	2/50 (4%)	0/50 (0%)
All Leukemia or Lymphoma (c)			
Overall Rates	6/50 (12%)	16/50 (32%)	14/50 (28%)
Adjusted Rates	16.4%	44.2%	40.6%
Terminal Rates	2/31 (6%)	8/27 (30%)	7/26 (27%)
Week of First Observation	83	58	63
Life Table Tests	P=0.032	P=0.017	P=0.037
Incidental Tumor Tests	P=0.099	P=0.050	P=0.114
Week of Observation of Mononuclear Cell Leukemia:	83 87 93 (d) 104 (2)	89 95 98 101 102 (2) (d) 104 (8)	63 92 93 94 97 103 (d) 104 (7)
FEMALE			
Mononuclear Cell Leukemia			
Overall Rates	14/50 (28%)	18/50 (36%)	13/50 (26%)

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) Historical incidence of leukemia in NTP studies (mean ± SD): 152/1,100 (14% ± 8%) (range: 2%-28%)
(c) Historical incidence of leukemia or lymphoma in NTP studies (mean ± SD): 162/1,100 (15% ± 8%) (range: 2%-28%)
(d) Number of animals found to have mononuclear cell leukemia at the terminal kill

Results of "staging" mononuclear cell leukemia are given in Table 10. Criteria are as follows.

Stage 1. Spleen not enlarged or only slightly enlarged with small numbers of neoplastic mononuclear cells in the red pulp; no or very few mononuclear cells in the liver sinusoids. No identifiable neoplastic cells in the other organs.

Stage 2. Spleen moderately enlarged with moderate to large numbers of mononuclear cells in the red pulp; architectural features including lymphoid follicles and periarteriolar lymphocytic sheaths remain intact. Minimal to moderate involvement of the liver. Mononuclear cells may be evident in blood vessels in other organs, but aggregates/masses of neoplastic cells generally limited to spleen and liver.

Stage 3. Advanced disease with multiple organ involvement. Spleen usually markedly enlarged with effacement of normal architectural features by accumulated neoplastic cells. Liver moderately to markedly enlarged and nodular; hepatic parenchyma shows variable degenerative changes associated with the accumulation of neoplastic cells. Accumulations of neoplastic mononuclear cells in other organs including lung, lymph nodes, kidney, brain, adrenal gland, and others.

Adrenal Gland: Focal cellular change of the adrenal cortex was observed at increased incidence in high dose male and female rats (male: vehicle control, 1/50; low dose, 5/50; high dose, 7/49; female: 6/50; 12/50; 15/49). Pheochromocytomas and pheochromocytomas or malignant pheochromocytomas (combined) of the adrenal medulla in male rats occurred with significant positive trends, and the incidences in the high dose group were significantly greater than those in the vehicle controls. The incidences of focal hyperplasia of the adrenal medulla were not increased in dosed male rats relative to vehicle controls. Adrenal medulla lesions were not increased in female rats (Table 11).

Mammary Gland: Hyperplasia was observed at an increased incidence in low dose male rats (vehicle control, 4/50; low dose, 11/50; high dose, 4/50). The incidence of mammary gland fibroadenomas was not increased in dosed male rats (1/50; 1/50; 0/50). The incidence of hyperplasia of the mammary gland was similar in dosed and vehicle control female rats (23/50; 23/50; 22/50). The incidence of fibroadenomas in low dose female rats was significantly greater than that in the vehicle controls by the incidental tumor test (P=0.019) (16/50; 25/50; 19/50).

TABLE 10. CLASSIFICATION OF MONONUCLEAR CELL LEUKEMIA IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF AMPICILLIN TRIHYDRATE

	Vehicle Control	750 mg/kg	1,500 mg/kg
Number of Animals with Mononuclear Cell Leukemia	5	14	13
Stage			
1	1	3	3
2	2	3	4
3	2	8	6

TABLE 11. ANALYSIS OF ADRENAL MEDULLARY LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF AMPICILLIN TRIHYDRATE

	Vehicle Control	750 mg/kg	1,500 mg/kg
MALE			
Focal Hyperplasia			
Overall Rates	14/50 (28%)	10/50 (20%)	8/49 (16%)
Pheochromocytoma			
Overall Rates	13/50 (26%)	12/50 (24%)	23/49 (47%)
Adjusted Rates	40.6%	39.6%	75.8%
Terminal Rates	12/31 (39%)	9/27 (33%)	19/26 (73%)
Week of First Observation	103	95	80
Life Table Tests	P=0.003	P=0.543	P=0.004
Incidental Tumor Tests	P=0.008	P=0.445N	P=0.007
Malignant Pheochromocytoma			
Overall Rates	1/50 (2%)	5/50 (10%)	1/49 (2%)
Adjusted Rates	3.2%	17.0%	3.8%
Terminal Rates	1/31 (3%)	4.2 (15%)	1/26 (4%)
Week of First Observation	104	89	104
Life Table Tests	P=0.537	P=0.084	P=0.723
Incidental Tumor Tests	P=0.507	P=0.065	P=0.723
Pheochromocytoma or Malignant Pheochromocytoma (a)			
Overall Rates	13/50 (26%)	16/50 (32%)	23/49 (47%)
Adjusted Rates	40.6%	50.9%	75.8%
Terminal Rates	12/31 (39%)	12/27 (44%)	19/26 (73%)
Week of First Observation	103	89	80
Life Table Tests	P=0.004	P=0.200	P=0.004
Incidental Tumor Tests	P=0.007	P=0.325	P=0.007
FEMALE			
Focal Hyperplasia			
Overall Rates	18/50 (36%)	7/50 (14%)	6/49 (12%)
Pheochromocytoma			
Overall Rates	3/50 (6%)	3/50 (6%)	4/49 (8%)
Malignant Pheochromocytoma			
Overall Rates	0/50 (0%)	0/50 (0%)	1/49 (2%)

(a) Historical incidence in NTP studies (mean ± SD): 247/1,092 (23% ± 9%) (range: 4%-40%)

Thyroid Gland: C-cell hyperplasia was observed at increased incidences in low dose male and high dose female rats (male: vehicle control, 4/50; low dose, 11/48; high dose, 7/46; female: 10/50; 12/49; 21/49). The incidences of C-cell adenomas or carcinomas (combined) in dosed rats were not significantly different from those in the vehicle controls (male: 2/50; 6/48; 3/46; female: 2/50; 1/49; 1/49).

Liver: Cytoplasmic vacuolization was observed at increased incidences in high dose male rats (male: vehicle control, 2/50; low dose, 5/49; high dose, 10/50; female: 2/50; 4/50; 4/50).

Forestomach: Hyperkeratosis and acanthosis were observed at increased incidences in high dose male rats (hyperkeratosis: vehicle control, 3/48; low dose, 6/44; high dose, 9/45; acanthosis: 0/48; 2/44; 5/45). The incidences of hyperkeratosis (2/49; 1/50; 3/47) and acanthosis (0/49; 0/50; 0/47) were not increased in dosed female rats.

Prostate: Inflammation was observed at an increased incidence in high dose male rats (vehicle control, 22/49, 45%; low dose, 27/48, 56%; high dose, 36/47, 77%).

Eye: Retinal degeneration, cataracts, hemorrhage, and posterior synechia were observed at notably greater incidences in vehicle control rats of each sex than in the dosed groups (Table 12). Vehicle control animals were positioned on the top two rows of the rack throughout the studies, and the appearance of eye lesions was probably due to the placement of the animals on the rack and proximity to the fluorescent light source rather than to chemical administration.

TABLE 12. NUMBERS OF RATS WITH EYE LESIONS IN THE TWO-YEAR GAVAGE STUDIES OF AMPICILLIN TRIHYDRATE (a)

Lesion	Vehicle Control	750 mg/kg	1,500 mg/kg
MALE			
Number of animals examined grossly	50	50	50
Cataract	15	1	0
Retinal degeneration	17	0	0
Posterior synechia	13	0	0
Hemorrhage	17	0	0
FEMALE			
Number of animals examined grossly	50	50	50
Cataract	17	2	2
Retinal degeneration	17	3	2
Posterior synechia	11	1	0
Hemorrhage	11	1	2

(a) Vehicle control animals were located on the top two rows of rack; high dose animals, on the middle two rows; low dose animals, on the bottom two rows.

FOURTEEN-DAY STUDIES

Seven males and four females died before the end of the studies due to gavage error (Table 13). Male mice that received 2,400 mg/kg lost weight during week 2 of the studies; no dose-related decreases in final mean body weights were seen in female mice. Dosed female mice receiving 200, 800, 1,600, or 2,400 mg/kg showed a slightly increased body weight (1.3%-13.4%) over the vehicle control group. Diarrhea of minimal severity was observed in mice that received 2,400 mg/kg. No dose-related gross pathologic changes were observed. No histopathologic alterations attributable to the chemical were seen in high dose animals.

Doses for the 13-week studies were set at 0, 250, 500, 1,000, 2,000, and 3,000 mg/kg. The high dose of 3,000 mg/kg was selected because histopathologic findings were not seen in the 14-day studies at 2,400 mg/kg, and this dose was the maximum one that was practical to give to mice at a volume of 10 ml/kg body weight.

TABLE 13. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOURTEEN-DAY GAVAGE STUDIES OF AMPICILLIN TRIHYDRATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	26.8 ± 0.8	29.6 ± 1.0	+ 2.8 ± 0.5	--
200	5/5	28.6 ± 0.8	29.2 ± 0.7	+ 0.6 ± 0.5	98.6
400	4/5	27.2 ± 0.9	29.3 ± 0.6	+ 1.5 ± 1.0	99.0
800	4/5	28.2 ± 1.2	30.8 ± 0.9	+ 2.8 ± 0.9	104.1
1,600	3/5	27.4 ± 1.1	28.7 ± 0.9	+ 1.0 ± 0.6	97.0
2,400	2/5	28.2 ± 0.9	28.5 ± 0.5	+ 1.5 ± 0.5	96.3
FEMALE					
0	5/5	23.8 ± 0.4	23.2 ± 1.0	− 0.6 ± 1.3	--
200	5/5	24.0 ± 0.3	23.6 ± 0.2	− 0.4 ± 0.2	101.7
400	5/5	23.4 ± 0.2	23.2 ± 0.4	− 0.2 ± 0.4	100.0
800	3/5	24.0 ± 0.3	26.3 ± 3.9	+ 2.0 ± 3.6	113.4
1,600	4/5	23.8 ± 0.4	23.8 ± 0.6	0.0 ± 0.6	102.6
2,400	4/5	24.0 ± 0.0	23.5 ± 0.9	− 0.5 ± 0.9	101.3

(a) Number surviving/number initially in group. All deaths were judged related to gavage technique.
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean

THIRTEEN-WEEK STUDIES

The 10 deaths observed in dosed and vehicle control mice were attributed to gavage error (Table 14). Final mean body weights were not dose related. One of 10 male mice at 2,000 mg/kg and 1/10 male mice at 3,000 mg/kg had diarrhea; other clinical signs were observed sporadically and were not clearly dose related. No compound-related gross or histopathologic effects were observed.

Dose Selection Rationale: No dose-related effects were seen in the 13-week studies at 1,500 and 3,000 mg/kg. Doses selected for mice for the 2-year studies were 0, 1,500, and 3,000 mg/kg ampicillin trihydrate in corn oil administered by gavage 5 days per week in a volume of 10 ml/kg body weight.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

The initial mean body weights of the low dose and high dose male mice were 5% and 6% greater than that of the vehicle controls (Table 15 and Figure 3). Mean body weights of low dose and high dose male mice were similar to those of the corresponding vehicle control group during year 1 of the study but were slightly below those of the vehicle control group during year 2. Mean body weights of low dose and high dose female mice were greater than those of the vehicle controls throughout most of the study. Increased salivation and decreased activity in dosed mice were considered to be compound related.

TABLE 14. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF AMPICILLIN TRIHYDRATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	9/10	26.1 ± 0.9	38.2 ± 1.7	+11.8 ± 1.4	--
250	9/10	23.4 ± 0.6	35.4 ± 1.0	+11.8 ± 0.4	92.7
500	10/10	23.8 ± 0.4	33.6 ± 0.8	+9.8 ± 0.6	88.0
1,000	9/10	26.4 ± 0.6	36.3 ± 1.1	+10.0 ± 0.8	95.0
2,000	8/10	25.7 ± 0.8	35.7 ± 0.5	+10.3 ± 1.0	93.5
3,000	7/10	26.7 ± 0.4	36.5 ± 0.8	+9.4 ± 0.7	95.5
FEMALE					
0	9/10	20.7 ± 0.3	27.6 ± 1.3	+6.9 ± 1.0	--
250	10/10	20.6 ± 0.4	26.9 ± 0.8	+6.3 ± 0.6	97.5
500	10/10	20.3 ± 0.4	26.9 ± 0.6	+6.6 ± 0.4	97.5
1,000	9/10	21.8 ± 0.4	28.6 ± 0.6	+6.7 ± 0.6	103.6
2,000	10/10	20.9 ± 0.6	29.1 ± 0.9	+8.2 ± 0.8	105.4
3,000	10/10	20.6 ± 0.3	26.3 ± 0.7	+5.7 ± 0.9	95.3

(a) Number surviving/number initially in group. All deaths were judged related to gavage techniques.
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean

TABLE 15. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF AMPICILLIN TRIHYDRATE

Weeks on Study	Vehicle Control		1,500 mg/kg			3,000 mg/kg		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors
MALE								
0	23.7	50	24.8	105	49	25.4	107	50
1	25.7	50	25.8	100	49	26.7	104	50
2	28.1	49	27.7	99	49	26.9	96	50
3	27.9	49	28.6	103	48	29.4	105	49
4	28.2	49	28.8	102	48	28.9	102	49
5	28.4	49	28.8	101	48	30.1	106	49
6	30.3	49	30.4	100	48	30.5	101	49
7	30.9	49	30.8	100	48	30.7	99	49
8	31.7	49	31.9	101	48	33.0	104	48
9	32.6	49	33.3	102	48	33.5	103	48
10	32.7	49	32.2	98	48	34.2	105	46
11	33.8	49	33.4	99	48	34.1	101	46
12	34.9	49	34.7	99	47	34.8	100	45
16	36.9	47	36.3	98	47	36.6	99	45
20	36.5	46	36.7	101	46	37.1	102	45
24	38.3	42	36.4	95	46	37.5	98	45
28	39.7	42	39.3	99	46	39.1	98	42
32	37.1	41	38.1	103	44	37.5	101	42
36	41.7	41	41.6	100	41	41.3	99	41
40	43.4	41	41.0	94	39	43.4	100	39
44	43.4	41	43.8	101	39	42.1	97	38
48	44.6	41	44.2	99	39	43.9	98	38
52	45.2	41	43.1	95	39	44.1	98	38
56	45.1	41	43.4	96	38	43.8	97	38
60	45.9	40	42.9	93	38	44.8	98	37
64	46.8	40	43.6	93	37	44.6	95	37
69	46.6	39	43.7	94	37	44.4	95	37
72	46.4	38	43.5	94	37	43.7	94	34
76	45.5	38	44.1	97	37	44.7	98	33
80	46.4	38	43.7	94	35	45.0	97	33
86	45.9	36	44.3	97	34	44.2	96	30
90	45.0	35	42.8	95	32	44.7	99	28
94	44.6	34	42.9	96	31	43.8	98	28
98	44.4	32	43.3	98	28	43.9	99	25
102	44.1	32	42.3	96	22	42.2	96	20
FEMALE								
0	23.2	50	24.1	104	50	23.0	99	50
1	23.1	50	24.5	106	50	24.6	106	50
2	23.7	50	24.7	104	50	25.3	107	50
3	22.9	50	24.6	107	50	24.9	109	50
4	22.1	50	22.4	101	50	23.2	105	50
5	21.6	50	23.0	106	50	23.1	107	50
6	22.6	50	23.9	106	50	25.3	112	50
7	23.4	50	24.1	103	50	24.5	105	50
8	23.7	50	25.2	106	50	25.4	107	50
9	24.6	50	26.1	106	50	26.1	106	50
10	24.1	50	25.4	105	50	25.4	105	50
11	25.3	49	26.2	104	50	26.3	104	50
12	24.4	49	26.2	107	50	26.4	108	50
16	26.2	49	27.7	106	50	27.9	106	50
20	27.1	49	28.2	104	50	28.8	106	50
24	27.9	49	30.0	108	50	30.2	108	50
28	29.0	49	30.8	106	50	31.6	109	50
32	29.3	49	31.6	108	50	32.2	110	49
36	32.2	49	33.4	104	50	34.4	107	40
40	33.5	49	35.4	106	50	35.9	107	40
44	35.7	49	36.9	103	50	38.4	108	40
48	37.3	49	36.9	99	50	38.4	103	40
52	38.2	49	38.0	99	50	40.1	105	40
56	38.1	48	38.0	100	50	39.2	103	40
60	38.5	48	38.8	101	50	40.3	105	40
64	40.4	47	39.6	98	50	41.2	102	40
69	39.0	46	40.0	103	50	41.9	107	40
72	38.6	46	39.7	103	50	41.7	108	40
76	38.2	46	39.0	102	49	39.5	103	39
80	39.1	45	38.3	98	47	41.2	105	38
86	39.3	44	39.0	99	42	40.8	104	38
90	39.6	43	39.5	100	38	41.7	105	35
94	40.5	40	38.8	96	36	40.6	100	32
98	40.8	39	39.4	97	31	42.8	105	28
102	40.5	36	39.7	98	28	39.2	97	28

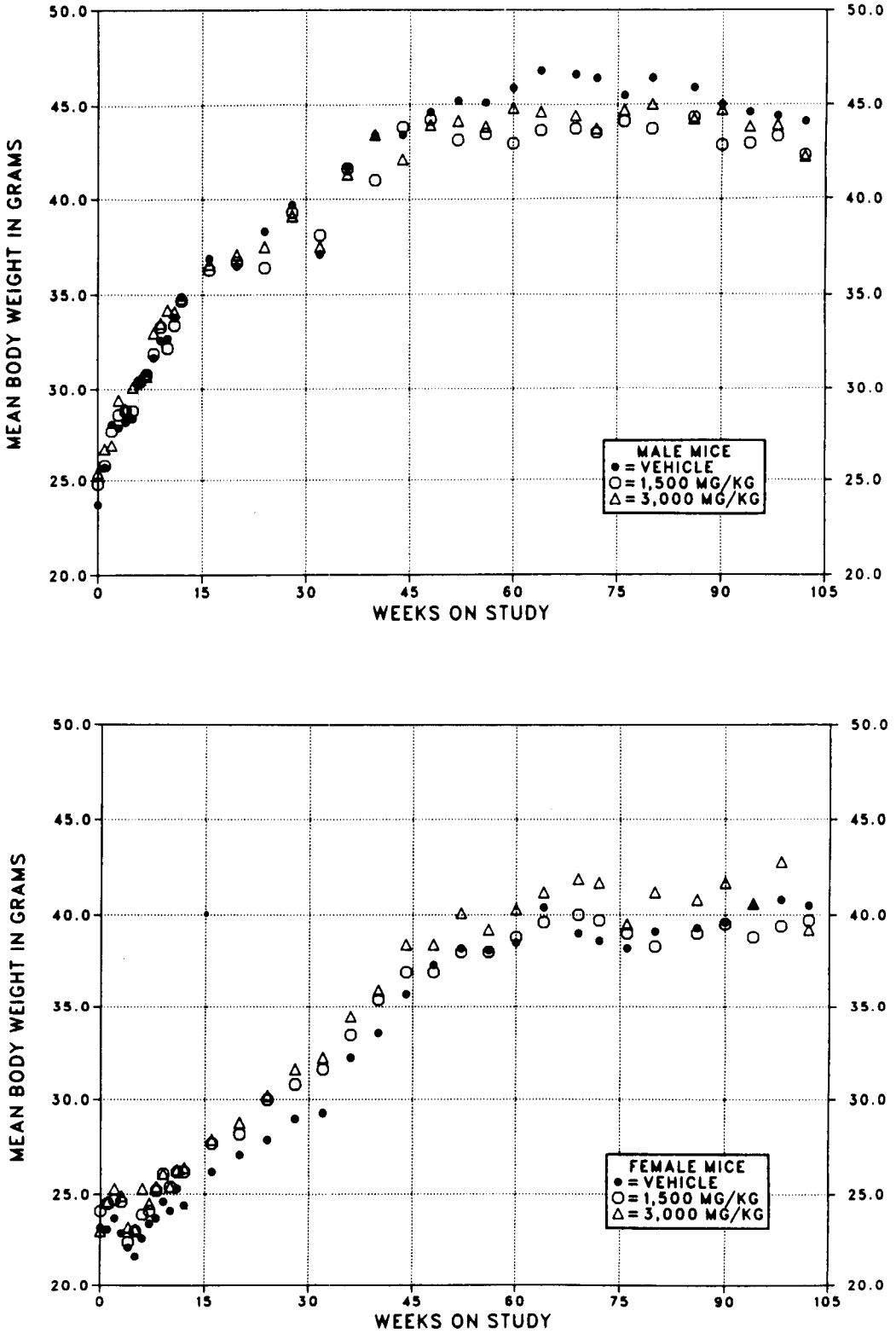


FIGURE 3. GROWTH CURVES FOR MICE ADMINISTERED AMPICILLIN TRIHYDRATE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered ampicillin trihydrate at the doses used in these studies and for vehicle controls are shown in the Kaplan and Meier curves in Figure 4. No significant differences in survival were observed between any groups of either sex (Table 16). Accidental deaths were due primarily to drowning (13) or gavage accidents (7).

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the forestomach, lung, and ovary, uterus, or multiple organs. Histopathologic findings on neoplasms in mice are summarized in Appendix B (Tables B1 and B2); Appendix B (Tables B3 and B4) also gives the survival and tumor status for individual male and female mice. Findings on nonneoplastic lesions are summarized in Appendix D (Tables D1 and D2). Appendix E (Tables E3 and E4) 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 E (footnotes). Historical incidences of tumors in corn oil vehicle control animals are listed in Appendix F.

TABLE 16. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF AMPICILLIN TRIHYDRATE

	Vehicle Control	1,500 mg/kg	3,000 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	17	22	23
Accidentally killed	1	6	6
Animals missing	0	1	1
Killed at termination	32	21	20
Survival P values (c)	0.189	0.374	0.238
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	16	22	12
Accidentally killed	0	0	10
Killed at termination	34	27	28
Died during termination period	0	1	0
Survival P values (c)	0.975	0.286	0.970

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

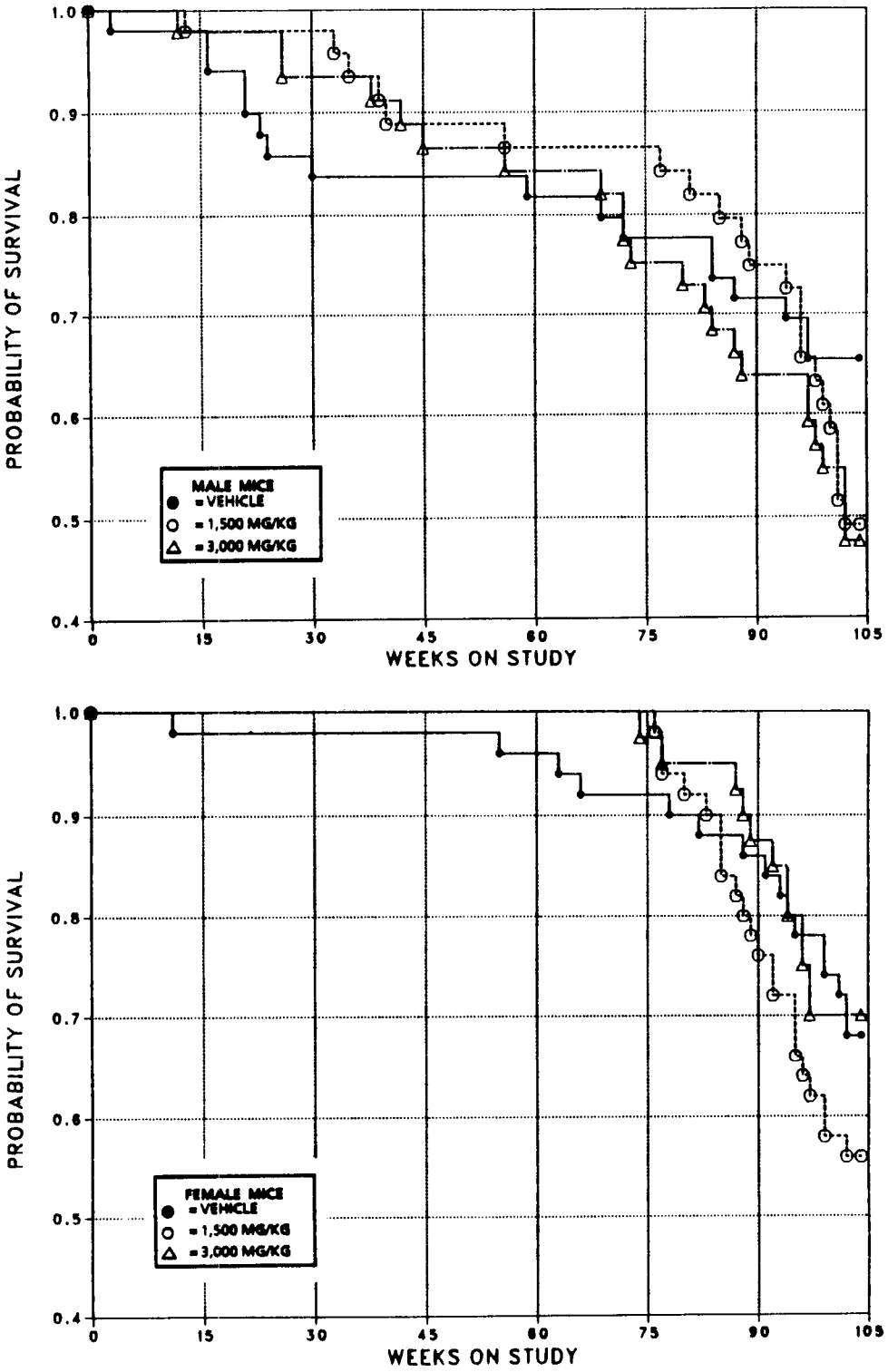


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED AMPICILLIN TRIHYDRATE IN CORN OIL BY GAVAGE FOR TWO YEARS

Forestomach: Ulcers, suppurative inflammation, fungal infections, hyperkeratosis, and acanthosis were observed at increased incidences in dosed male and female mice (Table 17).

Lung: Alveolar/bronchiolar adenomas in female mice occurred with a positive trend (vehicle control, 1/50; low dose, 0/50; high dose, 4/50; P=0.049 by the incidental tumor test), but the incidences of alveolar/bronchiolar adenomas or carcinomas (combined) in dosed and vehicle control female mice were not significantly different (2/50; 3/50; 4/50). No increased incidences of alveolar/bronchiolar adenomas or carcinomas (combined) were seen in dosed male mice (6/50; 6/49; 3/47).

Ovary, Uterus, or Multiple Organs: Suppurative inflammation or abscesses were observed in female mice (vehicle control, 11/50; low dose, 20/50; high dose, 2/50).

TABLE 17. NUMBERS OF MICE WITH LESIONS OF THE FORESTOMACH IN THE TWO-YEAR GAVAGE STUDIES OF AMPICILLIN TRIHYDRATE (a)

Lesion	Vehicle Control	1,500 mg/kg	3,000 mg/kg
MALE			
Number of animals examined	50	48	45
Ulcer	0	(b) 6	2
Suppurative inflammation	0	(c) 24	(c) 19
Fungal infection	0	(c) 8	(c) 6
Hyperkeratosis	11	(c) 28	(b) 20
Acanthosis	9	(c) 28	(c) 20
FEMALE			
Number of animals examined	47	49	49
Ulcer	0	2	(b) 6
Suppurative inflammation	5	(c) 29	(c) 27
Fungal infection	1	(c) 15	(b) 8
Hyperkeratosis	17	(c) 39	(c) 32
Acanthosis	11	(c) 37	(c) 34

(a) P values are versus the vehicle controls by the Fisher exact test.
(b) $P<0.05$
(c) $P<0.01$

IV. DISCUSSION AND CONCLUSIONS

IV. DISCUSSION AND CONCLUSIONS

Study Design

Studies of the toxicology and carcinogenicity of ampicillin trihydrate were conducted in F344/N rats and B6C3F$_1$ mice of each sex. For the 2-year studies, ampicillin trihydrate was administered by gavage as a corn oil suspension at doses of 0, 750, or 1,500 mg/kg body weight to male and female rats, 5 days per week for 103 weeks, and at 0, 1,500, or 3,000 mg/kg body weight to male and female mice on the same schedule. These doses for the 2-year studies were selected because no dose-related organ toxicity, decreases in body weight gain, or deaths were seen in the 13-week studies at doses up to 3,000 mg/kg body weight. Clinical signs in the 13-week studies included diarrhea at 3,000 mg/kg in male and female rats and male mice. The doses of ampicillin trihydrate used in the 2-year studies were limited because the maximum concentration of the chemical in corn oil that could be used as a gavage suspension was determined to be 300 mg/ml; the maximum volume of corn oil administered in NTP 2-year studies is usually 5 ml/kg body weight for rats and 10 ml/kg body weight for mice.

Survival, Body Weights, and Clinical Signs

Survival of vehicle control and dosed male and female rats and mice was similar in the 2-year studies. During the 2-year studies, mean body weights of rats were similar to or slightly greater than those of the corresponding vehicle control groups. Mean body weights of dosed male mice were similar to those of the corresponding vehicle control group during the 1st year of the study but were slightly below those of the vehicle control group during the 2nd year. Mean body weights of dosed female mice were greater than those of the vehicle controls throughout most of the study. Administration of ampicillin has been reported to increase body weight gain in rats when animals were started on the antibiotic at 4 weeks of age (King, 1975). Compound-related signs of toxicity in rats included diarrhea, chromodacryorrhea, and excessive urination and in mice included increased salivation and decreased activity.

Results in Rats

Adrenal medullary pheochromocytomas were observed with a dose-related positive trend in male rats (vehicle control, 13/50; low dose, 12/50; high dose, 23/49). Malignant pheochromocytomas were observed in male rats (1/50; 5/50; 1/49). The incidence of pheochromocytomas in the high dose group (47%) was significantly greater than that in the vehicle controls (26%), which was comparable to the mean historical vehicle control rate (23%); the highest rate observed in the historical vehicle controls was 20/49 (41%) (Appendix F, Table F2). The incidences of hyperplasia of the adrenal medulla were not increased in dosed male rats relative to that in vehicle controls. In rats, hyperplasia and pheochromocytomas of the adrenal gland are considered to represent a spectrum of the same lesion (Hollander and Snell, 1976; Strandberg, 1983). Thus, lack of increased incidences of hyperplasia in dosed male rats does not parallel the increased incidences of pheochromocytomas. Nonetheless, the neoplastic effect in the adrenal gland may have been related to the administration of ampicillin trihydrate.

Mononuclear cell leukemia was increased in dosed male rats (vehicle control, 5/50; low dose, 14/50; high dose, 13/50). Malignant lymphomas were observed in one additional vehicle control and two low dose male rats. Lymphocytic leukemia was seen in one high dose male rat. Incidences of mononuclear cell leukemia, malignant lymphomas, and lymphocytic leukemia were combined for statistical analysis because recent research suggests that mononuclear cell leukemia is a specific type of lymphocytic leukemia (Ward and Reynolds, 1983; Reynolds et al., 1982). Mononuclear cell leukemia develops spontaneously in F344 rats (Stromberg et al., 1983), and the rate in the NTP historical control data base for corn oil gavage vehicle control male rats (mean ± SD, 13.8% ± 8.1%; range, 2%-28%) is lower than the rate in untreated control male rats (mean ± SD, 26.5% ± 8.8%; range, 10%-46%) (Haseman et al., 1985). High dose male rats in this study received 70% of the amount of corn oil given to vehicle control male rats. The majority of

mononuclear cell leukemias observed in this study were stage 3 (advanced disease); however, the relative proportions of advanced cases were similar in dosed and vehicle control groups (see Table 10). The increased incidence of mononuclear cell leukemia observed in dosed male rats may have been related to the administration of ampicillin trihydrate.

Ampicillin trihydrate administration was associated with an increased incidence of C-cell hyperplasia of the thyroid gland in low dose male and high dose female rats (male: vehicle control, 4/50; low dose, 11/48; high dose, 7/46; female: 10/50; 12/49; 21/49). The incidence of mammary gland fibroadenomas was increased in low dose female rats (16/50; 25/50; 19/50), but because this increase was not seen in high dose animals, the lesion is not considered to be clearly dose related.

Incidences of cytoplasmic vacuolization of the liver and inflammation of the prostate were increased in high dose male rats. Eye lesions (cataracts, retinal degeneration, posterior synechia, hemorrhage) were seen in vehicle control male and female rats; these lesions were associated with the placement of the vehicle control animals on the top of the racks and thus in closer proximity to the light. Light-associated eye changes were previously reported in rats (Lai et al., 1978; Reuter and Hobbelen, 1977). Ampicillin trihydrate administration was associated with nonneoplastic lesions of the forestomach in male rats.

Results in Mice

Nonneoplastic lesions were seen in the forestomach in male and female mice, but these lesions were not accompanied by any neoplastic response in this organ. No neoplastic or nonneoplastic responses were observed in other organ systems. Ampicillin and other penicillins are reported to cause gastrointestinal side effects in humans (PDR, 1984).

Conclusions: Under the conditions of these 2-year gavage studies, there was *equivocal evidence of carcinogenicity** of ampicillin trihydrate for male F344/N rats as shown by increased incidences of pheochromocytomas of the adrenal medulla and by marginally increased incidences of mononuclear cell leukemia. There was *no evidence of carcinogenicity* for female F344/N rats receiving 750 or 1,500 mg/kg or for male and female $B6C3F_1$ mice receiving 1,500 or 3,000 mg/kg per day. Nonneoplastic lesions of the forestomach were seen in male rats and male and female mice.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 13-14.

V. REFERENCES

V. REFERENCES

1. Adamkin, D.; Marshall, E.; Weiner, L. (1984) The placental transfer of ampicillin. Am. J. Perinatol. 1:310-311 (Abstr.).

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

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

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

5. Brown, D.; Acred, P. (1961) "Penbritin"--A new broad-spectrum antibiotic, preliminary pharmacology and chemotherapy. Br. Med. J. 2:197-198.

6. Byarugaba, W.; Rudiger, H.; Koske-Westphal, T.; Wohler, W.; Passarge, E. (1975) Toxicity of antibiotics on cultured human skin fibroblasts. Humangenetik 28:263-267.

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

8. Code of Federal Regulations (CFR) (1977) Title 21, Food and Drugs, Parts 300 to 499, Section 436.204, April 1. U.S. Government Printing Office: Washington, DC, pp. 241-243.

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

10. Crippa, L.; Klein, D.; Linder, A. (1976) Etude cytogenetique et statistique d'un groupe de patients traites a la butazolidine (phenylbutazone). J. Genet. Hum. 24(1):1-13.

11. De Flora, S.; Zanacchi, P.; Camoirano, A.; Bennicelli, C.; Badolati, G. (1984) Genotoxic activity and potency of 135 compounds in the Ames reversion test and in a bacterial DNA-repair test. Mutat. Res. 133:161-198.

12. Elespuru, R.; Pennington, R. (1981) Alternate pathways of induction of bacteriophage lambda by diverse chemicals. Environ. Mutagen. 3:387.

13. Erffmeyer, J. (1981) Adverse reactions to penicillin. Ann. Allergy 47:288-300.

14. Fabre, J. (1977) Pharmacocinetique tissulaire de la doxycycline comparee a celle d'autres antibiotiques chez le rat. La Nouvelle Presse Medicale 9:71-76.

15. Florey, K. (1973) Analytical Profiles of Drug Substances, Vol. 2. New York: Academic Press, IR, p. 6; UV, p. 16.

16. Food and Drug Administration (FDA) (1983) Drug Utilization in the U.S.--1982, Fourth Annual Review. U.S. Department of Health and Human Services, p. 16.

17. Frank, P.; Nayler, J.; Smith, H. (1961) alpha-Aminobenzylpenicillins. U.S. Patent No. 2,985,648.

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

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

20. Goldenthal, E. (1971) A compilation of LD_{50} values in newborn and adult animals. Toxicol. Appl. Pharmacol. 18:185-207.

21. Green, M.; Tweats, D. (1981) An *Escherichia coli* differential killing test for carcinogens based on a uvrA recA lexA triple mutant. Stich, H.; San, R., Eds: Short-term Tests for Chemical Carcinogenesis. New York: Springer-Verlag, pp. 290-295.

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

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

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

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

26. Hollander, C.; Snell, K. (1976) Tumours of the adrenal gland. Turusov, V., Ed.: Pathology of Tumours in Laboratory Animals, Vol. I. Tumours of the Rat, Part 2. Lyon, France: International Agency for Research on Cancer, pp. 273-281.

27. Jaju, M.; Jaju, M.; Ahuja, Y. (1984) Evaluation of genotoxicity of ampicillin and carbenicillin on human lymphocytes in vitro: Chromosome aberrations, mitotic index, cell cycle kinetics, satellite associations of acrocentric chromosomes and sister chromatid exchanges. Hum. Tox. 3:173-191.

28. Jick, H.; Holmes, L.; Hunter, J.; Madsen, S.; Stergachis, A. (1981) First-trimester drug use and congenital disorders. J. Am. Med. Assoc. 246:343-346.

29. Johnson, D.; Hardcastle, H., Jr. (1964) D-(−)-α-Aminobenzylpenicillin trihydrate. U.S. Patent No. 3,157,640.

30. Johnson, D.; Wolfe, S. (1964) Process for the production of α-aminobenzylpenicillins. U.S. Patent No. 3,140,282.

31. Jusko, W.; Lewis, G. (1973) Comparison of ampicillin and hetacillin pharmacokinetics in man. J. Pharm. Sci. 62:69-76.

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

33. Kaufmann, W.; Bauer, K. (1963) Process for the enzymatic acylation of 6-aminopenicillanic acid. U.S. Patent No. 3,079,307.

34. Khosid, G.; Shteinberg, G.; Balabanova, E.; Baru, R.; Churagulova, N.; Lapchinskaya, A.; Lysenko, T.; Shtegel'man, L.; Vil'shanskaya, F. (1975) Toxicological characteristics of ampicillin. Antibiotiki (Moscow) 20:653-7.

35. King, J. (1975) The response of growing rats to a diet supplemented with the antibiotic ampicillin. Lab. Anim. 9:211-214.

36. Korzhova, V.; Lisitsyna, N.; Mikhailova, E. (1981) Effect of ampicillin and oxacillin on fetal and neonatal development. Bull. Exp. Biol. Med. (USSR) 91:169-171, 198.

37. Lai, Y.-L.; Jacoby, R.; Jonas, A. (1978) Age-related and light-associated retinal changes in Fischer rats. Intest. Ophthalmol. Vis. Sci. 17:634-638.

38. Ledger, W. (1977) Antibiotics in pregnancy. Clin. Obstet. Gynecol. 20:411-421.

39. Linhart, M.; Cooper, J.; Martin, R.; Page, N.; Peters, J. (1974) Carcinogenesis Bioassay Data System. Comp. Biomed. Res. 7:230-248.

40. Loo, J.; Foltz, E.; Wallick, H.; Kwan, K. (1974) Pharmacokinetics of pivampicillin and ampicillin in man. Clin. Pharmacol. Ther. 16:35-43.

41. Mandell, G.; Sande, M. (1980) Antimicrobial agents: penicillins and cephalosporins. Gilman, A.G.; Goodman, L.; Gilman, A., Eds.: The Pharmacological Basis of Therapeutics, 6th ed. New York: Macmillan Publishing Company, pp. 1126-1161.

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

V. REFERENCES

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

44. Masada, M.; Nakagawa, T.; Uno, T. (1979) A new metabolite of ampicillin in man. Chem. Pharm. Bull. 27:2877-2878.

45. Masada, M.; Kuroda, Y.; Nakagawa, T.; Uno, T. (1980) Structural investigation of new metabolites of amino-penicillins excreted in human urine. Chem. Pharm. Bull. 28:3427-3536.

46. McConnell, E.; Solleveld, H.; Swenberg, J.; Boorman, G. (1985) Guidelines for combining neoplasms for evaluation of rodent carcinogenesis. J. Natl. Cancer Inst. 76:283-289.

47. McCracken, G., Jr. (1983) Comparative evaluation of the aminopenicillins for oral use. Pediat. Infect. Dis. 2:317-320.

48. Merck Index (1976) 9th ed. Windholz, M., Ed. Rahway, NJ: Merck and Co., Inc., p. 80.

49. Milhaud, G.; Renault, L.; Vaissaire, J.; Maire, C. (1976) Sensibilite du lapin a l'ampicilline. Rec. Med. Vet. 152(12):843-847.

50. Mortelmans, K.; Haworth, S.; Lawlor, T.; Speck, W.; Tainer, B.; Zeiger, E. (1986) Salmonella mutagenicity tests. II. Results from the testing of 270 chemicals. Environ. Mutagen. 8(Suppl. 7):1-119.

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

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

53. Perry, J.; Le Blanc, A. (1967) Transfer of ampicillin across the human placenta. Tex. Rep. Biol. Med. 25:547-551.

54. Physicians' Desk Reference (PDR) (1984) 38th ed. Oradell, NJ: Medical Economics Company, Inc.

55. Pokorny, M; Vitezic, N.; Japelj, M. (1973) Detection of penicillins with chloroplatinic acid on thin-layer chromatoplates. J. Chromatog. 77:458-460.

56. Reuter, J.; Hobbelen, J. (1977) The effect of continuous light exposure on the retina in albino and pigmented rats. Physiol. Behav. 18:939-944.

57. Reynolds, C.; Ward, J.; Denn, A., III; Bere, E., Jr. (1982) Identification and characterization of large granular lymphocyte (LGL) leukemias in F344 rats. Herberman, R., Ed.: Natural Immunity, Vol. 2. Academic Press, pp. 1-5.

58. Schumacher, G. (1982) Pharmacokinetic and microbiologic evaluation of antibiotic dosage regimens. Clin. Pharm. 1:66-75.

59. Stewart, K.; Shafi, M.; Andrews, J.; Williams, J. (1973) Distribution of parenteral ampicillin and cephalosporins in late pregnancy. J. Obstet. Gynaecol. Br. Common. 80:902-908.

60. Strandberg, J. (1983) Hyperplasia, adrenal medulla, rat. Jones, T.; Mohr, U.; Hunt, R., Eds.: Endocrine System. Monographs on Pathology of Laboratory Animals, sponsored by The International Life Sciences Institute. New York: Springer-Verlag, pp. 18-22.

61. Stromberg, P.; Rojko, J.; Vogtsberger, L.; Cheney, C.; Berman, R. (1983) Immunologic, biochemical, and ultrastructural characterization of the leukemia cell in F344 rats. J. Natl. Cancer Inst. 71:173-179.

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

63. Triggs, E.; Johnson, J.; Learoyd, B. (1980) Absorption and disposition of ampicillin in the elderly. Eur. J. Clin. Pharmacol. 18: 195-198.

64. Tsuji, K.; Robertson, J. (1975) High-performance liquid chromatographic analysis of ampicillin. J. Pharm. Sci. 64:1542-1545.

65. United States Pharmacopeia (USP) (1975) 19th ed. Rockville, MD: U.S. Pharmacopeial Convention, Inc., pp. 31-32.

66. Ward, J.; Reynolds, C. (1983) Large granular lymphocyte leukemia--a heterogeneous lymphocytic leukemia in F344 rats. Am. J. Pathol. 111:1-10.

67. Waxman, D.; Strominger, J. (1983) Penicillin-binding proteins and the mechanism of action of β-lactam antibiotics. Ann. Rev. Biochem. 52:825-869.

68. Wilson, W. (1974) NMR spectrum of ampicillin trihydrate. J. Assoc. Off. Anal. Chem. 57:1306.

69. Wright, A.; Wilkowske, C. (1983) The penicillins. Mayo Clin. Proc. 58:21-32.

APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF AMPICILLIN TRIHYDRATE

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

	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)
Papilloma, NOS			1 (2%)
Squamous cell papilloma	†3 (6%)	3 (6%)	3 (6%)
Basal cell tumor	1 (2%)		4 (8%)
Basal cell carcinoma		1 (2%)	
Keratoacanthoma		1 (2%)	
Fibroma			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	4 (8%)		4 (8%)
Fibrosarcoma		1 (2%)	
Myxosarcoma			1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(49)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	3 (6%)	1 (2%)
Alveolar/bronchiolar carcinoma	2 (4%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, histiocytic type		1 (2%)	
Malignant lymphoma, mixed type	1 (2%)	1 (2%)	
Lymphocytic leukemia			1 (2%)
Leukemia, mononuclear cell	5 (10%)	14 (28%)	13 (26%)
#Spleen	(50)	(49)	(49)
Sarcoma, NOS	1 (2%)		
#Thymus	(38)	(32)	(38)
Thymoma, benign			1 (3%)
CIRCULATORY SYSTEM			
#Spleen	(50)	(49)	(49)
Hemangiosarcoma		1 (2%)	
#Heart	(50)	(49)	(50)
Neurilemoma, malignant			1 (2%)
DIGESTIVE SYSTEM			
#Salivary gland	(49)	(46)	(46)
Fibrosarcoma	1 (2%)		
#Liver	(50)	(49)	(50)
Neoplastic nodule			1 (2%)
#Stomach	(48)	(44)	(45)
Leiomyosarcoma			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(48)	(48)
Alveolar/bronchiolar carcinoma, metastatic	1 (2%)		
#Kidney/pelvis	(50)	(48)	(48)
Nephroblastoma	1 (2%)		
#Urinary bladder	(47)	(44)	(46)
Transitional cell papilloma			1 (2%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Pituitary intermedia	(46)	(49)	(46)
Adenoma, NOS	1 (2%)		
#Anterior pituitary	(46)	(49)	(46)
Carcinoma, NOS	1 (2%)	2 (4%)	2 (4%)
Adenoma, NOS	11 (24%)	18 (37%)	14 (30%)
#Adrenal	(50)	(50)	(49)
Cortical adenoma			2 (4%)
#Adrenal medulla	(50)	(50)	(49)
Pheochromocytoma	13 (26%)	12 (24%)	23 (47%)
Pheochromocytoma, malignant	1 (2%)	5 (10%)	1 (2%)
#Thyroid	(50)	(48)	(46)
Follicular cell adenoma			1 (2%)
Follicular cell carcinoma		1 (2%)	
C-cell adenoma	2 (4%)	3 (6%)	1 (2%)
C-cell carcinoma		3 (6%)	2 (4%)
#Parathyroid	(20)	(32)	(25)
Adenoma, NOS		1 (3%)	
#Pancreatic islets	(47)	(45)	(49)
Islet cell adenoma	5 (11%)		2 (4%)
Islet cell carcinoma	1 (2%)		1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Fibroadenoma	1 (2%)	1 (2%)	
*Penis	(50)	(50)	(50)
Papilloma, NOS		1 (2%)	
*Preputial gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)		
Adenocarcinoma, NOS	1 (2%)	1 (2%)	1 (2%)
Fibrosarcoma, unclear primary or metastatic			1 (2%)
#Prostate	(49)	(48)	(47)
Adenoma, NOS	2 (4%)		2 (4%)
#Testis	(50)	(49)	(50)
Interstitial cell tumor	32 (64%)	30 (61%)	31 (62%)
*Epididymis	(50)	(50)	(50)
Mesothelioma, NOS			1 (2%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Astrocytoma			1 (2%)
Meningioma	1 (2%)		
#Brain/thalamus	(50)	(50)	(50)
Carcinoma, NOS, invasive	1 (2%)		
#Cerebellum	(50)	(50)	(50)
Granular cell tumor, NOS			1 (2%)
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*Skeletal muscle	(50)	(50)	(50)
Chordoma		1 (2%)	
*Abdominal muscle	(50)	(50)	(50)
Sarcoma, NOS		1 (2%)	

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*Thoracic cavity	(50)	(50)	(50)
Mesothelioma, malignant		1 (2%)	
*Abdominal cavity	(50)	(50)	(50)
Undifferentiated carcinoma		1 (2%)	
Lipoma			1 (2%)
Mesothelioma, NOS	1 (2%)		
*Pleura	(50)	(50)	(50)
Mesothelioma, metastatic		1 (2%)	
*Tunica vaginalis	(50)	(50)	(50)
Mesothelioma, NOS			1 (2%)
Mesothelioma, malignant		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Sarcoma, NOS, metastatic		1 (2%)	
Fibrosarcoma, metastatic		1 (2%)	
Leiomyosarcoma, metastatic			1 (2%)
Mesothelioma, metastatic		1 (2%)	
Neurilemoma, metastatic			1 (2%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	5	10	10
Moribund sacrifice	10	13	11
Terminal sacrifice	31	27	26
Dosing accident	4		3
TUMOR SUMMARY			
Total animals with primary tumors**	45	47	46
Total primary tumors	96	110	123
Total animals with benign tumors	40	43	45
Total benign tumors	77	73	93
Total animals with malignant tumors	16	28	23
Total malignant tumors	18	37	25
Total animals with secondary tumors##	2	4	2
Total secondary tumors	2	4	2
Total animals with tumors uncertain--benign or malignant	1		4
Total uncertain tumors	1		4
Total animals with tumors uncertain--primary or metastatic			1
Total uncertain tumors			1

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
† Multiple occurrence of morphology in the same organ; tissue is counted once only.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF AMPICILLIN TRIHYDRATE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	3 (6%)	1 (2%)	3 (6%)
Fibrosarcoma			1 (2%)
Lipoma			1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(49)	(50)
Squamous cell carcinoma	1 (2%)		1 (2%)
Adenocarcinoma, NOS, metastatic			1 (2%)
Alveolar/bronchiolar adenoma	1 (2%)	1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	14 (28%)	18 (36%)	13 (26%)
#Spleen	(50)	(49)	(50)
Osteosarcoma, metastatic		1 (2%)	
Leukemia, mononuclear cell			2 (4%)
#Thymic lymph node	(43)	(45)	(45)
Carcinosarcoma, metastatic	1 (2%)		
#Liver	(50)	(50)	(50)
Leukemia, mononuclear cell		1 (2%)	
CIRCULATORY SYSTEM			
#Heart	(50)	(50)	(50)
Neurilemoma		1 (2%)	
#Uterus	(50)	(50)	(49)
Hemangiosarcoma			1 (2%)
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Neoplastic nodule		1 (2%)	
Hepatocellular carcinoma		1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(49)
Adenoma, NOS	1 (2%)		
Nephroblastoma			1 (2%)
#Kidney/pelvis	(50)	(50)	(49)
Transitional cell carcinoma		1 (2%)	
#Urinary bladder	(46)	(46)	(41)
Epithelial tumor, NOS, benign	1 (2%)		
Transitional cell papilloma	1 (2%)		1 (2%)

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF AMPICILLIN TRIHYDRATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(50)	(49)
Carcinoma, NOS		3 (6%)	3 (6%)
Adenoma, NOS	18 (37%)	20 (40%)	22 (45%)
#Adrenal	(50)	(50)	(49)
Cortical adenoma	1 (2%)	3 (6%)	4 (8%)
Cortical carcinoma			1 (2%)
#Adrenal medulla	(50)	(50)	(49)
Pheochromocytoma	3 (6%)	3 (6%)	4 (8%)
Pheochromocytoma, malignant			1 (2%)
#Thyroid	(50)	(49)	(49)
Follicular cell adenoma			1 (2%)
Follicular cell carcinoma	2 (4%)		
C-cell adenoma	1 (2%)		
C-cell carcinoma	2 (4%)	1 (2%)	1 (2%)
#Pancreatic islets	(48)	(49)	(49)
Islet cell adenoma		2 (4%)	1 (2%)
Islet cell carcinoma		2 (4%)	1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS	2 (4%)		1 (2%)
Carcinosarcoma	1 (2%)		
Fibroadenoma	16 (32%)	25 (50%)	19 (38%)
*Preputial gland	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)		
*Clitoral gland	(50)	(50)	(50)
Carcinoma, NOS		1 (2%)	
Adenoma, NOS	1 (2%)		2 (4%)
Adenocarcinoma, NOS			2 (4%)
Adenocarcinoma, NOS, invasive	1 (2%)		
#Uterus	(50)	(50)	(49)
Adenocarcinoma, NOS	1 (2%)		
Leiomyoma		1 (2%)	
Leiomyosarcoma		1 (2%)	
Endometrial stromal polyp	6 (12%)	5 (10%)	1 (2%)
Endometrial stromal sarcoma	2 (4%)		
#Endometrial gland	(50)	(50)	(49)
Adenomatous polyp, NOS			1 (2%)
#Ovary	(50)	(49)	(47)
Epithelial tumor, NOS, benign		1 (2%)	
Luteoma			2 (4%)
Granulosa cell tumor	1 (2%)		
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Carcinoma, NOS, invasive			1 (2%)
Carcinoma, NOS, metastatic		1 (2%)	
#Brain/thalamus	(50)	(50)	(50)
Carcinoma, NOS, invasive		1 (2%)	
#Cerebellum	(50)	(50)	(50)
Granular cell tumor, NOS			1 (2%)
SPECIAL SENSE ORGANS			
None			

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF AMPICILLIN TRIHYDRATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
*Femur	(50)	(50)	(50)
Osteosarcoma		1 (2%)	1 (2%)
*Intercostal muscle	(50)	(50)	(50)
Squamous cell carcinoma, invasive	1 (2%)		
*Muscle hip/thigh	(50)	(50)	(50)
Rhabdomyosarcoma			1 (2%)
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Squamous cell carcinoma, invasive	1 (2%)		1 (2%)
*Peritoneal cavity	(50)	(50)	(50)
Nephroblastoma, metastatic			1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Squamous cell carcinoma, metastatic			1 (2%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	5	6	10
Moribund sacrifice	13	11	8
Terminal sacrifice	32	31	31
Dosing accident		2	1
TUMOR SUMMARY			
Total animals with primary tumors**	44	41	45
Total primary tumors	82	94	95
Total animals with benign tumors	33	35	38
Total benign tumors	55	63	63
Total animals with malignant tumors	22	25	24
Total malignant tumors	26	30	31
Total animals with secondary tumors##	3	3	4
Total secondary tumors	4	3	5
Total animals with tumors uncertain-- benign or malignant	1	1	1
Total uncertain tumors	1	1	1

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

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

ANIMAL NUMBER	0041	0049	0038	0014	0001	0020	0043	0045	0003	0016	0015	0025	0044	0033	0050	0028	0012	0039	0035	0002	0004	0005	0006	0007	0008
WEEKS ON STUDY	017	017	023	043	071	071	075	076	083	083	085	085	085	087	087	088	093	093	103	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									X
Basal cell tumor																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma									X																
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								X	
Alveolar/bronchiolar carcinoma																	X								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																X									
Lymph nodes	+	+	+	+	+	−	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	−	+	+	+	+	+	+	+	−	−	−	+	+	−	+	−	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	−	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	−	+	+	−	+	−	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	−	−	−	−	+	−	−	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	−	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma metastatic																									
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nephroblastoma								X																	
Urinary bladder	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	−	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS					X																				
Adenoma, NOS											X			X							X		X		X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																			X		X				
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																									
Parathyroid	+	−	+	+	+	−	+	−	+	+	+	−	−	−	−	+	+	+	−	−	−	+	−	+	−
Pancreatic islets	+	+	+	+	+	+	−	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N
Fibroadenoma						X																			
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor												X	X					X		X	X	X		X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS								X													X				
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																		X							
Adenocarcinoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive					X																				
Meningioma																									
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N
Carcinoma, NOS																			X						
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS													X												
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, mixed type																	X								
Leukemia, mononuclear cell										X					X			X			X				

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed

: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

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

ANIMAL NUMBER	00 09	01 10	01 11	01 13	01 17	01 18	01 19	02 21	02 22	02 23	02 24	02 26	02 27	02 29	03 30	03 31	03 32	03 34	03 36	03 37	04 40	04 42	04 46	04 47	04 48	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma								X@									X									3
Basal cell tumor																						X				1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma		X												X									X			4
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma							X																			2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	45
Thymus	+	+	+	−	+	+	+	−	−	+	+	+	−	+	−	+	−	+	+	+	+	+	+	+	+	38
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	49
Fibrosarcoma						X																				1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Large intestine	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metas							X																			1
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nephroblastoma																										1
Urinary bladder	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	46
Carcinoma, NOS																										1
Adenoma, NOS					X		X	X		X							X				X		X			12
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma		X		X	X	X			X			X				X			X		X	X			X	13
Pheochromocytoma, malignant				X																						1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell adenoma												X								X						2
Parathyroid	+	−	−	−	−	−	−	−	+	−	−	+	−	−	−	−	+	+	+	−	−	+	−	−	−	20
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Islet cell adenoma	X									X							X						X	X		5
Islet cell carcinoma															X											1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	+	+	+	+	+	N	N	*50
Fibroadenoma																										1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	32
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	49
Adenoma, NOS																										2
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
Adenocarcinoma, NOS																		X								1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																										1
Meningioma																					X					1
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, mixed type																										1
Leukemia, mononuclear cell																						X				5

* Animals necropsied

@ Multiple occurrence of morphology

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

ANIMAL NUMBER	039	010	023	043	001	048	014	027	046	032	041	026	004	012	005	047	017	019	033	028	016	024	031	002	003
WEEKS ON STUDY	040	044	058	059	066	072	076	076	077	083	084	089	091	091	094	095	097	098	099	101	102	102	102	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																							X		
Basal cell carcinoma							X																		
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																			X						
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X	X										
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	−	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								X	
Lymph nodes	−	+	+	−	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	−
Thymus	+	+	+	−	+	+	+	+	+	−	−	−	+	−	−	−	+	+	−	−	−	+	−	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	−	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	−	+	+	+	+
Esophagus	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	−	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	−	−	+	+
Small intestine	−	−	+	−	+	+	−	+	+	+	−	+	+	+	−	+	+	+	+	+	−	−	−	+	+
Large intestine	−	+	+	−	+	+	−	+	+	+	−	+	−	+	−	+	+	+	−	+	−	−	−	+	+
URINARY SYSTEM																									
Kidney	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Urinary bladder	−	−	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Carcinoma, NOS																							X		
Adenoma, NOS					X				X	X		X	X		X		X			X				
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																X					X	X			
Pheochromocytoma, malignant												X													
Thyroid	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																									
C-cell adenoma												X	X												
C-cell carcinoma																									
Parathyroid	+	+	+	−	+	−	+	+	+	−	−	−	−	+	−	−	+	+	−	−	+	−	−	+	+
Adenoma, NOS									X																
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	+	N	N	N	N	N	N	N	N	N	+	N	N	N	+	+	N	N	+	+	N
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Interstitial cell tumor								X						X	X				X	X	X		X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+
Penis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papilloma, NOS				X																					
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS																						X			
Chordoma														X											
BODY CAVITIES																									
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, malignant																									
Mesothelioma, metastatic																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Undifferentiated carcinoma										X															
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+
Mesothelioma, malignant																							X		
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS, metastatic																						X			
Fibrosarcoma, metastatic																			X						
Mesothelioma, metastatic																							X		
Malignant lymphoma, histiocytic type			X																						
Malignant lymphoma, mixed type					X																				
Leukemia, mononuclear cell											X				X		X			X	X		X		

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

ANIMAL NUMBER	00006	00007	00008	00009	00011	00013	00015	00018	00020	00021	00022	00025	00029	00030	00034	00035	00036	00037	00038	00040	00042	00044	00045	00049	00050	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma	X					X																				3
Basal cell carcinoma																										1
Keratoacanthoma										X																1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma											X															3
Alveolar/bronchiolar carcinoma																					X					1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	46
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Lymph nodes	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	42
Thymus	+	+	+	–	+	+	–	–	+	+	–	+	+	–	+	–	+	+	+	+	+	+	+	+	–	32
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	41
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	38
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS															X											2
Adenoma, NOS	X		X	X						X				X					X	X	X	X			X	18
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma	X		X	X			X	X	X			X			X				X							12
Pheochromocytoma, malignant		X		X												X									X	5
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell carcinoma			X																							1
C-cell adenoma															X											3
C-cell carcinoma																		X		X					X	3
Parathyroid	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	–		32
Adenoma, NOS																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	+	N	N	N	N	N	N	N	+	N	N	+	+	N	N	+	+	N	N	N	N	N	+	*50
Fibroadenoma														X												1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor		X	X	X	X	X	X	X		X	X	X		X	X	X	X		X	X	X	X	X	X	X	30
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Penis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papilloma, NOS																										1
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenocarcinoma, NOS		X																								1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS																										1
Chordoma																										1
BODY CAVITIES																										
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, malignant																								X		1
Mesothelioma, metastatic																								X		1
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Undifferentiated carcinoma																										1
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, malignant																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS, metastatic																										1
Fibrosarcoma, metastatic																										1
Mesothelioma, metastatic																										1
Malig. lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type																										1
Leukemia, mononuclear cell		X	X			X		X						X	X						X		X			14

* Animals necropsied

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

ANIMAL NUMBER	0011	0444	0009	0500	0601	0005	0645	0748	0118	0084	0827	0003	0926	0943	0915	0925	0936	0932	0920	0002	0928	0830	0947	0924	0006
WEEKS ON STUDY	0336	0445	0449	0550	0663	0863	0663	0771	0880	0883	0889	0992	0992	0992	0993	0993	0993	0994	0996	0997	0997	0997	0998	1003	1004
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS																		X							
Squamous cell papilloma																									
Basal cell tumor								X								X									
Fibroma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma												X			X								X		
Myxosarcoma											X														
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X														
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	−	+	+	+	+	+	+	−	+	+	+	−	−	+	+	+	+	+	+	−	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	−	−	+	+	−	−	−	+	+	+	−	+	−	−	+
Thymoma, benign																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, malignant																									
DIGESTIVE SYSTEM																									
Salivary gland	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																				X					
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	−	+	+	+	−	+	−	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+
Leiomyosarcoma																				X					
Small intestine	+	+	−	−	+	+	−	+	−	+	+	+	+	−	+	+	+	+	+	+	−	−	+	+	
Large intestine	+	+	−	−	+	+	−	+	−	−	−	+	+	−	+	+	−	−	+	+	+	−	+	−	+
URINARY SYSTEM																									
Kidney	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	−	+	−	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma																									
ENDOCRINE SYSTEM																									
Pituitary	−	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
Carcinoma, NOS																			X						
Adenoma, NOS		X				X				X												X			
Adrenal	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																X									
Pheochromocytoma									X			X			X	X									X
Pheochromocytoma, malignant																									
Thyroid	+	+	−	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+
Follicular cell adenoma					X																				
C-cell adenoma																									
C-cell carcinoma																			X						
Parathyroid	−	−	+	+	+	−	+	−	+	−	−	−	−	−	+	−	−	−	+	−	+	−	+	−	−
Pancreatic islets	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									X
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	+	N	N	N	N	N	+	N	N	N	N	N	N	N	+	N	N	+	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor					X					X			X	X	X	X	X			X	X		X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	−	+
Adenoma, NOS																							X		
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS																									
Fibrosarcoma, unclear primary or metastatic																									
Epididymis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, NOS																								X	
Astrocytoma		X																							
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Lipoma												X													
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leiomyosarcoma, metastatic																					X				
Neurilemoma, metastatic																									
Lymphocytic leukemia															X										
Leukemia, mononuclear cell						X							X			X		X		X				X	

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

ANIMAL NUMBER	0007	0008	0010	0012	0013	0014	0016	0017	0019	0021	0022	0023	0029	0031	0033	0034	0035	0037	0038	0039	0040	0041	0042	0046	0049	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Papilloma, NOS																										1
Squamous cell papilloma						X								X	X											3
Basal cell tumor				X												X										4
Fibroma															X											1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma			X																							4
Myxosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	−	+	+	+	−	−	−	+	−	+	+	+	+	−	+	−	+	+	38
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	−	+	+	+	+	+	−	38
Thymoma, benign																		X								1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma, malignant																	X									1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	−	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Leiomyosarcoma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Large intestine	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	36
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Transitional cell papilloma												X														1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Carcinoma, NOS																			X							2
Adenoma, NOS	X				X				X		X	X					X			X		X	X		X	14
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma										X																2
Pheochromocytoma			X	X	X		X	X	X	X	X		X	X	X		X	X	X	X		X	X	X		23
Pheochromocytoma, malignant																				X						1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Follicular cell adenoma																										1
C-cell adenoma				X																						1
C-cell carcinoma											X															2
Parathyroid	+	+	+	−	+	+	+	−	+	+	−	+	−	−	−	+	−	+	+	+	+	+	−	+	−	25
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma																			X							2
Islet cell carcinoma											X															1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	+	N	N	N	+	N	N	N	N	N	N	+	+	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X		X	X	X	X	X	X		X	X	X			X		X	X	X		X	X		31
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS					X																					2
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenocarcinoma, NOS													X													1
Fibrosarcoma, unclear prim or meta																							X			1
Epididymis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, NOS											X															1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor, NOS																										1
Astrocytoma																										1
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Lipoma																										1
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS																			X							1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leiomyosarcoma, metastatic																	X									1
Neurilemoma, metastatic																										1
Lymphocytic leukemia																										1
Leukemia, mononuclear cell			X		X	X	X							X		X									X	13

* Animals necropsied

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

ANIMAL NUMBER	0211	0168	0111	0155	0332	0001	0002	0500	0444	0055	0266	0255	0191	0447	0244	0388	0355	0422	0033	0044	0066	0077	0088	0099	0100
WEEKS ON STUDY	0511	0558	0744	0775	0886	0887	0887	0870	0900	0933	0933	0944	0988	0988	1002	1002	1003	1003	1004	1004	1004	1004	1004	1004	1004
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+
Fibroma																							X		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma														X											
Alveolar/bronchiolar adenoma																	X								
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	−	−	−	+	+	+	+	+	+	+	−	+	−	−	+	+	+	+	−	+	+	+	+	+	+
Carcinosarcoma, metastatic									X																
Thymus	−	+	+	+	−	+	−	+	−	+	+	+	+	−	+	−	+	−	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	−	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Urinary bladder	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+
Epithelial tumor, NOS, benign																									
Transitional cell papilloma																							X		
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS			X	X		X		X									X	X		X	X				X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma														X		X									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																	X								
C-cell adenoma																X									
C-cell carcinoma																X									
Parathyroid	+	+	+	−	+	−	−	−	−	−	−	+	−	−	+	+	−	−	−	−	−	−	+	+	−
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	N	+	+	+	+
Adenocarcinoma, NOS													X	X											
Carcinosarcoma									X																
Fibroadenoma										X	X			X		X	X							X	X
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																								X	
Adenoma, NOS											X														
Adenocarcinoma, NOS, invasive													X												
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS														X											
Endometrial stromal polyp																X								X	
Endometrial stromal sarcoma	X						X																		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma, invasive														X											
BODY CAVITIES																									
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma, invasive														X											
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell					X						X	X			X	X		X				X	X	X	

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

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

ANIMAL NUMBER	012	013	014	017	018	020	022	023	027	028	029	030	031	033	034	036	037	039	040	041	043	045	046	048	049	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma		X																								1
Subcutaneous tissue	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																						X			X	3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																	X									1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Carcinosarcoma, metastatic																										1
Thymus	−	−	−	−	−	+	−	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	35
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	−	+	−	−	+	−	+	+	+	+	+	−	−	+	−	+	+	+	+	+	−	+	+	−	37
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS						X																				1
Urinary bladder	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Epithelial tumor, NOS, benign																			X							1
Transitional cell papilloma																										1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS		X	X	X						X		X						X	X	X		X				18
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																			X							1
Pheochromocytoma								X																		3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell carcinoma									X																	2
C-cell adenoma																										1
C-cell carcinoma																		X								2
Parathyroid	−	−	−	+	−	−	−	−	+	−	−	−	−	−	−	−	−	−	+	−	−	−	+	−	−	13
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										2
Carcinosarcoma																										1
Fibroadenoma					X	X	X			X		X			X				X	X			X			16
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma																										1
Adenoma, NOS																										1
Adenocarcinoma, NOS, invasive																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																										1
Endometrial stromal polyp	X					X	X							X												6
Endometrial stromal sarcoma																										2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor													X													1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma, invasive																										1
BODY CAVITIES																										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma, invasive																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell	X			X													X		X	X						14

* Animals necropsied

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

ANIMAL NUMBER	043	008	033	017	033	009	030	041	022	047	024	042	026	021	019	045	049	001	002	004	005	006	007	010	011
WEEKS ON STUDY	000	004	054	059	071	077	077	083	086	086	087	088	090	093	094	094	103	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																							X		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic																									
Lymph nodes	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	−	+	+	+	+
Thymus	+	+	−	+	+	+	+	+	+	+	−	−	+	−	+	+	+	+	+	+	−	+	−	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma																								X	
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Hepatocellular carcinoma																						X			
Leukemia, mononuclear cell																								X	
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	−	+	+	+	+	−	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	−	+	+	+	+	+	+	−	+	+	−	+	+	+	−	−	+	+	−	−	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma																									
Urinary bladder	+	−	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS													X				X						X		
Adenoma, NOS					X			X	X			X		X						X				X	
Adrenal	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																		X							
Pheochromocytoma																				X			X		
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
C-cell carcinoma																									
Parathyroid	−	+	+	−	+	−	−	+	+	−	−	+	−	−	−	−	+	−	−	−	−	−	−	+	−
Pancreatic islets	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																					X	X			
Islet cell carcinoma				X																					
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma						X		X					X	X			X	X		X			X	X	
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS							X																		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																		X							
Leiomyosarcoma														X											
Endometrial stromal polyp										X							X				X			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Epithelial tumor, NOS, benign																						X			
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive													X												
Carcinoma, NOS, metastatic																							X		
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell			X								X					X	X				X		X		

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

ANIMAL NUMBER	012	013	014	015	016	018	020	023	025	027	028	029	031	032	034	035	036	037	038	039	040	044	046	048	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																		X								1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Osteosarcoma, metastatic	X																									1
Lymph nodes	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Thymus	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	−	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	50
Neurilemoma																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule		X																								1
Hepatocellular carcinoma																										1
Leukemia, mononuclear cell																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Large intestine	−	+	+	+	+	+	−	−	+	+	+	+	−	+	+	+	+	+	−	+	+	+	−	+	−	36
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell carcinoma											X															1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																										3
Adenoma, NOS	X	X				X		X		X	X	X	X				X	X			X			X	X	20
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma											X										X					3
Pheochromocytoma														X												3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell carcinoma						X																				1
Parathyroid	−	+	+	−	+	−	+	−	+	+	+	−	−	−	−	−	+	+	−	+	−	+	−	+	−	20
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma																										2
Islet cell carcinoma																X										2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	N	+	+	+	*50
Fibroadenoma		X	X			X	X	X		X		X	X	X		X	X			X	X		X	X	X	25
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																										1
Leiomyosarcoma																										1
Endometrial stromal polyp			X												X											5
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Epithelial tumor, NOS, benign																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																										1
Carcinoma, NOS, metastatic																										1
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma	X																									1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell	X		X					X		X	X	X				X	X	X	X	X					X	18

* Animals necropsied

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

ANIMAL NUMBER	0013	0011	0024	0005	0041	0111	0049	0009	0036	0035	0050	0018	0044	0002	0039	0007	0008	0038	0048	0003	0004	0006	0010	0012	0014
WEEKS ON STUDY	058	074	076	080	084	091	092	093	093	095	096	097	097	098	100	102	102	103	103	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma								X	X																
Fibrosarcoma															X										
Lipoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma										X															
Adenocarcinoma, NOS, metastatic																					X				
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell						X												X							
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–
Thymus	+	+	+	+	+	–	+	+	–	+	–	+	+	+	+	–	+	–	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Small intestine	+	–	–	+	–	–	+	+	–	+	–	–	+	+	+	+	+	+	–	+	+	+	+	+	+
Large intestine	+	+	+	+	–	+	+	+	–	+	–	–	+	+	+	–	+	+	–	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Nephroblastoma																									
Urinary bladder	–	+	–	–	–	+	+	+	–	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma														X											
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS						X								X	X	X		X	X	X			X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma			X																	X				X	
Cortical carcinoma																						X			
Pheochromocytoma																	X				X				
Pheochromocytoma, malignant										X															
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
C-cell carcinoma																									
Parathyroid	–	–	–	+	+	–	–	–	–	+	–	+	–	+	–	–	+	+	–	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Islet cell adenoma																									
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	+	+	+	+	N	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																					X				
Fibroadenoma					X	X									X	X	X	X	X	X			X	X	
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																	X								
Adenocarcinoma, NOS																									
Uterus	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS																									
Endometrial stromal polyp																									
Hemangiosarcoma																									
Ovary	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Luteoma																						X			
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																									
Granular cell tumor, NOS													X												
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma																									
Muscle	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Rhabdomyosarcoma							X																		
BODY CAVITIES																									
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma, invasive										X															
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Nephroblastoma, metastatic																									
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
Squamous cell carcinoma, metastatic										X															
Leukemia, mononuclear cell		X		X						X		X	X				X					X		

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

ANIMAL NUMBER	0 1 5	0 1 6	0 1 7	0 1 9	0 2 0	0 2 1	0 2 2	0 2 3	0 2 5	0 2 6	0 2 7	0 2 8	0 2 9	0 3 0	0 3 1	0 3 2	0 3 3	0 3 4	0 3 7	0 4 0	0 4 2	0 4 3	0 4 5	0 4 7	0 4 8	TOTAL:
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma			X																							3
Fibrosarcoma																										1
Lipoma																							X			1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Adenocarcinoma, NOS, metastatic																										1
Alveolar/bronchiolar adenoma																			X							1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia, mononuclear cell																										2
Lymph nodes	−	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	45
Thymus	+	+	+	+	+	+	+	−	+	−	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	−	+	+	+	+	+	41
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nephroblastoma																					X					1
Urinary bladder	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Transitional cell papilloma																										1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS	X		X												X											3
Adenoma, NOS							X	X	X		X			X		X	X		X	X	X	X	X	X	X	22
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	49
Cortical adenoma	X																									4
Cortical carcinoma																										1
Pheochromocytoma			X																				X			4
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma					X																					1
C-cell carcinoma										X																1
Parathyroid	+	+	+	+	+	+	−	+	−	+	−	−	+	+	−	+	+	−	+	+	−	+	−	+	−	28
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma					X																					1
Islet cell carcinoma														X												1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	N	+	+	N	N	+	N	N	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										1
Fibroadenoma			X		X				X	X			X			X	X	X			X					19
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																								X		2
Adenocarcinoma, NOS										X														X		2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenomatous polyp, NOS																							X			1
Endometrial stromal polyp															X											1
Hemangiosarcoma																			X							1
Ovary	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Luteoma				X																						2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive	X																									1
Granular cell tumor, NOS																										1
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma															X											1
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Rhabdomyosarcoma																										1
BODY CAVITIES																										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma, invasive																										1
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Nephroblastoma, metastatic																					X					1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma, metastatic																										1
Leukemia, mononuclear cell	X				X		X			X									X						X	13

* Animals necropsied

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF AMPICILLIN TRIHYDRATE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF AMPICILLIN TRIHYDRATE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	1
ANIMALS NECROPSIED	50	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	49
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(49)	(49)
Sarcoma, NOS		1 (2%)	
Fibroma	1 (2%)	1 (2%)	
Fibrosarcoma	2 (4%)	7 (14%)	†5 (10%)
Fibrosarcoma, unclear primary or metastatic		1 (2%)	
Rhabdomyosarcoma	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(49)	(47)
Hepatocellular carcinoma, metastatic			1 (2%)
Alveolar/bronchiolar adenoma	1 (2%)	3 (6%)	1 (2%)
Alveolar/bronchiolar carcinoma	5 (10%)	3 (6%)	2 (4%)
Cortical carcinoma, metastatic	1 (2%)		
Fibrosarcoma, metastatic	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(49)	(49)
Malignant lymphoma, NOS			2 (4%)
Malignant lymphoma, lymphocytic type	1 (2%)	2 (4%)	1 (2%)
Malignant lymphoma, histiocytic type	1 (2%)		
*Mediastinum	(50)	(49)	(49)
Malignant lymphoma, lymphocytic type	1 (2%)		
#Spleen	(50)	(47)	(47)
Malignant lymphoma, lymphocytic type			1 (2%)
Malignant lymphoma, mixed type			1 (2%)
#Jejunum	(45)	(44)	(37)
Malignant lymphoma, mixed type	1 (2%)		
#Thymus	(28)	(22)	(24)
Malignant lymphoma, lymphocytic type	1 (4%)		
CIRCULATORY SYSTEM			
#Heart	(50)	(49)	(47)
Hemangioma	1 (2%)		
#Heart/ventricle	(50)	(49)	(47)
Hemangiosarcoma, metastatic	1 (2%)		
#Liver	(50)	(48)	(46)
Hemangiosarcoma	1 (2%)	1 (2%)	
#Pancreas	(47)	(44)	(42)
Hemangioma	1 (2%)		
DIGESTIVE SYSTEM			
#Liver	(50)	(48)	(46)
Hepatocellular adenoma	3 (6%)	2 (4%)	3 (7%)
Hepatocellular carcinoma	6 (12%)	2 (4%)	4 (9%)
Fibrosarcoma, metastatic	1 (2%)	1 (2%)	

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF AMPICILLIN TRIHYDRATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Adrenal	(48)	(48)	(45)
Cortical carcinoma	1 (2%)		
#Adrenal/capsule	(48)	(48)	(45)
Adenoma, NOS			1 (2%)
#Adrenal medulla	(48)	(48)	(45)
Pheochromocytoma	3 (6%)	1 (2%)	
#Thyroid	(42)	(44)	(39)
Follicular cell adenoma	3 (7%)	1 (2%)	1 (3%)
#Pancreatic islets	(47)	(44)	(42)
Islet cell adenoma		1 (2%)	
REPRODUCTIVE SYSTEM			
None			
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(49)	(49)
Papillary adenoma		1 (2%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
*Muscle of trunk	(50)	(49)	(49)
Fibrosarcoma, unclear primary or metastatic	1 (2%)		
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(49)	(49)
Fibrosarcoma, metastatic		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	12	14	17
Moribund sacrifice	5	8	6
Terminal sacrifice	32	21	20
Accidentally killed, nda		1	1
Accidentally killed, NOS	1	5	5
Animal missing		1	1

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF AMPICILLIN TRIHYDRATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
Total animals with primary tumors**	23	21	18
Total primary tumors	35	27	24
Total animals with benign tumors	11	9	6
Total benign tumors	13	10	7
Total animals with malignant tumors	15	16	14
Total malignant tumors	21	16	17
Total animals with secondary tumors##	3	2	1
Total secondary tumors	4	2	1
Total animals with tumors uncertain--primary or metastatic	1	1	
Total uncertain tumors	1	1	

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
† Multiple occurrence of morphology in the same organ; tissue is counted once only.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF AMPICILLIN TRIHYDRATE

	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)
Papilloma, NOS			1 (2%)
Squamous cell carcinoma		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)		1 (2%)
Fibrosarcoma	1 (2%)	1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)		4 (8%)
Alveolar/bronchiolar carcinoma	1 (2%)	3 (6%)	
Sarcoma, NOS, metastatic			1 (2%)
Fibrosarcoma, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS		1 (2%)	
Malignant lymphoma, undiffer type	1 (2%)		
Malignant lymphoma, lymphocytic type	12 (24%)	6 (12%)	9 (18%)
Malignant lymphoma, histiocytic type	1 (2%)		1 (2%)
Malignant lymphoma, mixed type	1 (2%)	3 (6%)	2 (4%)
Lymphocytic leukemia	1 (2%)		1 (2%)
#Spleen	(49)	(50)	(50)
Malignant lymphoma, lymphocytic type	1 (2%)		1 (2%)
#Thoracic lymph node	(32)	(37)	(37)
Sarcoma, NOS, metastatic			1 (3%)
#Liver	(49)	(50)	(49)
Malignant lymphoma, lymphocytic type			1 (2%)
*Mesentery	(50)	(50)	(50)
Malignant lymphoma, NOS	1 (2%)		
#Kidney	(49)	(50)	(50)
Malignant lymphoma, NOS	1 (2%)		
#Thymus	(27)	(26)	(30)
Malignant lymphoma, lymphocytic type	1 (4%)	2 (8%)	
CIRCULATORY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Hemangioma	2 (4%)		
Hemangiosarcoma		1 (2%)	
#Bone marrow	(48)	(50)	(49)
Hemangioma			1 (2%)
#Spleen	(49)	(50)	(50)
Hemangioma	1 (2%)		
DIGESTIVE SYSTEM			
#Forestomach	(47)	(49)	(49)
Squamous cell carcinoma		1 (2%)	
#Jejunum	(43)	(47)	(46)
Carcinoma, NOS		1 (2%)	

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF AMPICILLIN TRIHYDRATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Anterior pituitary	(44)	(40)	(36)
Carcinoma, NOS	1 (2%)	1 (3%)	1 (3%)
Adenoma, NOS	7 (16%)	1 (3%)	5 (14%)
Acidophil adenoma		1 (3%)	
#Adrenal/capsule	(47)	(48)	(47)
Adenoma, NOS	1 (2%)		1 (2%)
#Adrenal medulla	(47)	(48)	(47)
Pheochromocytoma	2 (4%)	1 (2%)	
#Thyroid	(42)	(47)	(43)
Follicular cell adenoma	1 (2%)	1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS	1 (2%)	1 (2%)	
#Uterus	(49)	(50)	(48)
Leiomyoma			1 (2%)
Endometrial stromal polyp			1 (2%)
#Ovary	(46)	(43)	(45)
Papillary cystadenoma, NOS		1 (2%)	
Granulosa cell tumor			1 (2%)
Teratoma, benign	1 (2%)		
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Meningioma	1 (2%)		
#Brain/thalamus	(50)	(50)	(50)
Carcinoma, NOS, invasive	1 (2%)		
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenocarcinoma, NOS			1 (2%)
Papillary cystadenoma, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mesentery	(50)	(50)	(50)
Lipoma	1 (2%)		
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Adenocarcinoma, NOS, metastatic			1 (2%)
Sarcoma, NOS, unclear primary or metastatic	1 (2%)		

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF AMPICILLIN TRIHYDRATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	12	19	10
Moribund sacrifice	4	4	2
Terminal sacrifice	34	27	28
Accidentally killed, NOS			10
TUMOR SUMMARY			
Total animals with primary tumors**	32	21	28
Total primary tumors	45	27	35
Total animals with benign tumors	16	5	12
Total benign tumors	18	5	15
Total animals with malignant tumors	25	18	19
Total malignant tumors	26	22	19
Total animals with secondary tumors##	1	1	2
Total secondary tumors	1	1	3
Total animals with tumors uncertain--benign or malignant			1
Total uncertain tumors			1
Total animals with tumors uncertain--primary or metastatic	1		
Total uncertain tumors	1		

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

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

ANIMAL NUMBER	0032	0042	0048	0030	0007	0045	0006	0043	0017	0027	0049	0026	0005	0015	0021	0040	0028	0029	0001	0002	0003	0004	0008	0009	0010
WEEKS ON STUDY	003	016	016	019	021	021	023	024	030	059	069	072	084	084	087	094	097	097	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+
Fibroma															X										
Fibrosarcoma																									
Rhabdomyosarcoma																X									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																							X		
Alveolar/bronchiolar carcinoma																									X
Cortical carcinoma, metastatic															X										
Fibrosarcoma, metastatic												X													
Trachea	+	+	+	−	−	+	+	+	−	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	−	+	+	−	+	−	−	+	−	+	−	+	+	+	−	−	+	+	−	+	−	+	−	+	−
Thymus	+	+	+	+	+	+	+	+	+	−	+	−	−	−	−	−	−	−	−	−	+	+	−	+	−
Malignant lymphoma, lymphocytic type																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma, metastatic																							X		
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma													X	X	X		X								
Fibrosarcoma, metastatic												X													
Hemangiosarcoma																							X		
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	N	N	N	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																								X	
Esophagus	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	−	−	+	+	−	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Large intestine	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	+	−	+	−	+	−	+	+	−	+	+	+	+	+	−	−	+	−	+	+	+	−	+	+
Adrenal	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical carcinoma															X										
Pheochromocytoma														X											
Thyroid	−	−	+	−	−	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+
Follicular cell adenoma																							X		
Parathyroid	−	−	+	−	−	+	+	+	−	−	−	−	+	−	+	−	−	−	+	−	−	−	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	−	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Muscle	N	+	+	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma, unclear primary or metastatic												X													
BODY CAVITIES																									
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, lymphocytic type																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, lymphocytic type																									
Malignant lymphoma, histiocytic type																									

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

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

ANIMAL NUMBER	0111	0112	0113	0114	0116	0118	0119	0120	0122	0123	0124	0125	0131	0133	0134	0135	0136	0137	0138	0139	0141	0144	0146	0147	0150	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										1
Fibrosarcoma							X											X								2
Rhabdomyosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma					X							X						X						X		5
Cortical carcinoma, metastatic																										1
Fibrosarcoma, metastatic																										1
Trachea	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	−	+	+	+	+	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	−	+	−	−	−	+	−	−	−	+	−	+	−	+	−	−	−	+	+	−	+	+	+	−	24
Thymus	+	−	+	+	+	−	+	+	+	+	−	−	+	−	−	−	+	−	+	+	+	+	+	−	−	28
Malig. lymphoma, lymphocytic type																							X			1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma		X																								1
Hemangiosarcoma, metastatic																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X										X								X							3
Hepatocellular carcinoma																	X							X		6
Fibrosarcoma, metastatic																										1
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	47
Hemangioma																										1
Esophagus	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Malignant lymphoma, mixed type																							X			1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cortical carcinoma																										1
Pheochromocytoma		X															X									3
Thyroid	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	42
Follicular cell adenoma															X										X	3
Parathyroid	+	+	+	+	+	−	+	+	−	+	+	+	+	+	−	+	−	+	−	+	+	+	+	−	+	29
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma, unclear prim or meta																										1
BODY CAVITIES																										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malig. lymphoma, lymphocytic type																		X								1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malig. lymphoma, lymphocytic type															X											1
Malignant lymphoma, histiocytic type							X																			1

* Animals necropsied

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

ANIMAL NUMBER	0018	0007	0424	0346	0448	0489	0335	0332	0006	0008	0449	0512	0623	0033	0137	0211	0055	0433	0550	0616	0199	0628	0444	0155	0411
WEEKS ON STUDY	000	000	011	019	029	029	033	034	035	039	040	056	061	077	081	085	088	089	094	096	096	096	098	099	100
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	M	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS														X											
Fibroma																									
Fibrosarcoma															X		X	X						X	
Fibrosarcoma, unclear primary or metastatic															X										
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																						X			X
Alveolar/bronchiolar carcinoma																			X						
Trachea	+	M	−	−	−	−	−	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Spleen	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Lymph nodes	+	M	+	+	+	+	+	−	−	−	−	−	+	−	+	+	−	−	−	−	+	−	+	−	+
Thymus	+	M	−	+	+	+	+	+	+	−	−	+	+	−	−	+	−	−	−	−	−	−	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Liver	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma																									
Fibrosarcoma, metastatic																	X								
Hemangiosarcoma																									
Bile duct	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	M	+	N	+	+	N	N	+	+	N	N	+	+	+	N	+	+	+	N	+	+	N	N	N
Pancreas	+	M	−	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	−
Esophagus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	M	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−
Large intestine	−	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	M	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	M	−	+	+	−	−	+	−	−	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+
Adrenal	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	M	+	+	−	−	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	−	M	−	−	−	−	−	+	−	−	−	−	+	−	−	+	+	−	−	−	+	+	+	+	+
Pancreatic islets	+	M	−	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	−
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	M	+	+	+	+	+	+	+	+	−	+	+	−	+	+	−	+	+	+	−	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary adenoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma, metastatic																		X							
Malignant lymphoma, lymphocytic type																									

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

ANIMAL NUMBER	004	026	027	030	001	002	009	010	011	014	017	020	022	024	025	029	031	033	036	037	038	039	040	045	047	TOTAL:
WEEKS ON STUDY	101	101	101	102	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Sarcoma, NOS																										1
Fibroma						X																				1
Fibrosarcoma		X				X																	X			7
Fibrosarcoma, unclear prim or meta																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																							X			3
Alveolar/bronchiolar carcinoma												X					X									3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	47
Spleen	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph nodes	−	+	−	+	+	−	+	+	+	+	−	−	−	−	+	+	−	+	+	−	+	+	−	+	+	27
Thymus	−	−	−	−	−	+	+	−	−	+	−	−	+	+	−	−	+	+	+	+	−	+	+	−	+	22
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular adenoma									X									X								2
Hepatocellular carcinoma			X																					X		2
Fibrosarcoma, metastatic																										1
Hemangiosarcoma																			X							1
Bile duct	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder & common bile duct	N	N	+	+	+	+	+	N	N	+	+	+	+	+	+	N	+	+	+	+	+	N	N	+	N	*49
Pancreas	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Esophagus	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Large intestine	−	−	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	43
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
ENDOCRINE SYSTEM																										
Pituitary	−	−	−	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	37
Adrenal	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma							X																			1
Thyroid	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Follicular cell adenoma												X														1
Parathyroid	−	−	−	−	+	+	+	−	−	−	+	−	+	−	+	+	+	+	−	+	−	+	+	+	+	23
Pancreatic islets	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Islet cell adenoma																							X			1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	−	+	−	−	+	+	+	40
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Papillary adenoma																			X							1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Fibrosarcoma, metastatic																										1
Malig. lymphoma, lymphocytic type																					X	X				2

* Animals necropsied

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

ANIMAL NUMBER	0 3 1	0 0 1	0 4 5	0 0 5	0 0 3	0 4 2	0 1 9	0 3 4	0 3 9	0 2 1	0 0 6	0 2 4	0 0 4	0 2 7	0 3 2	0 3 3	0 4 1	0 5 0	0 1 1	0 2 2	0 2 9	0 3 8	0 1 6	0 4 7	0 2 3
WEEKS ON STUDY	0 0 4	0 0 9	0 1 0	0 1 1	0 1 2	0 2 5	0 2 6	0 2 6	0 3 5	0 3 8	0 4 2	0 4 5	0 5 6	0 6 9	0 7 2	0 7 2	0 7 3	0 8 0	0 8 3	0 8 4	0 8 7	0 8 8	0 9 7	0 9 7	0 9 8
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	N	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N
Fibrosarcoma														X				X@						X	
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																					X				
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Trachea	−	+	+	+	−	−	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, lymphocytic type																									
Malignant lymphoma, mixed type																									
Lymph nodes	−	−	−	−	−	+	−	+	−	−	+	−	−	+	+	−	−	+	−	−	−	−	+	−	+
Thymus	+	+	−	+	+	+	+	+	+	+	−	−	−	+	+	+	−	−	+	−	−	−	+	−	+
CIRCULATORY SYSTEM																									
Heart	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma																					X		X		
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	N	+	+	+	+	+	N	+	N	+	+	N	+	+	+	+	+	N	N	+	+	+	N
Pancreas	+	+	+	−	+	−	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+
Esophagus	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	−	+	−
Large intestine	−	+	+	+	−	−	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	−	+	+	+	−	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	−
Adrenal	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Adenoma, NOS																									
Thyroid	−	+	+	−	+	−	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	−	−	+
Follicular cell adenoma																									
Parathyroid	−	−	−	−	+	−	−	+	−	−	−	+	−	+	+	−	+	−	−	+	−	+	−	−	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N
Testis	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary adenoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS																			X						X
Malignant lymphoma, lymphocytic type																							X		

@ Multiple occurrence of morphology

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

ANIMAL NUMBER	013	020	012	048	049	002	007	008	009	010	014	015	017	018	025	026	028	030	035	036	037	040	043	044	046	TOTAL:
WEEKS ON STUDY	099	101	102	102	102	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	M	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	*49
Fibrosarcoma																	X						X			5
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	M	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma																					X					1
Alveolar/bronchiolar carcinoma																	X	X								2
Trachea	+	M	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	M	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	47
Spleen	+	M	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Malig. lymphoma, lymphocytic type																						X				1
Malignant lymphoma, mixed type															X											1
Lymph nodes	+	M	–	–	–	–	+	–	+	+	+	+	+	+	+	+	–	+	+	–	+	+	–	–	+	23
Thymus	–	M	–	–	–	–	–	+	+	+	–	–	–	+	–	–	+	–	–	+	+	–	–	+	+	24
CIRCULATORY SYSTEM																										
Heart	+	M	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	47
DIGESTIVE SYSTEM																										
Salivary gland	+	M	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	M	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Hepatocellular adenoma						X												X		X						3
Hepatocellular carcinoma							X									X										4
Bile duct	+	M	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Gallbladder & common bile duct	N	M	N	N	N	+	+	+	N	+	N	+	N	+	N	N	+	+	+	+	+	+	+	N	+	*49
Pancreas	+	M	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Esophagus	+	M	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	44
Stomach	+	M	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Small intestine	–	M	–	–	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Large intestine	+	M	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	39
URINARY SYSTEM																										
Kidney	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	–	M	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
ENDOCRINE SYSTEM																										
Pituitary	+	M	–	–	–	+	+	–	+	+	+	+	+	+	–	+	–	–	–	–	+	+	+	+	–	33
Adrenal	+	M	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma, NOS																				X						1
Thyroid	+	M	–	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Follicular cell adenoma																			X							1
Parathyroid	+	M	–	+	–	+	+	+	+	–	+	–	+	+	+	–	+	+	–	+	+	+	+	+	+	27
REPRODUCTIVE SYSTEM																										
Mammary gland	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Testis	+	M	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	46
Prostate	+	M	–	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	42
NERVOUS SYSTEM																										
Brain	+	M	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SPECIAL SENSE ORGANS																										
Harderian gland	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Papillary adenoma															X											1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Malignant lymphoma, NOS																										2
Malig. lymphoma, lymphocytic type																										1

* Animals necropsied

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

ANIMAL NUMBER	0272	0455	0466	0222	0122	0144	0422	0300	0477	0311	0155	0199	0443	0381	0001	0411	0002	0003	0004	0005	0006	0007	0008	0009	0010
WEEKS ON STUDY	0111	0555	0683	0666	0778	0822	0888	0901	0933	0994	0995	0999	0999	1011	1022	1022	1044	1044	1044	1044	1044	1044	1044	1044	1044
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS															X										
Fibrosarcoma																									
Hemangioma														X											
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Trachea	+	–	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma														X											
Malignant lymphoma, lymphocytic type																								X	
Lymph nodes	+	+	–	+	+	+	+	–	–	–	–	–	+	+	–	+	+	–	–	+	+	+	+	+	+
Thymus	+	+	–	+	+	+	+	–	+	–	+	–	–	–	–	–	+	+	+	+	–	–	+	–	+
Malignant lymphoma, lymphocytic type																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	N	+	N	+	+	N	N	+	N	N	+	N	+	+	+	+	+	N	N	+	N	+
Pancreas	+	+	+	–	+	+	+	–	+	–	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	–	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	–	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	–	+	–	–	–	–	–	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	–	+	–	+	–	–	–	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS																		X					X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+
Adenoma, NOS																									
Pheochromocytoma																					X				
Thyroid	–	–	+	+	+	+	+	–	–	–	+	–	+	+	–	+	+	+	+	+	+	+	–	+	+
Follicular cell adenoma																								X	
Parathyroid	–	–	+	–	–	+	–	–	–	–	–	–	–	+	–	–	+	–	+	–	–	–	–	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	N	N	N	+	N	N	N	N	N	+	+	N	+	N	+	+	+	N	+	+	N	N
Adenocarcinoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	–	+	+	+	+	+	–	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+
Teratoma, benign	X																								
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																									
Meningioma																									
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary cystadenoma, NOS																									
BODY CAVITIES																									
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Lipoma																X									
Malignant lymphoma, NOS											X														
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS, unclear primary or metastatic					X																				
Malignant lymphoma, undiffer type																									
Malignant lymphoma, lymphocytic type																					X	X	X		X
Malignant lymphoma, histiocytic type						X																			
Malignant lymphoma, mixed type																									
Lymphocytic 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 B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0111	0113	0116	0117	0118	0200	0201	0203	0204	0205	0206	0208	0209	0302	0303	0304	0305	0306	0307	0309	0400	0404	0408	0409	0500	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES / TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibrosarcoma												X														1
Hemangioma		X																								2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X																							1
Alveolar/bronchiolar carcinoma															X											1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	45
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																										1
Malig. lymphoma, lymphocytic type																										1
Lymph nodes	+	+	+	+	+	–	–	+	–	+	–	+	+	+	+	+	–	–	–	+	–	+	–	+	+	32
Thymus	–	–	+	+	+	+	–	+	+	–	–	–	–	–	–	+	+	+	–	+	+	+	–	+	–	27
Malig. lymphoma, lymphocytic type																				X						1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	N	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Small intestine	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Large intestine	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, NOS						X																				1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	–	–	–	+	+	+	+	+	–	+	+	+	+	–	+	+	44
Carcinoma, NOS			X																							1
Adenoma, NOS						X							X			X								X	X	7
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	47
Adenoma, NOS																				X						1
Pheochromocytoma																									X	2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Follicular cell adenoma																										1
Parathyroid	+	+	+	+	+	+	–	–	–	+	+	+	–	+	+	–	+	+	+	–	–	+	–	+	+	24
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	+	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	+	+	N	N	N	*50
Adenocarcinoma, NOS																						X				1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Teratoma, benign																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive			X																							1
Meningioma	X																									1
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papillary cystadenoma, NOS									X																	1
BODY CAVITIES																										
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Lipoma																										1
Malignant lymphoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS, unclear prim or meta																										1
Malig. lymphoma, undiffer type																						X				1
Malig. lymphoma, lymphocytic type		X			X				X					X		X					X		X		X	12
Malig. lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type				X																						1
Lymphocytic leukemia																										1

* Animals necropsied

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

ANIMAL NUMBER	01 18	02 21	03 30	03 34	02 20	00 11	01 17	03 32	00 02	03 35	04 40	02 26	00 08	03 38	01 19	02 27	04 11	01 16	01 11	02 22	03 31	03 37	00 03	00 04	00 05
WEEKS ON STUDY	07 76	07 77	07 77	08 80	08 83	08 85	08 85	08 85	08 87	08 88	08 89	09 90	09 92	09 92	09 95	09 95	09 95	09 96	09 97	09 99	09 99	10 02	10 04	10 04	10 04
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																						X			
Hemangiosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma									X																
Fibrosarcoma, metastatic																						X			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	−	+	+	+	+	−	+	+	−	+	−	+	+	+	+	+	−	−	+	+	+	−
Thymus	+	−	+	−	−	+	+	+	+	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	+
Malignant lymphoma, lymphocytic type																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	+	N	+	N	+	+	+	N	N	N	+	N	N	+	N	+	+	+	N	+	N	+
Pancreas	−	+	+	+	+	+	+	+	+	−	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	−	+	+	+	+
Carcinoma, NOS																									
Large intestine	+	+	+	+	+	−	+	+	+	+	−	+	−	−	+	−	+	+	+	+	−	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	−	+	+	−	+	+	+	+	+	+	−	−	−	+	+	+	+	+	−	+	−	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	−	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS																									
Acidophil adenoma																									
Adrenal	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	+	−	−	−	−	−	+	+	+	−	+	+	+	−	+	−	+	−	+	−	−	+	+	−	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	N	+	+	N	N	N	+	N	+	N	N	N	N	+	N	N	N	N	N	N	N	+	N
Adenocarcinoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	−	−	+	+	+	−	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+
Papillary cystadenoma, NOS																									
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											
Malignant lymphoma, lymphocytic type																	X	X		X			X		
Malignant lymphoma, mixed type																									

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

ANIMAL NUMBER	0006	0007	0009	0110	0112	0113	0114	0115	0223	0224	0225	0228	0229	0233	0236	0239	0242	0243	0244	0245	0246	0247	0248	0249	0250	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	*50
Squamous cell carcinoma																							X			1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	*50
Fibrosarcoma																										1
Hemangiosarcoma														X												1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																X							X			3
Fibrosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	50
Lymph nodes	+	−	+	−	−	−	−	+	+	+	+	+	−	+	+	+	+	+	+	−	−	+	+	+	+	37
Thymus	+	+	+	+	−	+	−	+	+	+	−	+	+	+	+	−	+	−	−	−	+	+	+	+	−	26
Malig. lymphoma, lymphocytic type				X													X									2
CIRCULATORY SYSTEM																										
Heart	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	N	+	+	+	N	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Esophagus	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma																	X									1
Small intestine	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma, NOS	X																									1
Large intestine	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	42
ENDOCRINE SYSTEM																										
Pituitary	−	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	40
Carcinoma, NOS																			X							1
Adenoma, NOS												X														1
Acidophil adenoma													X													1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma															X											1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular cell adenoma																								X		1
Parathyroid	+	+	+	+	+	−	+	+	−	+	−	−	+	+	+	+	−	+	+	+	+	+	+	+	+	32
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	+	+	N	+	N	+	N	N	+	N	N	+	+	N	+	+	N	N	+	N	+	N	N	*50
Adenocarcinoma, NOS						X																				1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+		43
Papillary cystadenoma, NOS						X																				1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS																										1
Malig. lymphoma, lymphocytic type															X								X			6
Malignant lymphoma, mixed type								X			X								X							3

* Animals necropsied

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

ANIMAL NUMBER	0049	0006	0008	0009	0110	0311	0332	0333	0334	0335	0340	0002	0117	0220	0228	0444	0114	0119	0224	0550	0433	0446	0001	0003	0004
WEEKS ON STUDY	0381	0334	0334	0334	0334	0334	0334	0334	0334	0334	0747	0777	0887	0888	0899	0992	0994	0994	0996	0996	0997	0997	1004	1004	1004
INTEGUMENTARY SYSTEM																									
Skin	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS																									
Subcutaneous tissue	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																X									
Fibrosarcoma																				X					
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X											X		
Sarcoma, NOS, metastatic																X									
Trachea	−	+	+	−	−	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																			X						
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, lymphocytic type																									
Lymph nodes	+	−	−	+	+	−	+	−	−	+	−	−	−	+	+	+	+	+	+	+	+	+	−	+	−
Sarcoma, NOS, metastatic																X									
Thymus	−	+	−	−	−	−	+	−	+	+	+	+	+	−	−	−	−	+	−	−	+	+	+	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, lymphocytic type																									X
Bile duct	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	N	N	N	N	N	N	+	N	+	+	N	N	+	+	+	N	+	+	+	+	+	+	N
Pancreas	+	+	+	+	+	−	+	−	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+
Esophagus	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Small intestine	−	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	−	−	+	−	+	−	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	−	+	+	+	−	−	+	+	−	+	+	−	+	−	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	−	−	+	+	+	+	−	−	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS																									
Adrenal	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+
Adenoma, NOS																									
Thyroid	+	−	−	−	−	+	+	−	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	+	−	−	−	−	+	+	−	−	−	+	+	−	−	−	−	−	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	N	N	+	N	N	N	N	N	N	N	+	+	N	+	N	N	N	N	N	+	N	N
Uterus	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Leiomyoma																									
Endometrial stromal polyp																									
Ovary	+	+	+	+	+	+	+	−	+	−	+	+	−	−	+	+	+	−	+	+	+	+	+	+	+
Granulosa cell tumor																									X
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS, metastatic																									
Malignant lymphoma, lymphocytic type																					X				
Malignant lymphoma, histiocytic type																									
Malignant lymphoma, mixed type															X										
Lymphocytic leukemia																						X			

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

ANIMAL NUMBER	00 05	00 07	01 11	01 12	01 13	01 15	01 16	01 18	02 21	02 22	02 23	02 25	02 26	02 27	02 29	03 00	03 06	03 37	03 38	03 39	04 41	04 42	04 45	04 47	04 48	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Papilloma, NOS																						X				1
Subcutaneous tissue	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma									X					X												4
Sarcoma, NOS, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	49
Hemangioma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malig. lymphoma, lymphocytic type																								X		1
Lymph nodes	−	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Sarcoma, NOS, metastatic																										1
Thymus	+	+	+	+	−	+	+	+	+	−	+	−	−	+	+	+	+	−	+	+	+	+	+	−	−	30
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malig. lymphoma, lymphocytic type																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	N	N	N	N	+	N	N	N	+	+	+	+	+	N	N	+	N	+	+	+	+	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	45
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	43
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	−	−	+	−	+	+	+	+	+	+	+	−	+	+	−	+	−	+	+	−	−	36
Carcinoma, NOS							X																			1
Adenoma, NOS									X	X			X									X	X			5
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS																									X	1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Follicular cell adenoma				X																						1
Parathyroid	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	34
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	N	+	N	+	N	N	+	+	N	+	+	+	N	N	N	+	N	+	N	N	+	N	N	*50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leiomyoma																					X					1
Endometrial stromal polyp																									X	1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Granulosa cell tumor																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenocarcinoma, NOS					X																					1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenocarcinoma, NOS, metastatic					X																					1
Malig. lymphoma, lymphocytic type	X		X			X		X				X	X			X				X						9
Malig. lymphoma, histiocytic type														X												1
Malignant lymphoma, mixed type																						X				2
Lymphocytic leukemia																										1

* Animals necropsied

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF AMPICILLIN TRIHYDRATE

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF AMPICILLIN TRIHYDRATE

	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)
Hemorrhage	1 (2%)		
Inflammation, acute focal	1 (2%)		
Inflammation, chronic focal			1 (2%)
Hyperplasia, epithelial	1 (2%)	1 (2%)	
Hyperkeratosis	1 (2%)	3 (6%)	
Acanthosis	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Steatitis		1 (2%)	
Inflammation, acute focal	1 (2%)		
Inflammation, chronic focal			2 (4%)
RESPIRATORY SYSTEM			
#Trachea	(50)	(46)	(50)
Inflammation, acute diffuse	1 (2%)		
Inflammation, chronic focal			1 (2%)
#Tracheal gland	(50)	(46)	(50)
Dilatation, NOS	1 (2%)	2 (4%)	1 (2%)
Hyperplasia, focal	1 (2%)		
#Lung	(50)	(49)	(50)
Foreign body, NOS	2 (4%)		2 (4%)
Vegetable foreign body	1 (2%)		1 (2%)
Congestion, acute passive	5 (10%)	4 (8%)	5 (10%)
Edema, NOS	2 (4%)	1 (2%)	
Hemorrhage	4 (8%)	4 (8%)	1 (2%)
Lymphocytic inflammatory infiltrate	2 (4%)	1 (2%)	
Inflammation, multifocal	1 (2%)		
Inflammation, acute necrotizing	2 (4%)		
Inflammation, chronic focal	7 (14%)	4 (8%)	9 (18%)
Inflammation, granulomatous	1 (2%)		
Inflammation, granulomatous focal	18 (36%)	5 (10%)	1 (2%)
Inflammation, pyogranulomatous		1 (2%)	
Foreign material, NOS			1 (2%)
Hyperplasia, alveolar epithelium	2 (4%)	1 (2%)	2 (4%)
Histiocytosis	5 (10%)		2 (4%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(48)	(50)
Hemorrhage	1 (2%)	1 (2%)	
Necrosis, focal	1 (2%)		
Necrosis, diffuse		1 (2%)	
Hyperplasia, focal		1 (2%)	
Myelofibrosis	1 (2%)	2 (4%)	1 (2%)
Hyperplasia, hematopoietic	7 (14%)	16 (33%)	17 (34%)
#Spleen	(50)	(49)	(49)
Hemorrhage	1 (2%)		
Amyloidosis	1 (2%)	1 (2%)	
Hemosiderosis	4 (8%)	4 (8%)	2 (4%)
Depletion, lymphoid		2 (4%)	
Lipomatosis	1 (2%)		
Hyperplasia, hematopoietic			1 (2%)
Hyperplasia, lymphoid	2 (4%)		1 (2%)
Hematopoiesis	4 (8%)	2 (4%)	2 (4%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Splenic capsule	(50)	(49)	(49)
Fibrosis, multifocal			1 (2%)
#Splenic follicles	(50)	(49)	(49)
Necrosis, focal	1 (2%)		
#Lymph node	(45)	(42)	(38)
Hemorrhage		1 (2%)	
#Mandibular lymph node	(45)	(42)	(38)
Cyst, NOS		1 (2%)	
Edema, NOS			1 (3%)
Inflammation, chronic focal			1 (3%)
Necrosis, focal	1 (2%)		
Histiocytosis	1 (2%)		1 (3%)
Plasmacytosis	8 (18%)	6 (14%)	6 (16%)
Erythrophagocytosis			1 (3%)
Hyperplasia, plasma cell	2 (4%)		
Hyperplasia, lymphoid	3 (7%)	5 (12%)	3 (8%)
#Bronchial lymph node	(45)	(42)	(38)
Edema, NOS			1 (3%)
Histiocytosis			1 (3%)
#Pancreatic lymph node	(45)	(42)	(38)
Edema, NOS			1 (3%)
Hemorrhage		1 (2%)	
#Renal lymph node	(45)	(42)	(38)
Dilatation/sinus			1 (3%)
Hemorrhage		1 (2%)	
Erythrophagocytosis		1 (2%)	
Hyperplasia, lymphoid			1 (3%)
#Thymic lymph node	(45)	(42)	(38)
Cyst, NOS			1 (3%)
Congestion, acute passive			1 (3%)
Hemorrhage	4 (9%)	5 (12%)	1 (3%)
Hemosiderosis			1 (3%)
Histiocytosis	1 (2%)		1 (3%)
Plasmacytosis	3 (7%)		
Erythrophagocytosis	2 (4%)	2 (5%)	1 (3%)
Hyperplasia, lymphoid		1 (2%)	
#Liver	(50)	(49)	(50)
Hematopoiesis	1 (2%)	3 (6%)	1 (2%)
#Colon	(39)	(38)	(36)
Hyperplasia, lymphoid		1 (3%)	
#Adrenal	(50)	(50)	(49)
Hematopoiesis		1 (2%)	
#Thymus	(38)	(32)	(38)
Cyst, NOS	1 (3%)		
Congestion, acute passive	1 (3%)		
Hemorrhage	4 (11%)	1 (3%)	3 (8%)
Hyperplasia, epithelial	4 (11%)	3 (9%)	4 (11%)
CIRCULATORY SYSTEM			
#Left atrium	(50)	(49)	(50)
Thrombus, organized		1 (2%)	
#Left ventricle	(50)	(49)	(50)
Inflammation, focal	1 (2%)		
Hyperplasia, focal		1 (2%)	1 (2%)
#Myocardium	(50)	(49)	(50)
Degeneration, NOS	41 (82%)	45 (92%)	40 (80%)
*Testicular artery	(50)	(50)	(50)
Inflammation, chronic diffuse			1 (2%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#Salivary gland	(49)	(46)	(46)
Dilatation/ducts	1 (2%)		1 (2%)
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, acute/chronic			1 (2%)
Inflammation, chronic focal	3 (6%)	4 (9%)	5 (11%)
Inflammation, chronic diffuse	2 (4%)	1 (2%)	2 (4%)
Fibrosis, multifocal	2 (4%)		
Cytoplasmic vacuolization			1 (2%)
Atrophy, focal		1 (2%)	
Hyperplasia, focal	2 (4%)	2 (4%)	2 (4%)
Hyperplasia, diffuse			1 (2%)
Metaplasia, NOS	7 (14%)	4 (9%)	6 (13%)
#Salivary mucous gland	(49)	(46)	(46)
Inflammation, chronic focal		1 (2%)	
Metaplasia, NOS		1 (2%)	
#Parotid gland	(49)	(46)	(46)
Inflammation, chronic focal	1 (2%)		
Fibrosis, multifocal		1 (2%)	
Atrophy, focal	2 (4%)		
#Liver	(50)	(49)	(50)
Cyst, NOS	1 (2%)		
Congestion, acute passive	3 (6%)		2 (4%)
Congestion, chronic passive	1 (2%)		
Inflammation, acute/chronic			1 (2%)
Inflammation, granulomatous focal	1 (2%)	5 (10%)	5 (10%)
Fibrosis, multifocal			1 (2%)
Necrosis, coagulative		3 (6%)	
Amyloidosis			1 (2%)
Cholesterol deposit			1 (2%)
Basophilic cyto change	36 (72%)	34 (69%)	23 (46%)
Eosinophilic cyto change	1 (2%)		
Clear cell change	14 (28%)	12 (24%)	10 (20%)
Cell size alteration	1 (2%)		1 (2%)
#Liver/hepatocytes	(50)	(49)	(50)
Cytoplasmic vacuolization	2 (4%)	5 (10%)	10 (20%)
Hyperplasia, focal			1 (2%)
#Bile duct	(50)	(49)	(50)
Fibrosis, focal		4 (8%)	
Hyperplasia, focal	35 (70%)	24 (49%)	18 (36%)
#Pancreas	(47)	(45)	(49)
Hemorrhage	1 (2%)		
#Pancreatic duct	(47)	(45)	(49)
Inflammation, chronic focal		1 (2%)	
Hyperplasia, focal			1 (2%)
#Pancreatic acinus	(47)	(45)	(49)
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, chronic focal	4 (9%)	5 (11%)	3 (6%)
Inflammation, chronic diffuse	1 (2%)		
Atrophy, focal	9 (19%)	15 (33%)	13 (27%)
Atrophy, diffuse	2 (4%)		
Hyperplasia, focal		1 (2%)	
#Peripancreatic tissue	(47)	(45)	(49)
Inflammation, acute/chronic		1 (2%)	
#Esophagus	(50)	(48)	(49)
Vegetable foreign body			1 (2%)
Inflammation, acute/chronic		1 (2%)	
Hyperkeratosis		1 (2%)	

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Stomach	(48)	(44)	(45)
Ulcer, NOS	1 (2%)	1 (2%)	
Inflammation, chronic focal		1 (2%)	2 (4%)
Infection, fungal			1 (2%)
#Gastric submucosa	(48)	(44)	(45)
Fibrosis, diffuse		1 (2%)	
#Gastric muscularis	(48)	(44)	(45)
Inflammation, acute/chronic			1 (2%)
#Gastric serosa	(48)	(44)	(45)
Inflammation, focal			1 (2%)
Inflammation, chronic focal		1 (2%)	
#Cardiac stomach	(48)	(44)	(45)
Ulcer, NOS		1 (2%)	1 (2%)
Inflammation, acute focal		1 (2%)	2 (4%)
Inflammation, acute/chronic			2 (4%)
Inflammation, chronic focal	2 (4%)	1 (2%)	1 (2%)
Erosion			1 (2%)
Necrosis, focal	1 (2%)		
Hyperplasia, epithelial	3 (6%)	3 (7%)	7 (16%)
Hyperplasia, diffuse			1 (2%)
Hyperkeratosis	3 (6%)	6 (14%)	9 (20%)
Acanthosis		2 (5%)	5 (11%)
#Colon	(39)	(38)	(36)
Dilatation, NOS		1 (3%)	
Parasitism	4 (10%)	4 (11%)	1 (3%)
Hyperplasia, diffuse		1 (3%)	
#Cecum	(39)	(38)	(36)
Edema, NOS		1 (3%)	
*Rectum	(50)	(50)	(50)
Hyperplasia, diffuse			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(48)	(48)
Hydronephrosis		1 (2%)	
Cyst, NOS		2 (4%)	2 (4%)
Hemorrhage		1 (2%)	1 (2%)
Glomerulonephritis, NOS	1 (2%)		
Lymphocytic inflammatory infiltrate			4 (8%)
Pyelonephritis, acute		1 (2%)	2 (4%)
Inflammation, chronic focal			1 (2%)
Nephropathy	41 (82%)	40 (83%)	43 (90%)
Nephrosis, NOS	1 (2%)		
Infarct, focal			1 (2%)
#Perirenal tissue	(50)	(48)	(48)
Hemorrhage		1 (2%)	
Inflammation, chronic focal		1 (2%)	
#Kidney/tubule	(50)	(48)	(48)
Cast, NOS	1 (2%)		
#Kidney/pelvis	(50)	(48)	(48)
Inflammation, acute focal			1 (2%)
Hyperplasia, epithelial	1 (2%)	1 (2%)	
#Urinary bladder	(47)	(44)	(46)
Cast, NOS	4 (9%)	1 (2%)	1 (2%)
Hemorrhage	1 (2%)	1 (2%)	
Inflammation, acute focal		1 (2%)	
Inflammation, acute diffuse			1 (2%)
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic focal	2 (4%)		
Inflammation with fibrosis	1 (2%)		
Hyperplasia, epithelial		2 (5%)	
Hyperplasia, diffuse			1 (2%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM (Continued)			
#Urinary bladder/mucosa	(47)	(44)	(46)
Erosion		2 (5%)	1 (2%)
Hyperplasia, epithelial		1 (2%)	
#Urinary bladder/serosa	(47)	(44)	(46)
Erosion		1 (2%)	
*Prostatic urethra	(50)	(50)	(50)
Cast, NOS	8 (16%)	4 (8%)	10 (20%)
Inflammation, acute		1 (2%)	1 (2%)
Erosion	1 (2%)		
Hyperplasia, epithelial			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(46)	(49)	(46)
Cyst, NOS	3 (7%)	2 (4%)	1 (2%)
Multiple cysts		2 (4%)	
Hemorrhage	2 (4%)		2 (4%)
Hemorrhage, chronic		1 (2%)	
Necrosis, focal	1 (2%)		
Hyperplasia, focal	4 (9%)	5 (10%)	10 (22%)
#Adrenal	(50)	(50)	(49)
Atypia, NOS		1 (2%)	
Hyperplasia, focal			1 (2%)
#Adrenal cortex	(50)	(50)	(49)
Accessory structure		1 (2%)	2 (4%)
Hemorrhagic cyst	1 (2%)	1 (2%)	
Degeneration, lipoid			1 (2%)
Cytoplasmic vacuolization	2 (4%)	2 (4%)	2 (4%)
Focal cellular change	1 (2%)	5 (10%)	7 (14%)
Atypia, NOS			1 (2%)
Hypertrophy, focal			2 (4%)
Hyperplasia, focal	1 (2%)	2 (4%)	5 (10%)
#Adrenal medulla	(50)	(50)	(49)
Hemorrhage			1 (2%)
Hemorrhagic cyst	1 (2%)		
Focal cellular change	1 (2%)		
Hyperplasia, focal	14 (28%)	10 (20%)	8 (16%)
#Thyroid	(50)	(48)	(46)
Follicular cyst, NOS	1 (2%)		
Hemorrhage, chronic			1 (2%)
Hyperplasia, C-cell	4 (8%)	11 (23%)	7 (15%)
Hyperplasia, follicular cell			1 (2%)
#Pancreatic islets	(47)	(45)	(49)
Hyperplasia, focal	3 (6%)	5 (11%)	2 (4%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Hyperplasia, focal	3 (6%)	5 (10%)	2 (4%)
Hyperplasia, diffuse		1 (2%)	
Hyperplasia, cystic	1 (2%)	5 (10%)	2 (4%)
*Preputial gland	(50)	(50)	(50)
Abscess, NOS	1 (2%)		
Inflammation, acute/chronic		1 (2%)	1 (2%)
Hyperkeratosis			1 (2%)
#Prostate	(49)	(48)	(47)
Hemorrhage	1 (2%)		
Inflammation, acute focal	4 (8%)	1 (2%)	2 (4%)
Inflammation, acute diffuse		1 (2%)	

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
#Prostate (Continued)	(49)	(48)	(47)
Abscess, NOS		1 (2%)	1 (2%)
Inflammation, active chronic		1 (2%)	
Inflammation, acute/chronic	12 (24%)	16 (33%)	28 (60%)
Inflammation, chronic focal	5 (10%)	8 (17%)	5 (11%)
Inflammation, granulomatous focal			1 (2%)
Inflammation with fibrosis	1 (2%)		
Hyperplasia, focal	2 (4%)		3 (6%)
*Seminal vesicle	(50)	(50)	(50)
Cast, NOS	2 (4%)		
Atrophy, NOS	2 (4%)	3 (6%)	1 (2%)
Hyperplasia, diffuse			1 (2%)
#Periprostatic tissue	(49)	(48)	(47)
Inflammation, acute/chronic	1 (2%)		
#Testis	(50)	(49)	(50)
Degeneration, NOS			1 (2%)
Atrophy, NOS	3 (6%)	3 (6%)	3 (6%)
Atrophy, diffuse			1 (2%)
Hyperplasia, interstitial cell	20 (40%)	14 (29%)	20 (40%)
#Testis/tubule	(50)	(49)	(50)
Atrophy, diffuse			1 (2%)
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Inflammation, chronic focal		1 (2%)	
#Brain	(50)	(50)	(50)
Hydrocephalus, NOS	1 (2%)	2 (4%)	
Hemorrhage	2 (4%)	1 (2%)	3 (6%)
#Brain/thalamus	(50)	(50)	(50)
Malacia			1 (2%)
Atrophy, pressure	2 (4%)	2 (4%)	1 (2%)
#Cerebellum	(50)	(50)	(50)
Malacia	1 (2%)		1 (2%)
*Spinal nerve	(50)	(50)	(50)
Degeneration, Wallerian		1 (2%)	
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Hemorrhage	10 (20%)		
Hemorrhage, chronic	7 (14%)		
Inflammation, acute diffuse	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
Synechia, anterior	1 (2%)		
Synechia, posterior	13 (26%)		
Cataract	6 (12%)		
*Eye/retina	(50)	(50)	(50)
Degeneration, NOS	17 (34%)		
*Eye/crystalline lens	(50)	(50)	(50)
Cataract	9 (18%)	1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Skull	(50)	(50)	(50)
Osteosclerosis		1 (2%)	
*Skeletal muscle	(50)	(50)	(50)
Hemorrhage	1 (2%)		

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Foreign body, NOS	1 (2%)		
Vegetable foreign body	1 (2%)		1 (2%)
Hemorrhage	2 (4%)	1 (2%)	1 (2%)
Inflammation, acute focal	2 (4%)		
Inflammation, granulomatous focal	1 (2%)		
*Abdominal cavity	(50)	(50)	(50)
Hemorrhage		1 (2%)	
Inflammation, acute focal			1 (2%)
*Mesentery	(50)	(50)	(50)
Mineralization		1 (2%)	
Hemorrhage	1 (2%)		
Inflammation, diffuse		1 (2%)	
Inflammation, acute/chronic		2 (4%)	
Inflammation, chronic focal	2 (4%)	4 (8%)	1 (2%)
Inflammation, chronic diffuse		2 (4%)	
Necrosis, fat	4 (8%)	9 (18%)	2 (4%)
ALL OTHER SYSTEMS			
Adipose tissue			
Hemorrhage		1	
Hemorrhage, chronic		1	
Inflammation, chronic focal		1	
Fibrosis, multifocal		1	
SPECIAL MORPHOLOGY SUMMARY			
None			

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

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF AMPICILLIN TRIHYDRATE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Epidermal inclusion cyst		1 (2%)	2 (4%)
Ulcer, NOS			1 (2%)
Inflammation, chronic focal			2 (4%)
Hyperplasia, epithelial	1 (2%)		
Hyperkeratosis	4 (8%)	1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
RESPIRATORY SYSTEM			
*Maxillary sinus	(50)	(50)	(50)
Inflammation, pyogranulomatous	1 (2%)		
#Trachea	(50)	(50)	(50)
Inflammation, chronic focal	4 (8%)	3 (6%)	
#Tracheal gland	(50)	(50)	(50)
Dilatation, NOS	1 (2%)		2 (4%)
#Lung	(50)	(49)	(50)
Foreign body, NOS		1 (2%)	2 (4%)
Atelectasis			1 (2%)
Congestion, acute passive	1 (2%)	5 (10%)	2 (4%)
Hemorrhage	3 (6%)	4 (8%)	3 (6%)
Lymphocytic inflammatory infiltrate	2 (4%)		2 (4%)
Inflammation, acute focal			1 (2%)
Inflammation, acute/chronic			1 (2%)
Inflammation, chronic focal	10 (20%)	12 (24%)	4 (8%)
Inflammation, granulomatous focal	12 (24%)		3 (6%)
Inflammation, necrotizing granulomatous	1 (2%)		
Infection, fungal	1 (2%)		
Foreign material, NOS		1 (2%)	
Hyperplasia, alveolar epithelium	1 (2%)	1 (2%)	2 (4%)
Histiocytosis	2 (4%)	1 (2%)	5 (10%)
#Lung/alveoli	(50)	(49)	(50)
Mineralization		1 (2%)	
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(49)	(50)
Hemorrhage			1 (2%)
Osteosclerosis		1 (2%)	1 (2%)
Histiocytosis	1 (2%)		
Myelofibrosis	3 (6%)	5 (10%)	6 (12%)
Hyperplasia, hematopoietic	13 (26%)	22 (45%)	25 (50%)
Mastocytosis		1 (2%)	
#Spleen	(50)	(49)	(50)
Fibrosis, focal			2 (4%)
Fibrosis, diffuse		1 (2%)	
Necrosis, focal	1 (2%)		
Necrosis, diffuse		1 (2%)	
Hemosiderosis	5 (10%)	2 (4%)	3 (6%)
Depletion, lymphoid	1 (2%)		1 (2%)
Hyperplasia, lymphoid	1 (2%)		
Hematopoiesis	3 (6%)	7 (14%)	6 (12%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Lymph node	(43)	(45)	(45)
Edema, NOS		1 (2%)	
#Mandibular lymph node	(43)	(45)	(45)
Cyst, NOS	1 (2%)		
Edema, NOS	1 (2%)		2 (4%)
Hemorrhage	2 (5%)	2 (4%)	1 (2%)
Histiocytosis	1 (2%)		
Plasmacytosis	8 (19%)	8 (18%)	11 (24%)
Hyperplasia, lymphoid	1 (2%)	2 (4%)	4 (9%)
#Pancreatic lymph node	(43)	(45)	(45)
Hemorrhage	1 (2%)		1 (2%)
Erythrophagocytosis	1 (2%)		
#Thymic lymph node	(43)	(45)	(45)
Congestion, acute passive			1 (2%)
Edema, NOS		1 (2%)	1 (2%)
Hemorrhage	1 (2%)	11 (24%)	3 (7%)
Inflammation, chronic diffuse	1 (2%)		
Pigmentation, NOS	1 (2%)		1 (2%)
Histiocytosis		1 (2%)	
Plasmacytosis		1 (2%)	
Erythrophagocytosis	2 (5%)		
Hyperplasia, lymphoid		1 (2%)	
#Liver	(50)	(50)	(50)
Hematopoiesis	2 (4%)	3 (6%)	2 (4%)
#Adrenal	(50)	(50)	(49)
Hematopoiesis	2 (4%)		
#Thymus	(35)	(41)	(41)
Cyst, NOS	1 (3%)		
Multiple cysts			1 (2%)
Hemorrhage		2 (5%)	2 (5%)
Inflammation, acute			1 (2%)
Hyperplasia, epithelial	1 (3%)	4 (10%)	
Hyperplasia, lymphoid	1 (3%)		
CIRCULATORY SYSTEM			
#Myocardium	(50)	(50)	(50)
Degeneration, NOS	40 (80%)	32 (64%)	39 (78%)
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Cyst, NOS			1 (2%)
#Salivary gland	(48)	(49)	(49)
Dilatation/ducts	1 (2%)	2 (4%)	1 (2%)
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, acute focal		1 (2%)	
Inflammation, acute/chronic	1 (2%)	1 (2%)	
Inflammation, chronic focal	8 (17%)	2 (4%)	2 (4%)
Necrosis, focal			1 (2%)
Atrophy, focal		1 (2%)	1 (2%)
Atrophy, diffuse			1 (2%)
Hyperplasia, focal	2 (4%)		2 (4%)
Metaplasia, NOS	5 (10%)	3 (6%)	2 (4%)
#Liver	(50)	(50)	(50)
Mineralization			1 (2%)
Congestion, acute passive		2 (4%)	1 (2%)
Congestion, chronic passive	1 (2%)		1 (2%)
Inflammation, chronic focal		3 (6%)	
Inflammation, granulomatous focal	17 (34%)	17 (34%)	23 (46%)
Fibrosis, focal		2 (4%)	

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#Liver (Continued)	(50)	(50)	(50)
Necrosis, focal			3 (6%)
Necrosis, coagulative	1 (2%)	1 (2%)	1 (2%)
Basophilic cyto change	38 (76%)	36 (72%)	33 (66%)
Focal cellular change			1 (2%)
Clear cell change	7 (14%)	1 (2%)	4 (8%)
Atrophy, diffuse			1 (2%)
Angiectasis		1 (2%)	
#Liver/hepatocytes	(50)	(50)	(50)
Cytoplasmic vacuolization	2 (4%)	4 (8%)	4 (8%)
#Bile duct	(50)	(50)	(50)
Inflammation, chronic focal			2 (4%)
Fibrosis, focal	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, focal	27 (54%)	13 (26%)	13 (26%)
#Pancreas	(48)	(49)	(49)
Dilatation/ducts	1 (2%)		
Cystic ducts	1 (2%)		
#Pancreatic duct	(48)	(49)	(49)
Hyperplasia, focal			1 (2%)
#Pancreatic acinus	(48)	(49)	(49)
Inflammation, chronic focal	4 (8%)	2 (4%)	2 (4%)
Nuclear aggregate, NOS			1 (2%)
Atrophy, focal	16 (33%)	13 (27%)	11 (22%)
Hyperplasia, focal	1 (2%)	1 (2%)	
#Peripancreatic tissue	(48)	(49)	(49)
Inflammation, chronic focal	1 (2%)		
#Esophagus	(48)	(48)	(50)
Hemorrhage	1 (2%)		
#Gastric mucosa	(49)	(50)	(47)
Dilatation, NOS	1 (2%)	1 (2%)	
#Gastric submucosa	(49)	(50)	(47)
Inflammation, chronic focal	2 (4%)	2 (4%)	
#Cardiac stomach	(49)	(50)	(47)
Ulcer, NOS	3 (6%)		
Inflammation, chronic focal	1 (2%)	1 (2%)	1 (2%)
Necrosis, focal		1 (2%)	
Hyperplasia, epithelial	3 (6%)	1 (2%)	1 (2%)
Hyperkeratosis	2 (4%)	1 (2%)	3 (6%)
#Duodenal mucosa	(48)	(46)	(42)
Lymphocytic inflammatory infiltrate			1 (2%)
#Colon	(37)	(36)	(41)
Parasitism		3 (8%)	4 (10%)
#Cecum	(37)	(36)	(41)
Infarct, hemorrhagic			1 (2%)
*Rectum	(50)	(50)	(50)
Parasitism			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(49)
Cyst, NOS			1 (2%)
Congestion, acute passive		1 (2%)	
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic	1 (2%)		
Nephropathy	34 (68%)	32 (64%)	36 (73%)
Nephrosis, NOS		2 (4%)	
Nephrosis, hemoglobinuric	1 (2%)		
Glomerulosclerosis, NOS	1 (2%)		
Infarct, healed			2 (4%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM (Continued)			
#Kidney/tubule	(50)	(50)	(49)
Pigmentation, NOS	1 (2%)	1 (2%)	
#Kidney/pelvis	(50)	(50)	(49)
Cyst, NOS		1 (2%)	
Hemorrhage	1 (2%)		
Inflammation, focal	1 (2%)		
Erosion	1 (2%)		
*Ureter	(50)	(50)	(50)
Hyperplasia, epithelial	1 (2%)		
#Urinary bladder	(46)	(46)	(41)
Inflammation, focal	1 (2%)		
Inflammation, chronic focal	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, epithelial			1 (2%)
ENDOCRINE SYSTEM			
#Pituitary	(49)	(50)	(49)
Hemorrhagic cyst			1 (2%)
#Anterior pituitary	(49)	(50)	(49)
Cyst, NOS	5 (10%)	5 (10%)	5 (10%)
Multiple cysts	2 (4%)	4 (8%)	6 (12%)
Hemorrhagic cyst	4 (8%)	3 (6%)	2 (4%)
Hemorrhage, chronic	3 (6%)	2 (4%)	1 (2%)
Abscess, NOS		1 (2%)	
Hyperplasia, focal	8 (16%)		6 (12%)
Hyperplasia, diffuse			1 (2%)
#Adrenal	(50)	(50)	(49)
Accessory structure	1 (2%)		
Atypia, NOS		1 (2%)	2 (4%)
#Adrenal cortex	(50)	(50)	(49)
Cyst, NOS		1 (2%)	
Hemorrhage			1 (2%)
Hemorrhagic cyst	2 (4%)	1 (2%)	
Necrosis, focal		1 (2%)	2 (4%)
Amyloidosis	1 (2%)		
Cytoplasmic vacuolization	1 (2%)	7 (14%)	3 (6%)
Basophilic cyto change			1 (2%)
Focal cellular change	6 (12%)	12 (24%)	15 (31%)
Atypia, NOS		1 (2%)	
Hypertrophy, focal	3 (6%)	2 (4%)	
Hyperplasia, focal	5 (10%)	6 (12%)	3 (6%)
#Adrenal medulla	(50)	(50)	(49)
Hyperplasia, focal	18 (36%)	7 (14%)	6 (12%)
#Thyroid	(50)	(49)	(49)
Follicular cyst, NOS	1 (2%)		
Inflammation, chronic focal			1 (2%)
Hyperplasia, C-cell	10 (20%)	12 (24%)	21 (43%)
Hyperplasia, follicular cell		1 (2%)	
#Pancreatic islets	(48)	(49)	(49)
Hyperplasia, focal	1 (2%)	2 (4%)	2 (4%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
Hyperplasia, focal	6 (12%)	2 (4%)	2 (4%)
Hyperplasia, diffuse	1 (2%)	6 (12%)	
Hyperplasia, cystic	16 (32%)	15 (30%)	20 (40%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
*Preputial gland	(50)	(50)	(50)
Dilatation/ducts		1 (2%)	
Inflammation, chronic focal	1 (2%)		
Fibrosis, multifocal	1 (2%)		
Hyperplasia, focal	1 (2%)		1 (2%)
Hyperkeratosis			1 (2%)
#Uterus	(50)	(50)	(49)
Prolapse		1 (2%)	
Dilatation, NOS	4 (8%)	3 (6%)	3 (6%)
Hemorrhage, chronic			1 (2%)
Abscess, NOS	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic focal	1 (2%)	1 (2%)	2 (4%)
#Cervix uteri	(50)	(50)	(49)
Cyst, NOS	1 (2%)		
Inflammation, acute focal		1 (2%)	
Inflammation, chronic focal			1 (2%)
Hyperplasia, diffuse		1 (2%)	
#Endometrial gland	(50)	(50)	(49)
Dilatation, NOS		1 (2%)	
Hyperplasia, focal	3 (6%)	2 (4%)	3 (6%)
Hyperplasia, diffuse		2 (4%)	2 (4%)
Hyperplasia, cystic	3 (6%)	2 (4%)	3 (6%)
Metaplasia, squamous	1 (2%)		
#Ovary	(50)	(49)	(47)
Parovarian cyst	5 (10%)	4 (8%)	
Hemorrhage			1 (2%)
Hyperplasia, epithelial		1 (2%)	
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
Fibrosis, multifocal			1 (2%)
#Cerebrum	(50)	(50)	(50)
Inflammation, chronic focal	1 (2%)		
Gliosis			1 (2%)
#Brain	(50)	(50)	(50)
Hydrocephalus, NOS	1 (2%)	1 (2%)	1 (2%)
Hemorrhage		2 (4%)	1 (2%)
Necrosis, focal			1 (2%)
#Brain/thalamus	(50)	(50)	(50)
Atrophy, pressure	1 (2%)	3 (6%)	5 (10%)
*Facial nerve	(50)	(50)	(50)
Inflammation, pyogranulomatous	1 (2%)		
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Hemorrhage, chronic	11 (22%)	1 (2%)	2 (4%)
Inflammation, acute diffuse	1 (2%)	1 (2%)	
Inflammation, chronic focal			1 (2%)
Synechia, anterior	2 (4%)		
Synechia, posterior	11 (22%)	1 (2%)	
*Eye/cornea	(50)	(50)	(50)
Hyperplasia, epithelial	1 (2%)		
Vascularization			1 (2%)
Dysplasia, NOS			1 (2%)
*Eyeball, tunica vasculosa	(50)	(50)	(50)
Degeneration, NOS			1 (2%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS (Continued)			
*Eye/retina	(50)	(50)	(50)
Degeneration, NOS	17 (34%)	3 (6%)	2 (4%)
Atrophy, diffuse	1 (2%)		
*Eye/crystalline lens	(50)	(50)	(50)
Degeneration, NOS			1 (2%)
Cataract	17 (34%)	2 (4%)	2 (4%)
*Eye/conjunctiva	(50)	(50)	(50)
Inflammation, necrotizing	1 (2%)		
*Harderian gland	(50)	(50)	(50)
Pigmentation, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Skull	(50)	(50)	(50)
Osteosclerosis		1 (2%)	
*Temporal bone	(50)	(50)	(50)
Osteosclerosis		1 (2%)	
*Femur	(50)	(50)	(50)
Osteosclerosis		2 (4%)	2 (4%)
*Tibia	(50)	(50)	(50)
Osteosclerosis		1 (2%)	1 (2%)
*Muscle of neck	(50)	(50)	(50)
Inflammation, chronic focal	1 (2%)		
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Foreign body, NOS			1 (2%)
Hemorrhage			1 (2%)
*Abdominal cavity	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
Inflammation, chronic focal		1 (2%)	
*Pleura	(50)	(50)	(50)
Fibrosis, focal		1 (2%)	
*Epicardium	(50)	(50)	(50)
Inflammation, chronic focal	1 (2%)		
*Mesentery	(50)	(50)	(50)
Inflammation, acute/chronic	2 (4%)	1 (2%)	
Inflammation, chronic focal	3 (6%)		1 (2%)
Inflammation, chronic diffuse	1 (2%)	1 (2%)	1 (2%)
Inflammation, granulomatous focal		1 (2%)	
Fibrosis, focal		1 (2%)	
Necrosis, focal			1 (2%)
Necrosis, fat	7 (14%)	9 (18%)	6 (12%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Hemorrhage		1 (2%)	
Inflammation, acute focal		1 (2%)	
Adipose tissue			
Hemorrhage			1
Inflammation, chronic diffuse	1		
Necrosis, fat	1		
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF AMPICILLIN TRIHYDRATE

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF AMPICILLIN TRIHYDRATE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	1
ANIMALS NECROPSIED	50	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	49
INTEGUMENTARY SYSTEM			
*Skin	(50)	(49)	(49)
Edema, NOS	1 (2%)		
Ulcer, NOS		1 (2%)	1 (2%)
Inflammation, suppurative		1 (2%)	2 (4%)
Inflammation, chronic	1 (2%)	2 (4%)	
Ulcer, chronic			2 (4%)
Parasitism		1 (2%)	
Atrophy, NOS		1 (2%)	
Hyperkeratosis	5 (10%)	5 (10%)	3 (6%)
Acanthosis		7 (14%)	3 (6%)
*Subcutaneous tissue	(50)	(49)	(49)
Inflammation, acute diffuse			1 (2%)
Inflammation chronic suppurative			1 (2%)
Inflammation, granulomatous focal		1 (2%)	
Infection, fungal		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(50)	(49)	(47)
Aspiration, foreign body		3 (6%)	1 (2%)
Congestion, acute	2 (4%)	7 (14%)	7 (15%)
Hemorrhage	2 (4%)		
Lymphocytic inflammatory infiltrate	7 (14%)	13 (27%)	8 (17%)
Inflammation, suppurative		1 (2%)	
Fibrosis, focal			1 (2%)
Hyperplasia, alveolar epithelium	1 (2%)	2 (4%)	1 (2%)
Histiocytosis	2 (4%)	1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(49)	(49)
Leukemoid reaction	3 (6%)	3 (6%)	1 (2%)
Hyperplasia, lymphoid	1 (2%)		
#Bone marrow	(45)	(47)	(47)
Hemorrhage		1 (2%)	
Infarct, NOS	1 (2%)		
Infarct, focal			1 (2%)
Myelofibrosis		1 (2%)	
Hyperplasia, erythroid			2 (4%)
Hyperplasia, granulocytic	7 (16%)	13 (28%)	13 (28%)
#Spleen	(50)	(47)	(47)
Depletion, lymphoid	6 (12%)	6 (13%)	9 (19%)
Hyperplasia, lymphoid	14 (28%)	3 (6%)	6 (13%)
#Splenic red pulp	(50)	(47)	(47)
Hemosiderosis			1 (2%)
Atrophy, diffuse	1 (2%)		4 (9%)
Hematopoiesis	8 (16%)	11 (23%)	7 (15%)
#Lymph node	(24)	(27)	(23)
Cyst, NOS			1 (4%)
Hyperplasia, diffuse	1 (4%)		

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Mandibular lymph node	(24)	(27)	(23)
Inflammation, suppurative		1 (4%)	
Inflammation, acute/chronic			1 (4%)
Plasma cell infiltrate	1 (4%)		
Histiocytosis	1 (4%)		1 (4%)
Hyperplasia, lymphoid	1 (4%)		2 (9%)
Hematopoiesis		1 (4%)	
#Mesenteric lymph node	(24)	(27)	(23)
Hemorrhage	1 (4%)		
Hyperplasia, lymphoid	1 (4%)		
#Lung	(50)	(49)	(47)
Leukemoid reaction		1 (2%)	
#Liver	(50)	(48)	(46)
Leukemoid reaction		1 (2%)	
Hematopoiesis		3 (6%)	1 (2%)
*Mesentery	(50)	(49)	(49)
Hematopoiesis		1 (2%)	
#Thymus	(28)	(22)	(24)
Cyst, NOS		1 (5%)	
Necrosis, diffuse	1 (4%)	2 (9%)	1 (4%)
Depletion, lymphoid	2 (7%)	2 (9%)	4 (17%)
CIRCULATORY SYSTEM			
#Heart	(50)	(49)	(47)
Fibrosis, focal	1 (2%)		
#Heart/atrium	(50)	(49)	(47)
Inflammation, focal	1 (2%)		
#Myocardium	(50)	(49)	(47)
Mineralization			1 (2%)
*Pulmonary artery	(50)	(49)	(49)
Hypertrophy, NOS		1 (2%)	
#Hepatic sinusoid	(50)	(48)	(46)
Dilatation, NOS		1 (2%)	
*Preputial gland	(50)	(49)	(49)
Lymphangiectasis		1 (2%)	
DIGESTIVE SYSTEM			
#Salivary gland	(47)	(47)	(44)
Multiple cysts		1 (2%)	
Lymphocytic inflammatory infiltrate	15 (32%)	18 (38%)	14 (32%)
Inflammation, acute/chronic		1 (2%)	
Inflammation, granulomatous focal	1 (2%)		
Necrosis, focal			1 (2%)
Atrophy, focal	1 (2%)		
Hypertrophy, diffuse	1 (2%)		
#Liver	(50)	(48)	(46)
Inflammation, focal	1 (2%)		
Lymphocytic inflammatory infiltrate		3 (6%)	
Inflammation, granulomatous focal	1 (2%)	1 (2%)	
Necrosis, coagulative	1 (2%)	1 (2%)	2 (4%)
Infarct, NOS		1 (2%)	
Cytoplasmic vacuolization	1 (2%)	3 (6%)	2 (4%)
Basophilic cyto change			2 (4%)
Eosinophilic cyto change	1 (2%)	1 (2%)	
Hyperplasia, focal		2 (4%)	1 (2%)
Angiectasis	1 (2%)		
Histiocytosis		1 (2%)	

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Liver/centrilobular	(50)	(48)	(46)
Congestion, acute			1 (2%)
Degeneration, NOS		1 (2%)	
Cytoplasmic change, NOS		1 (2%)	1 (2%)
Cytoplasmic vacuolization			2 (4%)
#Liver/periportal	(50)	(48)	(46)
Eosinophilic cyto change	1 (2%)		
#Liver/hepatocytes	(50)	(48)	(46)
Mitotic alteration		1 (2%)	
*Gallbladder	(50)	(49)	(49)
Calculus, microscopic examination		1 (2%)	
Inflammation, granulomatous focal	1 (2%)		
Eosinophilic cyto change	1 (2%)		
#Pancreas	(47)	(44)	(42)
Lymphocytic inflammatory infiltrate	1 (2%)		
Necrosis, fat	1 (2%)		
Hypoplasia, NOS	2 (4%)		
Atrophy, focal	1 (2%)		
Hyperplasia, NOS	1 (2%)		
Hyperplasia, focal			1 (2%)
#Esophagus	(47)	(48)	(44)
Hyperkeratosis			1 (2%)
#Gastric fundal gland	(50)	(48)	(45)
Dilatation, NOS		3 (6%)	
#Glandular stomach	(50)	(48)	(45)
Ulcer, acute		1 (2%)	
#Forestomach	(50)	(48)	(45)
Ulcer, NOS		6 (13%)	2 (4%)
Inflammation, focal		1 (2%)	1 (2%)
Inflammation, suppurative		24 (50%)	19 (42%)
Infection, fungal		8 (17%)	6 (13%)
Hyperkeratosis	11 (22%)	28 (58%)	20 (44%)
Acanthosis	9 (18%)	28 (58%)	20 (44%)
#Jejunum	(45)	(44)	(37)
Ulcer, NOS	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(49)	(49)
Congestion, acute			1 (2%)
Lymphocytic inflammatory infiltrate	26 (52%)	35 (71%)	13 (27%)
Glomerulonephritis, subacute	1 (2%)	2 (4%)	
Infarct, healed	1 (2%)		
Hyperplasia, tubular cell		1 (2%)	
Metaplasia, osseous	1 (2%)		
#Kidney/interstitial tissue	(50)	(49)	(49)
Inflammation, chronic		1 (2%)	
#Kidney/medulla	(50)	(49)	(49)
Congestion, acute		1 (2%)	
#Renal papilla	(50)	(49)	(49)
Necrosis, NOS		1 (2%)	
#Kidney/tubule	(50)	(49)	(49)
Mineralization	2 (4%)		1 (2%)
Dilatation, NOS	6 (12%)	3 (6%)	4 (8%)
Cyst, NOS		3 (6%)	
Necrosis, focal	2 (4%)		
Cytoplasmic change, NOS			1 (2%)
Cytoplasmic vacuolization			1 (2%)
Atrophy, focal	6 12%)	4 (8%)	3 (6%)
Atrophy, diffuse		1 (2%)	

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM (Continued)			
*Ureter	(50)	(49)	(49)
Inflammation, suppurative	1 (2%)		
#Urinary bladder	(47)	(45)	(44)
Distention	21 (45%)	20 (44%)	14 (32%)
Lymphocytic inflammatory infiltrate	6 (13%)	1 (2%)	6 (14%)
Inflammation, suppurative	1 (2%)		
Hyperplasia, epithelial	1 (2%)		
#Urinary bladder/submucosa	(47)	(45)	(44)
Edema, NOS		1 (2%)	
*Urethra	(50)	(49)	(49)
Obstruction, NOS	2 (4%)	3 (6%)	2 (4%)
Inflammation, suppurative	1 (2%)	1 (2%)	
Inflammation, chronic suppurative			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(40)	(37)	(33)
Cyst, NOS		1 (3%)	
Congestion, NOS			1 (3%)
Hyperplasia, NOS	1 (3%)		
Hyperplasia, focal	2 (5%)		
#Adrenal/capsule	(48)	(48)	(45)
Hyperplasia, focal	38 (79%)	35 (73%)	30 (67%)
Hyperplasia, diffuse			2 (4%)
#Adrenal cortex	(48)	(48)	(45)
Accessory structure		2 (4%)	
Eosinophilic cyto change	2 (4%)	2 (4%)	
Hyperplasia, focal	7 (15%)	2 (4%)	2 (4%)
#Adrenal medulla	(48)	(48)	(45)
Hyperplasia, NOS	3 (6%)		
#Thyroid	(42)	(44)	(39)
Follicular cyst, NOS	1 (2%)	1 (2%)	
Lymphocytic inflammatory infiltrate		1 (2%)	
Hyperplasia, follicular cell		1 (2%)	1 (3%)
#Parathyroid	(29)	(23)	(27)
Cyst, NOS		1 (4%)	
REPRODUCTIVE SYSTEM			
*Penis	(50)	(49)	(49)
Ulcer, NOS	2 (4%)		
Inflammation, chronic focal	1 (2%)		
*Prepuce	(50)	(49)	(49)
Inflammation, suppurative	1 (2%)		1 (2%)
Inflammation, chronic		1 (2%)	1 (2%)
Ulcer, chronic	1 (2%)		
Hyperkeratosis			1 (2%)
*Preputial gland	(50)	(49)	(49)
Retention of content		2 (4%)	1 (2%)
Inflammation, focal	1 (2%)		
Inflammation, suppurative		3 (6%)	3 (6%)
Inflammation, chronic		1 (2%)	3 (6%)
#Prostate	(46)	(40)	(42)
Spermatocele	1 (2%)		
Hemorrhage		1 (3%)	
Lymphocytic inflammatory infiltrate	3 (7%)	2 (5%)	2 (5%)
Inflammation, suppurative	3 (7%)	4 (10%)	2 (5%)
Hyperplasia, focal	1 (2%)		
*Seminal vesicle	(50)	(49)	(49)
Distention	6 (12%)	5 (10%)	3 (6%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
#Testis	(50)	(49)	(46)
Atrophy, focal		1 (2%)	
Hyperplasia, interstitial cell		3 (6%)	
#Testis/tubule	(50)	(49)	(46)
Mineralization			1 (2%)
Degeneration, NOS		1 (2%)	
#Spermatogonia	(50)	(49)	(46)
Dysplasia, NOS	1 (2%)		
NERVOUS SYSTEM			
#Brain	(50)	(49)	(47)
Mineralization	16 (32%)	14 (29%)	13 (28%)
Hydrocephalus, internal			1 (2%)
SPECIAL SENSE ORGANS			
*Eye/cornea	(50)	(49)	(49)
Ulcer, chronic			1 (2%)
*Ear	(50)	(49)	(49)
Inflammation chronic suppurative	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(49)	(49)
Osteosclerosis	1 (2%)		1 (2%)
*Knee joint	(50)	(49)	(49)
Ankylosis	1 (2%)		
Osteoarthritis			1 (2%)
*Tarsal joint	(50)	(49)	(49)
Ankylosis	9 (18%)	5 (10%)	3 (6%)
*Skeletal muscle	(50)	(49)	(49)
Mineralization		2 (4%)	1 (2%)
Inflammation, suppurative			1 (2%)
BODY CAVITIES			
*Mesentery	(50)	(49)	(49)
Necrosis, fat	3 (6%)	2 (4%)	3 (6%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(49)	(49)
Lymphocytic inflammatory infiltrate	6 (12%)		5 (10%)
Inflammation, suppurative		1 (2%)	1 (2%)
SPECIAL MORPHOLOGY SUMMARY			
Animal missing/no necropsy		1	1

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

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF AMPICILLIN TRIHYDRATE

	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)
Edema, NOS			1 (2%)
Inflammation, suppurative	1 (2%)		5 (10%)
Ulcer, chronic		1 (2%)	
Inflammation chronic suppurative		1 (2%)	
Hyperkeratosis	7 (14%)	4 (8%)	4 (8%)
Acanthosis		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Aspiration, foreign body			4 (8%)
Bronchiectasis	1 (2%)		
Congestion, acute			9 (18%)
Hemorrhage	1 (2%)	2 (4%)	
Lymphocytic inflammatory infiltrate	6 (12%)	13 (26%)	3 (6%)
Inflammation, interstitial		1 (2%)	1 (2%)
Inflammation, suppurative	1 (2%)	1 (2%)	1 (2%)
Hemosiderosis	1 (2%)		
Histiocytosis	2 (4%)		
HEMATOPOIETIC SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Hyperplasia, lymphoid			1 (2%)
*Multiple organs	(50)	(50)	(50)
Leukemoid reaction	1 (2%)	1 (2%)	
Hyperplasia, lymphoid			3 (6%)
Hematopoiesis		1 (2%)	
*Blood erythrocytes	(50)	(50)	(50)
Reticulocytosis		1 (2%)	
#Bone marrow	(48)	(50)	(49)
Atrophy, NOS	1 (2%)	1 (2%)	
Histiocytosis	1 (2%)		
Myelofibrosis	15 (31%)	15 (30%)	6 (12%)
Hyperplasia, erythroid	3 (6%)		1 (2%)
Hyperplasia, granulocytic	11 (23%)	19 (38%)	6 (12%)
#Spleen	(49)	(50)	(50)
Depletion, lymphoid	5 (10%)	9 (18%)	7 (14%)
Hyperplasia, lymphoid	14 (29%)	16 (32%)	13 (26%)
#Splenic red pulp	(49)	(50)	(50)
Congestion, NOS			1 (2%)
Hematopoiesis	17 (35%)	22 (44%)	12 (24%)
#Lymph node	(32)	(37)	(37)
Hemorrhage	1 (3%)		
Abscess, NOS		1 (3%)	
Hyperplasia, lymphoid		1 (3%)	1 (3%)
#Mandibular lymph node	(32)	(37)	(37)
Inflammation, suppurative		1 (3%)	
Plasma cell infiltrate			1 (3%)
Hemosiderosis	1 (3%)	1 (3%)	
Histiocytosis	1 (3%)		
Hyperplasia, lymphoid	1 (3%)	7 (19%)	9 (24%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Cervical lymph node	(32)	(37)	(37)
Inflammation, suppurative		1 (3%)	
#Mediastinal lymph node	(32)	(37)	(37)
Hemorrhage	2 (6%)		
Abscess, NOS		1 (3%)	
Plasma cell infiltrate		1 (3%)	
Hyperplasia, lymphoid			1 (3%)
#Pancreatic lymph node	(32)	(37)	(37)
Histiocytosis		1 (3%)	
#Mesenteric lymph node	(32)	(37)	(37)
Inflammation, suppurative	1 (3%)		
Plasma cell infiltrate		1 (3%)	
Inflammation, granulomatous focal			1 (3%)
Hyperplasia, lymphoid	1 (3%)		1 (3%)
#Renal lymph node	(32)	(37)	(37)
Inflammation, acute/chronic		1 (3%)	
Plasma cell infiltrate	1 (3%)		
#Liver	(49)	(50)	(49)
Hematopoiesis	15 (31%)	20 (40%)	9 (18%)
#Stomach wall	(47)	(49)	(49)
Hyperplasia, lymphoid		1 (2%)	
#Peyers patch	(43)	(47)	(46)
Hyperplasia, lymphoid			1 (2%)
#Adrenal cortex	(47)	(48)	(47)
Hematopoiesis	2 (4%)	5 (10%)	
#Thymus	(27)	(26)	(30)
Plasma cell infiltrate	1 (4%)		
Depletion, lymphoid	2 (7%)	3 (12%)	3 (10%)
Hyperplasia, lymphoid	1 (4%)	1 (4%)	
CIRCULATORY SYSTEM			
#Brain stem	(50)	(50)	(50)
Embolus, foreign body	1 (2%)		
#Heart/atrium	(50)	(49)	(50)
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic focal	1 (2%)		
Inflammation, chronic suppurative	1 (2%)		
#Left ventricle	(50)	(49)	(50)
Thrombosis, NOS		1 (2%)	
#Myocardium	(50)	(49)	(50)
Bacterial septicemia		1 (2%)	
Necrosis, focal		1 (2%)	
#Hepatic sinusoid	(49)	(50)	(49)
Dilatation, NOS		1 (2%)	1 (2%)
DIGESTIVE SYSTEM			
#Salivary gland	(48)	(48)	(47)
Mineralization		1 (2%)	1 (2%)
Lymphocytic inflammatory infiltrate	9 (19%)	7 (15%)	7 (15%)
#Liver	(49)	(50)	(49)
Lymphocytic inflammatory infiltrate	3 (6%)	2 (4%)	3 (6%)
Inflammation, suppurative		1 (2%)	
Inflammation, granulomatous focal			1 (2%)
Fibrosis, focal		1 (2%)	
Necrosis, coagulative	3 (6%)		
Cytoplasmic vacuolization	2 (4%)	1 (2%)	1 (2%)
Eosinophilic cyto change		1 (2%)	
Hyperplasia, focal			2 (4%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Liver/centrilobular	(49)	(50)	(49)
Necrosis, coagulative		1 (2%)	
Cytoplasmic vacuolization	1 (2%)		1 (2%)
#Liver/Kupffer cell	(49)	(50)	(49)
Hyperplasia, diffuse		2 (4%)	
*Gallbladder	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
Plasma cell infiltrate		1 (2%)	
Hyperplasia, focal		1 (2%)	
#Pancreas	(44)	(46)	(45)
Lymphocytic inflammatory infiltrate	3 (7%)	1 (2%)	1 (2%)
Plasma cell infiltrate		1 (2%)	
Hypoplasia, NOS			1 (2%)
Atrophy, focal		1 (2%)	1 (2%)
Hyperplasia, focal	2 (5%)		
#Gastric fundal gland	(47)	(49)	(49)
Dilatation, NOS	1 (2%)	4 (8%)	1 (2%)
#Glandular stomach	(47)	(49)	(49)
Multiple cysts			1 (2%)
Ulcer, chronic	1 (2%)		
Inflammation, chronic suppurative			2 (4%)
Necrosis, focal			1 (2%)
Eosinophilic cyto change		1 (2%)	1 (2%)
#Gastric submucosa	(47)	(49)	(49)
Inflammation, granulomatous focal	1 (2%)		
#Gastric subserosa	(47)	(49)	(49)
Inflammation, suppurative		1 (2%)	
#Forestomach	(47)	(49)	(49)
Ulcer, NOS		2 (4%)	6 (12%)
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, suppurative	5 (11%)	29 (59%)	27 (55%)
Plasma cell infiltrate		1 (2%)	
Infection, fungal	1 (2%)	15 (31%)	8 (16%)
Hyperkeratosis	17 (36%)	39 (80%)	32 (65%)
Acanthosis	11 (23%)	37 (76%)	34 (69%)
#Small intestine	(43)	(47)	(46)
Inflammation, acute/chronic		1 (2%)	
Ulcer, chronic		1 (2%)	
#Jejunum	(43)	(47)	(46)
Amyloid, NOS			1 (2%)
#Colon	(43)	(42)	(44)
Inflammation, granulomatous focal			1 (2%)
URINARY SYSTEM			
#Kidney	(49)	(50)	(50)
Hydronephrosis			1 (2%)
Lymphocytic inflammatory infiltrate	8 (16%)	21 (42%)	10 (20%)
Inflammation, suppurative		2 (4%)	
Glomerulonephritis, subacute	5 (10%)	9 (18%)	1 (2%)
Plasma cell infiltrate	3 (6%)	4 (8%)	
Infection, bacterial			1 (2%)
Infarct, healed			1 (2%)
Keratin pearl formation		1 (2%)	
#Kidney/cortex	(49)	(50)	(50)
Necrosis, NOS			1 (2%)
Eosinophilic cyto change			1 (2%)
#Renal papilla	(49)	(50)	(50)
Necrosis, NOS		3 (6%)	2 (4%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM (Continued)			
#Kidney/glomerulus	(49)	(50)	(50)
Inflammation, suppurative	1 (2%)		
#Kidney/tubule	(49)	(50)	(50)
Dilatation, NOS		1 (2%)	
Cast, hemoglobin	1 (2%)		
Degeneration, granular	3 (6%)	2 (4%)	
Cytoplasmic change, NOS		1 (2%)	
Cytoplasmic vacuolization			1 (2%)
Eosinophilic cyto change		3 (6%)	2 (4%)
Atrophy, focal	3 (6%)	2 (4%)	4 (8%)
Regeneration, NOS		1 (2%)	
#Kidney/pelvis	(49)	(50)	(50)
Inflammation, suppurative		1 (2%)	
#Urinary bladder	(48)	(42)	(43)
Distention	1 (2%)		
Hemorrhage		1 (2%)	
Lymphocytic inflammatory infiltrate	11 (23%)	10 (24%)	10 (23%)
ENDOCRINE SYSTEM			
#Pituitary	(44)	(40)	(36)
Angiectasis	1 (2%)		
#Anterior pituitary	(44)	(40)	(36)
Congestion, NOS	1 (2%)		
Hyperplasia, focal	2 (5%)	5 (13%)	3 (8%)
#Adrenal/capsule	(47)	(48)	(47)
Lymphocytic inflammatory infiltrate			1 (2%)
Plasma cell infiltrate	1 (2%)		
Hyperplasia, focal	30 (64%)	21 (44%)	26 (55%)
Hyperplasia, diffuse	17 (36%)	25 (52%)	21 (45%)
#Adrenal cortex	(47)	(48)	(47)
Hamartoma			2 (4%)
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, suppurative	1 (2%)		
Amyloid, NOS		5 (10%)	5 (11%)
Cytoplasmic vacuolization	1 (2%)	1 (2%)	
Eosinophilic cyto change	4 (9%)	3 (6%)	5 (11%)
Hyperplasia, focal	3 (6%)	1 (2%)	2 (4%)
#Thyroid	(42)	(47)	(43)
Follicular cyst, NOS		1 (2%)	1 (2%)
Inflammation, focal			1 (2%)
Hyperplasia, follicular cell	5 (12%)	1 (2%)	2 (5%)
#Pancreatic islets	(44)	(46)	(45)
Hyperplasia, focal		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Inflammation, NOS		1 (2%)	
Lymphocytic inflammatory infiltrate	1 (2%)	1 (2%)	
#Uterus	(49)	(50)	(48)
Inflammation, suppurative	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic suppurative	1 (2%)	1 (2%)	
#Cervix uteri	(49)	(50)	(48)
Inflammation, suppurative	1 (2%)		
#Uterus/endometrium	(49)	(50)	(48)
Congestion, NOS		1 (2%)	
Inflammation, suppurative	9 (18%)	7 (14%)	1 (2%)
Hyperplasia, cystic	38 (78%)	44 (88%)	38 (79%)
Angiectasis		1 (2%)	1 (2%)
Metaplasia, squamous			1 (2%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
#Endometrial stroma	(49)	(50)	(48)
Hyperplasia, focal	1 (2%)	1 (2%)	
#Fallopian tube	(49)	(50)	(48)
Lymphocytic inflammatory infiltrate	1 (2%)	1 (2%)	
Inflammation, suppurative	1 (2%)	1 (2%)	2 (4%)
Hyperplasia, intraductal			1 (2%)
#Ovary	(46)	(43)	(45)
Cyst, NOS	6 (13%)	12 (28%)	6 (13%)
Hematoma, NOS			1 (2%)
Hematoma, organized		2 (5%)	
Hemorrhagic cyst			1 (2%)
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, suppurative	2 (4%)	1 (2%)	
Abscess, NOS	1 (2%)	2 (5%)	
Abscess, chronic	3 (7%)	8 (19%)	1 (2%)
Hyperplasia, granulosa cell			1 (2%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Mineralization	20 (40%)	19 (38%)	12 (24%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Synechia, NOS	1 (2%)		
Phthisis bulbi		1 (2%)	
*Eye/cornea	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Osteosclerosis	4 (8%)	1 (2%)	2 (4%)
*Joint of lower extremity	(50)	(50)	(50)
Inflammation, active chronic		1 (2%)	
*Muscle of trunk	(50)	(50)	(50)
Necrosis, focal			1 (2%)
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Abscess, NOS		1 (2%)	
*Peritoneum	(50)	(50)	(50)
Inflammation, suppurative		3 (6%)	
*Peritoneal cavity	(50)	(50)	(50)
Abscess, chronic		2 (4%)	
*Mesentery	(50)	(50)	(50)
Hematoma, NOS	1 (2%)		
Inflammation, suppurative			1 (2%)
Plasma cell infiltrate	1 (2%)	1 (2%)	
Necrosis, fat	1 (2%)		5 (10%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	25 (50%)	18 (36%)	20 (40%)
Inflammation, suppurative		4 (8%)	1 (2%)
Abscess, chronic		1 (2%)	
Site unknown			
Abscess, NOS			1
Adipose tissue			
Necrosis, fat	1		
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX E

ANALYSES OF PRIMARY TUMORS IN RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF AMPICILLIN TRIHYDRATE

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF AMPICILLIN TRIHYDRATE

	Vehicle Control	750 mg/kg	1,500 mg/kg
Skin: Squamous Cell Papilloma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	9.7%	10.5%	11.5%
Terminal Rates (c)	3/31 (10%)	2/27 (7%)	3/26 (12%)
Week of First Observation	104	102	104
Life Table Tests (d)	P=0.495	P=0.604	P=0.581
Incidental Tumor Tests (d)	P=0.558	P=0.642N	P=0.581
Cochran-Armitage Trend Test (d)	P=0.583		
Fisher Exact Test (d)		P=0.661	P=0.661
Skin: Papilloma or Squamous Cell Papilloma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	4/50 (8%)
Adjusted Rates (b)	9.7%	10.5%	14.2%
Terminal Rates (c)	3/31 (10%)	2/27 (7%)	3/26 (12%)
Week of First Observation	104	102	94
Life Table Tests (d)	P=0.341	P=0.604	P=0.420
Incidental Tumor Tests (d)	P=0.444	P=0.642N	P=0.502
Cochran-Armitage Trend Test (d)	P=0.421		
Fisher Exact Test (d)		P=0.661	P=0.500
Skin: Basal Cell Tumor			
Overall Rates (a)	1/50 (2%)	0/50 (0%)	4/50 (8%)
Adjusted Rates (b)	3.2%	0.0%	12.3%
Terminal Rates (c)	1/31 (3%)	0/27 (0%)	2/26 (8%)
Week of First Observation	104		71
Life Table Tests (d)	P=0.070	P=0.528N	P=0.152
Incidental Tumor Tests (d)	P=0.086	P=0.528N	P=0.210
Cochran-Armitage Trend Test (d)	P=0.082		
Fisher Exact Test (d)		P=0.500N	P=0.181
Skin: Basal Cell Tumor or Carcinoma			
Overall Rates (a)	1/50 (2%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (b)	3.2%	2.3%	12.3%
Terminal Rates (c)	1/31 (3%)	0/27 (0%)	2/26 (8%)
Week of First Observation	104	76	71
Life Table Tests (d)	P=0.088	P=0.748	P=0.152
Incidental Tumor Tests (d)	P=0.102	P=0.717N	P=0.210
Cochran-Armitage Trend Test (d)	P=0.101		
Fisher Exact Test (d)		P=0.753	P=0.181
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	4/50 (8%)	0/50 (0%)	4/50 (8%)
Adjusted Rates (b)	11.8%	0.0%	12.2%
Terminal Rates (c)	3/31 (10%)	0/27 (0%)	1/26 (4%)
Week of First Observation	83		92
Life Table Tests (d)	P=0.548	P=0.079N	P=0.595
Incidental Tumor Tests (d)	P=0.556N	P=0.095N	P=0.585N
Cochran-Armitage Trend Test (d)	P=0.588		
Fisher Exact Test (d)		P=0.059N	P=0.643
Integumentary System: Fibroma			
Overall Rates (a)	4/50 (8%)	0/50 (0%)	5/50 (10%)
Adjusted Rates (b)	11.8%	0.0%	15.7%
Terminal Rates (c)	3/31 (10%)	0/27 (0%)	2/26 (8%)
Week of First Observation	83		92
Life Table Tests (d)	P=0.373	P=0.079N	P=0.443
Incidental Tumor Tests (d)	P=0.437	P=0.095N	P=0.551
Cochran-Armitage Trend Test (d)	P=0.417		
Fisher Exact Test (d)		P=0.059N	P=0.500

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF AMPICILLIN TRIHYDRATE (Continued)

	Vehicle Control	750 mg/kg	1,500 mg/kg
Integumentary System: Fibroma or Fibrosarcoma			
Overall Rates (a)	4/50 (8%)	1/50 (2%)	5/50 (10%)
Adjusted Rates (b)	11.8%	3.1%	15.7%
Terminal Rates (c)	3/31 (10%)	0/27 (0%)	2/26 (8%)
Week of First Observation	83	99	92
Life Table Tests (d)	P=0.371	P=0.210N	P=0.443
Incidental Tumor Tests (d)	P=0.491	P=0.168N	P=0.551
Cochran-Armitage Trend Test (d)	P=0.421		
Fisher Exact Test (d)		P=0.181N	P=0.500
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	1/50 (2%)	3/49 (6%)	1/50 (2%)
Adjusted Rates (b)	3.2%	8.8%	2.5%
Terminal Rates (c)	1/31 (3%)	1/27 (4%)	0/26 (0%)
Week of First Observation	104	91	89
Life Table Tests (d)	P=0.606	P=0.303	P=0.760
Incidental Tumor Tests (d)	P=0.608	P=0.325	P=0.708
Cochran-Armitage Trend Test (d)	P=0.609		
Fisher Exact Test (d)		P=0.301	P=0.753
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	4/49 (8%)	1/50 (2%)
Adjusted Rates (b)	9.2%	12.3%	2.5%
Terminal Rates (c)	2/31 (6%)	2/27 (7%)	0/26 (0%)
Week of First Observation	93	91	89
Life Table Tests (d)	P=0.272N	P=0.480	P=0.319N
Incidental Tumor Tests (d)	P=0.223N	P=0.579	P=0.261N
Cochran-Armitage Trend Test (d)	P=0.253N		
Fisher Exact Test (d)		P=0.489	P=0.309N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	5/50 (10%)	14/50 (28%)	13/50 (26%)
Adjusted Rates (b)	13.8%	41.9%	38.8%
Terminal Rates (c)	2/31 (6%)	8/27 (30%)	7/26 (27%)
Week of First Observation	83	89	63
Life Table Tests (d)	P=0.024	P=0.019	P=0.029
Incidental Tumor Tests (d)	P=0.069	P=0.040	P=0.066
Cochran-Armitage Trend Test (d)	P=0.034		
Fisher Exact Test (d)		P=0.020	P=0.033
Hematopoietic System: Leukemia			
Overall Rates (a)	5/50 (10%)	14/50 (28%)	14/50 (28%)
Adjusted Rates (b)	13.8%	41.7%	40.6%
Terminal Rates (c)	2/31 (6%)	8/27 (30%)	7/26 (27%)
Week of First Observation	83	89	63
Life Table Tests (d)	P=0.015	P=0.019	P=0.019
Incidental Tumor Tests (d)	P=0.049	P=0.040	P=0.052
Cochran-Armitage Trend Test (d)	P=0.020		
Fisher Exact Test (d)		P=0.020	P=0.020
Hematopoietic System: Leukemia or Lymphoma			
Overall Rates (a)	6/50 (12%)	16/50 (32%)	14/50 (28%)
Adjusted Rates (b)	16.4%	44.1%	40.6%
Terminal Rates (c)	2/31 (6%)	8/27 (30%)	7/26 (27%)
Week of First Observation	83	58	63
Life Table Tests (d)	P=0.032	P=0.017	P=0.037
Incidental Tumor Tests (d)	P=0.099	P=0.050	P=0.114
Cochran-Armitage Trend Test (d)	P=0.040		
Fisher Exact Test (d)		P=0.014	P=0.039

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF AMPICILLIN TRIHYDRATE (Continued)

	Vehicle Control	750 mg/kg	1,500 mg/kg
Pituitary Gland: Adenoma			
Overall Rates (a)	11/46 (24%)	18/49 (37%)	14/46 (30%)
Adjusted Rates (b)	35.1%	49.2%	44.4%
Terminal Rates (c)	10/30 (33%)	10/27 (37%)	10/26 (38%)
Week of First Observation	87	66	45
Life Table Tests (d)	P=0.199	P=0.073	P=0.211
Incidental Tumor Tests (d)	P=0.232	P=0.095	P=0.207
Cochran-Armitage Trend Test (d)	P=0.286		
Fisher Exact Test (d)		P=0.128	P=0.320
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	12/46 (26%)	20/49 (41%)	16/46 (35%)
Adjusted Rates (b)	36.5%	53.8%	49.5%
Terminal Rates (c)	10/30 (33%)	11/27 (41%)	11/26 (42%)
Week of First Observation	71	66	45
Life Table Tests (d)	P=0.148	P=0.054	P=0.158
Incidental Tumor Tests (d)	P=0.206	P=0.089	P=0.181
Cochran-Armitage Trend Test (d)	P=0.221		
Fisher Exact Test (d)		P=0.096	P=0.249
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	13/50 (26%)	12/50 (24%)	23/49 (47%)
Adjusted Rates (b)	40.6%	39.6%	75.8%
Terminal Rates (c)	12/31 (39%)	9/27 (33%)	19/26 (73%)
Week of First Observation	103	95	80
Life Table Tests (d)	P=0.003	P=0.543	P=0.004
Incidental Tumor Tests (d)	P=0.008	P=0.445N	P=0.007
Cochran-Armitage Trend Test (d)	P=0.017		
Fisher Exact Test (d)		P=0.500N	P=0.025
Adrenal Gland: Malignant Pheochromocytoma			
Overall Rates (a)	1/50 (2%)	5/50 (10%)	1/49 (2%)
Adjusted Rates (b)	3.2%	17.0%	3.8%
Terminal Rates (c)	1/31 (3%)	4/27 (15%)	1/26 (4%)
Week of First Observation	104	89	104
Life Table Tests (d)	P=0.537	P=0.084	P=0.723
Incidental Tumor Tests (d)	P=0.507	P=0.065	P=0.723
Cochran-Armitage Trend Test (d)	P=0.585		
Fisher Exact Test (d)		P=0.102	P=0.748
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	13/50 (26%)	16/50 (32%)	23/49 (47%)
Adjusted Rates (b)	40.6%	50.9%	75.8%
Terminal Rates (c)	12/31 (39%)	12/27 (44%)	19/26 (73%)
Week of First Observation	103	89	80
Life Table Tests (d)	P=0.004	P=0.200	P=0.004
Incidental Tumor Tests (d)	P=0.007	P=0.325	P=0.007
Cochran-Armitage Trend Test (d)	P=0.019		
Fisher Exact Test (d)		P=0.330	P=0.025
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	2/50 (4%)	3/48 (6%)	1/46 (2%)
Adjusted Rates (b)	6.5%	8.6%	3.8%
Terminal Rates (c)	2/31 (6%)	1/27 (4%)	1/26 (4%)
Week of First Observation	104	89	104
Life Table Tests (d)	P=0.428N	P=0.485	P=0.562N
Incidental Tumor Tests (d)	P=0.518N	P=0.340	P=0.562N
Cochran-Armitage Trend Test (d)	P=0.432N		
Fisher Exact Test (d)		P=0.480	P=0.532N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF AMPICILLIN TRIHYDRATE (Continued)

	Vehicle Control	750 mg/kg	1,500 mg/kg
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	0/50 (0%)	3/48 (6%)	2/46 (4%)
Adjusted Rates (b)	0.0%	11.1%	6.9%
Terminal Rates (c)	0/31 (0%)	3/27 (11%)	1/26 (4%)
Week of First Observation		104	96
Life Table Tests (d)	P=0.168	P=0.097	P=0.220
Incidental Tumor Tests (d)	P=0.204	P=0.097	P=0.328
Cochran-Armitage Trend Test (d)	P=0.180		
Fisher Exact Test (d)		P=0.114	P=0.227
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	2/50 (4%)	6/48 (13%)	3/46 (7%)
Adjusted Rates (b)	6.5%	19.2%	10.6%
Terminal Rates (c)	2/31 (6%)	4/27 (15%)	2/26 (8%)
Week of First Observation	104	89	96
Life Table Tests (d)	P=0.369	P=0.114	P=0.436
Incidental Tumor Tests (d)	P=0.345	P=0.062	P=0.528
Cochran-Armitage Trend Test (d)	P=0.378		
Fisher Exact Test (d)		P=0.121	P=0.460
Pancreatic Islets: Islet Cell Adenoma			
Overall Rates (a)	5/47 (11%)	0/45 (0%)	2/49 (4%)
Adjusted Rates (b)	16.1%	0.0%	7.7%
Terminal Rates (c)	5/31 (16%)	0/27 (0%)	2/26 (8%)
Week of First Observation	104		104
Life Table Tests (d)	P=0.160N	P=0.045N	P=0.289N
Incidental Tumor Tests (d)	P=0.160N	P=0.045N	P=0.289N
Cochran-Armitage Trend Test (d)	P=0.111N		
Fisher Exact Test (d)		P=0.031N	P=0.201N
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (a)	6/47 (13%)	0/45 (0%)	3/49 (6%)
Adjusted Rates (b)	19.4%	0.0%	11.5%
Terminal Rates (c)	6/31 (19%)	0/27 (0%)	3/26 (12%)
Week of First Observation	104		104
Life Table Tests (d)	P=0.201N	P=0.025N	P=0.331N
Incidental Tumor Tests (d)	P=0.201N	P=0.025N	P=0.331N
Cochran-Armitage Trend Test (d)	P=0.136N		
Fisher Exact Test (d)		P=0.015N	P=0.223N
Testis: Interstitial Cell Tumor			
Overall Rates (a)	32/50 (64%)	30/49 (61%)	31/50 (62%)
Adjusted Rates (b)	94.1%	88.0%	83.4%
Terminal Rates (c)	29/31 (94%)	23/27 (85%)	20/26 (77%)
Week of First Observation	85	76	63
Life Table Tests (d)	P=0.260	P=0.442	P=0.311
Incidental Tumor Tests (d)	P=0.509N	P=0.533N	P=0.576N
Cochran-Armitage Trend Test (d)	P=0.459N		
Fisher Exact Test (d)		P=0.469N	P=0.500N

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

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF AMPICILLIN TRIHYDRATE

	Vehicle Control	750 mg/kg	1,500 mg/kg
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	9.4%	3.0%	7.7%
Terminal Rates (c)	3/32 (9%)	1/33 (3%)	1/31 (3%)
Week of First Observation	104	104	93
Life Table Tests (d)	P=0.590	P=0.293N	P=0.659
Incidental Tumor Tests (d)	P=0.557N	P=0.293N	P=0.628N
Cochran-Armitage Trend Test (d)	P=0.594		
Fisher Exact Test (d)		P=0.309N	P=0.661
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (b)	9.4%	3.0%	10.3%
Terminal Rates (c)	3/32 (9%)	1/33 (3%)	1/31 (3%)
Week of First Observation	104	104	93
Life Table Tests (d)	P=0.410	P=0.293N	P=0.498
Incidental Tumor Tests (d)	P=0.467	P=0.293N	P=0.557
Cochran-Armitage Trend Test (d)	P=0.412		
Fisher Exact Test (d)		P=0.309N	P=0.500
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	14/50 (28%)	19/50 (38%)	15/50 (30%)
Adjusted Rates (b)	36.1%	50.9%	36.7%
Terminal Rates (c)	8/32 (25%)	15/33 (45%)	7/31 (23%)
Week of First Observation	86	54	74
Life Table Tests (d)	P=0.443	P=0.215	P=0.489
Incidental Tumor Tests (d)	P=0.531	P=0.098	P=0.576
Cochran-Armitage Trend Test (d)	P=0.457		
Fisher Exact Test (d)		P=0.198	P=0.500
Pituitary Gland: Adenoma			
Overall Rates (a)	18/49 (37%)	20/50 (40%)	22/49 (45%)
Adjusted Rates (b)	47.2%	51.8%	59.2%
Terminal Rates (c)	12/31 (39%)	15/33 (45%)	16/31 (52%)
Week of First Observation	74	71	91
Life Table Tests (d)	P=0.252	P=0.460	P=0.282
Incidental Tumor Tests (d)	P=0.253	P=0.491	P=0.296
Cochran-Armitage Trend Test (d)	P=0.236		
Fisher Exact Test (d)		P=0.449	P=0.269
Pituitary Gland: Carcinoma			
Overall Rates (a)	0/49 (0%)	3/50 (6%)	3/49 (6%)
Adjusted Rates (b)	0.0%	8.4%	9.7%
Terminal Rates (c)	0/31 (0%)	1/33 (3%)	3/31 (10%)
Week of First Observation		90	104
Life Table Tests (d)	P=0.104	P=0.122	P=0.120
Incidental Tumor Tests (d)	P=0.106	P=0.090	P=0.120
Cochran-Armitage Trend Test (d)	P=0.100		
Fisher Exact Test (d)		P=0.125	P=0.121
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	18/49 (37%)	23/50 (46%)	25/49 (51%)
Adjusted Rates (b)	47.2%	56.9%	67.3%
Terminal Rates (c)	12/31 (39%)	16/33 (48%)	19/31 (61%)
Week of First Observation	74	71	91
Life Table Tests (d)	P=0.113	P=0.255	P=0.126
Incidental Tumor Tests (d)	P=0.103	P=0.244	P=0.127
Cochran-Armitage Trend Test (d)	P=0.093		
Fisher Exact Test (d)		P=0.232	P=0.111

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF AMPICILLIN TRIHYDRATE (Continued)

	Vehicle Control	750 mg/kg	1,500 mg/kg
Adrenal Gland: Cortical Adenoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	4/49 (8%)
Adjusted Rates (b)	3.1%	9.1%	11.9%
Terminal Rates (c)	1/32 (3%)	3/33 (9%)	3/30 (10%)
Week of First Observation	104	104	76
Life Table Tests (d)	P=0.118	P=0.315	P=0.168
Incidental Tumor Tests (d)	P=0.114	P=0.315	P=0.166
Cochran-Armitage Trend Test (d)	P=0.127		
Fisher Exact Test (d)		P=0.309	P=0.175
Adrenal Gland: Cortical Adenoma or Carcinoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	5/49 (10%)
Adjusted Rates (b)	3.1%	9.1%	15.1%
Terminal Rates (c)	1/32 (3%)	3/33 (9%)	4/30 (13%)
Week of First Observation	104	104	76
Life Table Tests (d)	P=0.060	P=0.315	P=0.094
Incidental Tumor Tests (d)	P=0.057	P=0.315	P=0.092
Cochran-Armitage Trend Test (d)	P=0.067		
Fisher Exact Test (d)		P=0.309	P=0.098
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	4/49 (8%)
Adjusted Rates (b)	8.3%	9.1%	12.6%
Terminal Rates (c)	1/32 (3%)	3/33 (9%)	3/30 (10%)
Week of First Observation	98	104	102
Life Table Tests (d)	P=0.394	P=0.657	P=0.474
Incidental Tumor Tests (d)	P=0.455	P=0.550	P=0.547
Cochran-Armitage Trend Test (d)	P=0.410		
Fisher Exact Test (d)		P=0.661	P=0.489
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	5/49 (10%)
Adjusted Rates (b)	8.3%	9.1%	14.8%
Terminal Rates (c)	1/32 (3%)	3/33 (9%)	3/30 (10%)
Week of First Observation	98	104	96
Life Table Tests (d)	P=0.265	P=0.657	P=0.341
Incidental Tumor Tests (d)	P=0.331	P=0.550	P=0.417
Cochran-Armitage Trend Test (d)	P=0.273		
Fisher Exact Test (d)		P=0.661	P=0.346
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (a)	0/48 (0%)	4/49 (8%)	2/49 (4%)
Adjusted Rates (b)	0.0%	11.0%	6.5%
Terminal Rates (c)	0/32 (0%)	3/33 (9%)	2/31 (6%)
Week of First Observation		59	104
Life Table Tests (d)	P=0.214	P=0.067	P=0.231
Incidental Tumor Tests (d)	P=0.209	P=0.084	P=0.231
Cochran-Armitage Trend Test (d)	P=0.228		
Fisher Exact Test (d)		P=0.061	P=0.253
Mammary Gland: Fibroadenoma			
Overall Rates (a)	16/50 (32%)	25/50 (50%)	19/50 (38%)
Adjusted Rates (b)	42.6%	65.4%	49.5%
Terminal Rates (c)	11/32 (34%)	20/33 (61%)	12/31 (39%)
Week of First Observation	93	77	84
Life Table Tests (d)	P=0.288	P=0.063	P=0.323
Incidental Tumor Tests (d)	P=0.357	P=0.019	P=0.402
Cochran-Armitage Trend Test (d)	P=0.305		
Fisher Exact Test (d)		P=0.052	P=0.338

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF AMPICILLIN TRIHYDRATE (Continued)

	Vehicle Control	750 mg/kg	1,500 mg/kg
Clitoral Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	2.4%	0.0%	9.1%
Terminal Rates (c)	0/32 (0%)	0/33 (0%)	2/31 (6%)
Week of First Observation	93		102
Life Table Tests (d)	P=0.177	P=0.520N	P=0.304
Incidental Tumor Tests (d)	P=0.225	P=0.662N	P=0.351
Cochran-Armitage Trend Test (d)	P=0.176		
Fisher Exact Test (d)		P=0.500N	P=0.309
Clitoral Gland: Adenoma, Squamous Cell Papilloma, Adenocarcinoma, or Carcinoma (e)			
Overall Rates (a)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	5.5%	2.2%	9.1%
Terminal Rates (c)	1/32 (3%)	0/33 (0%)	2/31 (6%)
Week of First Observation	93	77	102
Life Table Tests (d)	P=0.398	P=0.511N	P=0.493
Incidental Tumor Tests (d)	P=0.442	P=0.528N	P=0.543
Cochran-Armitage Trend Test (d)	P=0.399		
Fisher Exact Test (d)		P=0.500N	P=0.500
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	6/50 (12%)	5/50 (10%)	1/49 (2%)
Adjusted Rates (b)	18.0%	14.3%	3.2%
Terminal Rates (c)	5/32 (16%)	4/33 (12%)	1/31 (3%)
Week of First Observation	102	87	104
Life Table Tests (d)	P=0.052N	P=0.494N	P=0.064N
Incidental Tumor Tests (d)	P=0.053N	P=0.520N	P=0.056N
Cochran-Armitage Trend Test (d)	P=0.051N		
Fisher Exact Test (d)		P=0.500N	P=0.059N
Uterus: Endometrial Stromal Polyp or Sarcoma			
Overall Rates (a)	8/50 (16%)	5/50 (10%)	1/49 (2%)
Adjusted Rates (b)	21.4%	14.3%	3.2%
Terminal Rates (c)	5/32 (16%)	4/33 (12%)	1/31 (3%)
Week of First Observation	51	87	104
Life Table Tests (d)	P=0.015N	P=0.283N	P=0.022N
Incidental Tumor Tests (d)	P=0.019N	P=0.251N	P=0.039N
Cochran-Armitage Trend Test (d)	P=0.014N		
Fisher Exact Test (d)		P=0.277N	P=0.017N

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

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF AMPICILLIN TRIHYDRATE

	Vehicle Control	1,500 mg/kg	3,000 mg/kg
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	2/50 (4%)	7/49 (14%)	5/49 (10%)
Adjusted Rates (b)	6.3%	23.5%	18.1%
Terminal Rates (c)	2/32 (6%)	2/21 (10%)	2/20 (10%)
Week of First Observation	104	81	69
Life Table Tests (d)	P=0.092	P=0.041	P=0.111
Incidental Tumor Tests (d)	P=0.226	P=0.106	P=0.210
Cochran-Armitage Trend Test (d)	P=0.186		
Fisher Exact Test (d)		P=0.075	P=0.210
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	7/49 (14%)	5/49 (10%)
Adjusted Rates (b)	8.9%	23.5%	18.1%
Terminal Rates (c)	2/32 (6%)	2/21 (10%)	2/20 (10%)
Week of First Observation	87	81	69
Life Table Tests (d)	P=0.163	P=0.091	P=0.209
Incidental Tumor Tests (d)	P=0.373	P=0.209	P=0.385
Cochran-Armitage Trend Test (d)	P=0.297		
Fisher Exact Test (d)		P=0.151	P=0.346
Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Overall Rates (a)	2/50 (4%)	8/49 (16%)	5/49 (10%)
Adjusted Rates (b)	6.3%	25.5%	18.1%
Terminal Rates (c)	2/32 (6%)	2/21 (10%)	2/20 (10%)
Week of First Observation	104	77	69
Life Table Tests (d)	P=0.097	P=0.024	P=0.111
Incidental Tumor Tests (d)	P=0.254	P=0.064	P=0.210
Cochran-Armitage Trend Test (d)	P=0.193		
Fisher Exact Test (d)		P=0.043	P=0.210
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	8/49 (16%)	5/49 (10%)
Adjusted Rates (b)	8.9%	25.5%	18.1%
Terminal Rates (c)	2/32 (6%)	2/21 (10%)	2/20 (10%)
Week of First Observation	87	77	69
Life Table Tests (d)	P=0.167	P=0.057	P=0.209
Incidental Tumor Tests (d)	P=0.402	P=0.132	P=0.385
Cochran-Armitage Trend Test (d)	P=0.301		
Fisher Exact Test (d)		P=0.094	P=0.346
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	1/50 (2%)	3/49 (6%)	1/47 (2%)
Adjusted Rates (b)	3.1%	11.4%	5.0%
Terminal Rates (c)	1/32 (3%)	1/21 (5%)	1/20 (5%)
Week of First Observation	104	96	104
Life Table Tests (d)	P=0.466	P=0.213	P=0.654
Incidental Tumor Tests (d)	P=0.552	P=0.439	P=0.654
Cochran-Armitage Trend Test (d)	P=0.588		
Fisher Exact Test (d)		P=0.301	P=0.737
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	5/50 (10%)	3/49 (6%)	2/47 (4%)
Adjusted Rates (b)	15.6%	12.4%	10.0%
Terminal Rates (c)	5/32 (16%)	2/21 (10%)	2/20 (10%)
Week of First Observation	104	94	104
Life Table Tests (d)	P=0.351N	P=0.575N	P=0.437N
Incidental Tumor Tests (d)	P=0.321N	P=0.482N	P=0.437N
Cochran-Armitage Trend Test (d)	P=0.178N		
Fisher Exact Test (d)		P=0.369N	P=0.244N

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF AMPICILLIN TRIHYDRATE (Continued)

	Vehicle Control	1,500 mg/kg	3,000 mg/kg
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	6/49 (12%)	3/47 (6%)
Adjusted Rates (b)	18.8%	22.7%	15.0%
Terminal Rates (c)	6/32 (19%)	3/21 (14%)	3/20 (15%)
Week of First Observation	104	94	104
Life Table Tests (d)	P=0.461N	P=0.370	P=0.511N
Incidental Tumor Tests (d)	P=0.383N	P=0.611	P=0.511N
Cochran-Armitage Trend Test (d)	P=0.232N		
Fisher Exact Test (d)		P=0.606	P=0.275N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	3/50 (6%)	2/49 (4%)	2/49 (4%)
Adjusted Rates (b)	9.4%	9.5%	8.4%
Terminal Rates (c)	3/32 (9%)	2/21 (10%)	1/20 (5%)
Week of First Observation	104	104	97
Life Table Tests (d)	P=0.583	P=0.676	P=0.677
Incidental Tumor Tests (d)	P=0.557N	P=0.676	P=0.598N
Cochran-Armitage Trend Test (d)	P=0.415N		
Fisher Exact Test (d)		P=0.510N	P=0.510N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	4/50 (8%)	2/49 (4%)	5/49 (10%)
Adjusted Rates (b)	12.5%	9.5%	19.2%
Terminal Rates (c)	4/32 (13%)	2/21 (10%)	2/20 (10%)
Week of First Observation	104	104	83
Life Table Tests (d)	P=0.223	P=0.543N	P=0.279
Incidental Tumor Tests (d)	P=0.309	P=0.543N	P=0.452
Cochran-Armitage Trend Test (d)	P=0.413		
Fisher Exact Test (d)		P=0.349N	P=0.487
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	3/50 (6%)	1/49 (2%)	0/49 (0%)
Adjusted Rates (b)	9.4%	4.8%	0.0%
Terminal Rates (c)	3/32 (9%)	1/21 (5%)	0/20 (0%)
Week of First Observation	104	104	
Life Table Tests (d)	P=0.128N	P=0.464N	P=0.214N
Incidental Tumor Tests (d)	P=0.128N	P=0.464N	P=0.214N
Cochran-Armitage Trend Test (d)	P=0.063N		
Fisher Exact Test (d)		P=0.316N	P=0.125N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	3/50 (6%)	2/48 (4%)	3/46 (7%)
Adjusted Rates (b)	9.4%	9.5%	15.0%
Terminal Rates (c)	3/32 (9%)	2/21 (10%)	3/20 (15%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.357	P=0.676	P=0.433
Incidental Tumor Tests (d)	P=0.357	P=0.676	P=0.433
Cochran-Armitage Trend Test (d)	P=0.549		
Fisher Exact Test (d)		P=0.520N	P=0.621
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	6/50 (12%)	2/48 (4%)	4/46 (9%)
Adjusted Rates (b)	16.2%	8.7%	16.1%
Terminal Rates (c)	2/32 (6%)	1/21 (5%)	2/20 (10%)
Week of First Observation	84	101	87
Life Table Tests (d)	P=0.475N	P=0.233N	P=0.565N
Incidental Tumor Tests (d)	P=0.270N	P=0.057N	P=0.307N
Cochran-Armitage Trend Test (d)	P=0.333N		
Fisher Exact Test (d)		P=0.148N	P=0.425N

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF AMPICILLIN TRIHYDRATE (Continued)

	Vehicle Control	1,500 mg/kg	3,000 mg/kg
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	9/50 (18%)	4/48 (8%)	7/46 (15%)
Adjusted Rates (b)	24.6%	17.9%	30.1%
Terminal Rates (c)	5/32 (16%)	3/21 (14%)	5/20 (25%)
Week of First Observation	84	101	87
Life Table Tests (d)	P=0.484	P=0.279N	P=0.512
Incidental Tumor Tests (d)	P=0.474N	P=0.111N	P=0.503N
Cochran-Armitage Trend Test (d)	P=0.390N		
Fisher Exact Test (d)		P=0.133N	P=0.465N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	3/48 (6%)	1/48 (2%)	0/45 (0%)
Adjusted Rates (b)	8.7%	4.8%	0.0%
Terminal Rates (c)	2/32 (6%)	1/21 (5%)	0/20 (0%)
Week of First Observation	84	104	
Life Table Tests (d)	P=0.117N	P=0.431N	P=0.197N
Incidental Tumor Tests (d)	P=0.090N	P=0.394N	P=0.142N
Cochran-Armitage Trend Test (d)	P=0.066N		
Fisher Exact Test (d)		P=0.308N	P=0.133N
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	3/42 (7%)	1/44 (2%)	1/39 (3%)
Adjusted Rates (b)	10.0%	4.8%	5.3%
Terminal Rates (c)	3/30 (10%)	1/21 (5%)	1/19 (5%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.344N	P=0.439N	P=0.478N
Incidental Tumor Tests (d)	P=0.344N	P=0.439N	P=0.478N
Cochran-Armitage Trend Test (d)	P=0.217N		
Fisher Exact Test (d)		P=0.291N	P=0.336N

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

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF AMPICILLIN TRIHYDRATE

	Vehicle Control	1,500 mg/kg	3,000 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	1/50 (2%)	0/50 (0%)	4/50 (8%)
Adjusted Rates (b)	2.9%	0.0%	13.0%
Terminal Rates (c)	1/34 (3%)	0/28 (0%)	3/28 (11%)
Week of First Observation	104		77
Life Table Tests (d)	P=0.060	P=0.539N	P=0.129
Incidental Tumor Tests (d)	P=0.049	P=0.539N	P=0.104
Cochran-Armitage Trend Test (d)	P=0.082		
Fisher Exact Test (d)		P=0.500N	P=0.181
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	2.9%	9.4%	0.0%
Terminal Rates (c)	1/34 (3%)	2/28 (7%)	0/28 (0%)
Week of First Observation	104	87	
Life Table Tests (d)	P=0.439N	P=0.252	P=0.539N
Incidental Tumor Tests (d)	P=0.409N	P=0.351	P=0.539N
Cochran-Armitage Trend Test (d)	P=0.378N		
Fisher Exact Test (d)		P=0.309	P=0.500N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	4/50 (8%)
Adjusted Rates (b)	5.9%	9.4%	13.0%
Terminal Rates (c)	2/34 (6%)	2/28 (7%)	3/28 (11%)
Week of First Observation	104	87	77
Life Table Tests (d)	P=0.194	P=0.425	P=0.254
Incidental Tumor Tests (d)	P=0.181	P=0.535	P=0.220
Cochran-Armitage Trend Test (d)	P=0.264		
Fisher Exact Test (d)		P=0.500	P=0.339
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	14/50 (28%)	8/50 (16%)	11/50 (22%)
Adjusted Rates (b)	41.2%	25.1%	37.9%
Terminal Rates (c)	14/34 (41%)	5/28 (18%)	10/28 (36%)
Week of First Observation	104	95	97
Life Table Tests (d)	P=0.478N	P=0.235N	P=0.545N
Incidental Tumor Tests (d)	P=0.480N	P=0.214N	P=0.547N
Cochran-Armitage Trend Test (d)	P=0.273N		
Fisher Exact Test (d)		P=0.114N	P=0.323N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	2.9%	10.7%	6.3%
Terminal Rates (c)	1/34 (3%)	3/28 (11%)	1/28 (4%)
Week of First Observation	104	104	89
Life Table Tests (d)	P=0.326	P=0.237	P=0.435
Incidental Tumor Tests (d)	P=0.342	P=0.237	P=0.488
Cochran-Armitage Trend Test (d)	P=0.399		
Fisher Exact Test (d)		P=0.309	P=0.500
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	19/50 (38%)	12/50 (24%)	14/50 (28%)
Adjusted Rates (b)	52.3%	36.5%	46.3%
Terminal Rates (c)	17/34 (50%)	8/28 (29%)	12/28 (43%)
Week of First Observation	82	92	89
Life Table Tests (d)	P=0.375N	P=0.240N	P=0.430N
Incidental Tumor Tests (d)	P=0.343N	P=0.142N	P=0.392N
Cochran-Armitage Trend Test (d)	P=0.163N		
Fisher Exact Test (d)		P=0.097N	P=0.198N

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF AMPICILLIN TRIHYDRATE (Continued)

	Vehicle Control	1,500 mg/kg	3,000 mg/kg
Hematopoietic System: Lymphoma or Leukemia			
Overall Rates (a)	20/50 (40%)	12/50 (24%)	15/50 (30%)
Adjusted Rates (b)	53.4%	36.5%	48.1%
Terminal Rates (c)	17/34 (50%)	8/28 (29%)	12/28 (43%)
Week of First Observation	82	92	89
Life Table Tests (d)	P=0.391N	P=0.186N	P=0.453N
Incidental Tumor Tests (d)	P=0.348N	P=0.079N	P=0.395N
Cochran-Armitage Trend Test (d)	P=0.166N		
Fisher Exact Test (d)		P=0.067N	P=0.201N
Pituitary Gland: Adenoma			
Overall Rates (a)	7/44 (16%)	2/40 (5%)	5/36 (14%)
Adjusted Rates (b)	24.1%	8.7%	25.0%
Terminal Rates (c)	7/29 (24%)	2/23 (9%)	5/20 (25%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.536N	P=0.140N	P=0.605
Incidental Tumor Tests (d)	P=0.536N	P=0.140N	P=0.605
Cochran-Armitage Trend Test (d)	P=0.422N		
Fisher Exact Test (d)		P=0.102N	P=0.528N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	8/44 (18%)	3/40 (7%)	6/36 (17%)
Adjusted Rates (b)	27.6%	13.0%	30.0%
Terminal Rates (c)	8/29 (28%)	3/23 (13%)	6/20 (30%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.550	P=0.178N	P=0.554
Incidental Tumor Tests (d)	P=0.550	P=0.178N	P=0.554
Cochran-Armitage Trend Test (d)	P=0.453N		
Fisher Exact Test (d)		P=0.130N	P=0.549N

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

APPENDIX F

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

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

	Incidence in Vehicle Controls		
	Leukemia	Lymphoma	Leukemia or Lymphoma
No 2-year studies by Springborn Institute for Bioresearch, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	152/1,100 (13.8%)	10/1,100 (0.91%)	162/1,100 (14.7%)
SD (b)	8.12%	1.72%	8.25%
Range (c)			
High	14/50	3/50	14/50
Low	1/50	0/50	1/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks. The reported range is the same for both leukemia and lymphoma or leukemia (combined).
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

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

	Incidence in Vehicle Controls		
	Pheochromocytoma	Malignant Pheochromocytoma	Pheochromocytoma or Malignant Pheochromocytoma
No 2-year studies by Springborn Institute for Bioresearch, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	243/1,092 (22.3%)	6/1,092 (0.5%)	247/1,092 (22.6%)
SD (b)	9.18%	0.93%	9.05%
Range (c)			
High	20/49	1/45	20/49
Low	2/50	0/50	2/50

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

TABLE F3. HISTORICAL INCIDENCE OF MAMMARY GLAND TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Fibroadenoma	Adenocarcinoma	Fibroadenoma or Adenocarcinoma
No 2-year studies by Springborn Institute for Bioresearch, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	(b) 280/1,100 (25.5%)	(c) 17/1,100 (1.5%)	(b,c) 288/1,100 (26.2%)
SD (d)	8.08%	1.50%	8.21%
Range (e)			
High	19/50	2/50	19/50
Low	7/50	0/50	7/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Includes seven adenomas, NOS, one papillary adenoma, four papillary cystadenomas, and one papillary cystadenoma
(c) Includes one papillary cystadenocarcinoma
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

TABLE F4. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Fibroma	Fibrosarcoma	Fibroma or Fibrosarcoma
No 2-year studies by Springborn Institute for Bioresearch, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	19/1,097 (1.7%)	(d) 57/1,097 (5.2%)	(d) 76/1,097 (6.9%)
SD (b)	2.42%	4.49%	6.06%
Range (c)			
High	4/50	7/50	11/50
Low	0/50	0/50	0/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes 6 neurofibrosarcomas and 19 sarcomas, NOS

APPENDIX G

GENETIC TOXICOLOGY OF AMPICILLIN TRIHYDRATE

TABLE G1. MUTAGENICITY OF AMPICILLIN TRIHYDRATE IN *SALMONELLA TYPHIMURIUM*

Strain	Dose (μg/plate)	Revertants/plate (a,b) −S9	+S9 (rat)	+S9 (hamster)
TA100	0	165 ± 11.8	138 ± 9.5	130 ± 6.1
	10	149 ± 7.7	148 ± 12.2	141 ± 4.9
	33	135 ± 3.2	133 ± 2.6	140 ± 2.0
	100	125 ± 4.6	153 ± 4.5	126 ± 3.8
	333	129 ± 3.5	139 ± 8.2	137 ± 4.6
	1,000	(c) 97 ± 6.2	(c) 123 ± 3.2	113 ± 4.3
TA1535	0	24 ± 3.3	19 ± 0.9	15 ± 0.9
	0.03	24 ± 0.9	12 ± 2.4	11 ± 1.2
	0.10	27 ± 2.9	16 ± 1.8	12 ± 0.9
	0.30	26 ± 5.2	12 ± 2.1	12 ± 0.6
	1.00	25 ± 2.1	14 ± 3.3	10 ± 3.0
	2.00	--	6 ± 2.4	(c) 7 ± 1.5
	3.30	(c) 10 ± 3.9	--	--
TA1537	0	6 ± 1.5	8 ± 0.7	10 ± 1.2
	0.03	6 ± 0.9	8 ± 0.9	4 ± 0.9
	0.10	7 ± 2.2	8 ± 2.1	7 ± 1.5
	0.30	6 ± 0.9	6 ± 1.2	8 ± 2.0
	1.00	7 ± 1.3	6 ± 1.5	5 ± 0.6
	2.00	--	1 ± 0.3	(c) 3 ± 1.2
	3.30	(c) 1 ± 0.0	--	--
TA98	0	18 ± 3.2	27 ± 0.7	24 ± 2.7
	10	16 ± 1.5	21 ± 0.3	27 ± 3.8
	33	16 ± 2.6	24 ± 4.4	24 ± 0.9
	100	13 ± 2.7	23 ± 4.5	27 ± 3.8
	333	15 ± 0.9	30 ± 1.3	25 ± 1.9
	1,000	(c) 9 ± 0.6	(c) 17 ± 2.1	(c) 19 ± 0.7

(a) The S9 fractions were prepared from the liver of Aroclor 1254-induced male Sprague-Dawley rats and male Syrian hamsters. Cells and study compound or solvent (DMSO) were incubated for 20 minutes at 37° C in the presence of either S9 or buffer. After the addition of soft agar, the contents of each tube were poured onto minimal medium, and the plates were incubated at 37° C for 48 hours (Haworth et al., 1983). The experiment was performed twice, each in triplicate; because the results were similar, data from only one experiment are shown.
(b) Mean ± standard error
(c) Slight toxicity

TABLE G2. MUTAGENICITY OF AMPICILLIN TRIHYDRATE IN L5178Y MOUSE LYMPHOMA CELLS IN THE ABSENCE OF S9 (a)

Compound	Dose (μg/ml)	Total Mutant Clones	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutation Frequency (mutants/10^6 clonable cells)
DMSO	1%	167	111.7	100	50
		123	88.3	100	46
		161	101.2	100	53
		187	89.0	100	70
Ethylmethane sulfonate	250	1,104	92.8	63.8	396
		977	107.0	69.5	304
Ampicillin trihydrate	313	154	98.5	104.7	52
		130	107.8	115.6	40
		143	88.7	80.6	54
	625	133	98.7	108.2	45
		120	105.2	125.5	38
		172	92.7	106.2	62
	1,250	165	105.7	118.7	52
		210	98.7	91.6	71
		163	93.3	100.5	58
	2,500	180	94.3	97.9	64
		184	112.0	128.2	55
		206	94.0	97.6	73
	5,000	147	95.7	99.1	51
		166	93.8	91.3	59
		131	99.3	124.7	44

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

TABLE G3. MUTAGENICITY OF AMPICILLIN TRIHYDRATE IN L5178Y MOUSE LYMPHOMA CELLS IN THE PRESENCE OF S9 (a)

Compound	Dose (μg/ml)	Total Mutant Clones	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutation Frequency (mutants/10^6 clonable cells)
DMSO	1%	67	92.3	100	24
		47	89.0	100	18
		65	91.5	100	24
		95	115.0	100	28
3-Methylcholanthrene	2.5	636	107.5	74.3	197
		624	88.8	50.7	234
		658	87.2	57.8	252
Ampicillin trihydrate	500	59	64.0	76.7	31
		59	90.5	99.3	22
		60	94.2	107.4	21
	1,000	94	91.7	91.0	34
		81	95.2	103.1	28
		39	102.5	110.1	13
	2,000	92	104.0	117.1	29
		66	93.2	108.7	24
	3,000	58	107.8	95.5	18
		89	85.8	102.4	35
	5,000	78	80.2	83.8	32
		70	81.7	99.3	29
		42	102.7	114.3	14

(a) Experiments were performed twice, all doses were tested in duplicate, except the solvent control (DMSO), which was tested in triplicate. Because the results were similar, data from only one experiment are shown. The protocol was basically that of Clive et al. (1979). Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium to determine the percentage of viable cells. S9 was prepared from the liver of Aroclor 1254-induced male F344 rats.

TABLE G4. INDUCTION OF SISTER-CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY AMPICILLIN TRIHYDRATE (a)

−S9 (b)		+S9 (c)	
Dose (μg/ml)	SCE/Cell (d)	Dose (μg/ml)	SCE/Cell (d)
DMSO		DMSO	
10 μl	8.2	10 μl	8.1
Ampicillin trihydrate		Ampicillin trihydrate	
50	8.9	50	7.8
160	9.3	160	7.9
500	9.5	500	8.8
1,500	8.0	1,500	9.0
Mitomycin C		Cyclophosphamide	
0.001	24.0	0.30	12.7
0.010	72.9	2.00	41.5

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

TABLE G5. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY AMPICILLIN TRIHYDRATE (a)

−S9 (b)		+S9 (c)	
Dose (μg/ml)	Abs/100 Cells (percent cells with abs)	Dose (μg/ml)	Abs/100 Cells (percent cells with abs)
DMSO		DMSO	
10 μl	0 (0)	10 μl	1 (1)
Ampicillin trihydrate		Ampicillin trihydrate	
250	1 (1)	250	0 (0)
500	1 (1)	500	3 (3)
1,000	1 (1)	1,000	0 (0)
1,500	1 (1)	1,500	2 (2)
Mitomycin C		Cyclophosphamide	
0.25	18 (16)	15	32 (24)
1.00	50 (40)	50	52 (38)

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

APPENDIX H

CHEMICAL CHARACTERIZATION OF AMPICILLIN TRIHYDRATE

APPENDIX H. CHEMICAL CHARACTERIZATION

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

	Determined	Literature Values
A. Lot no. 61849K		
1. Physical properties		
a. Melting point:	197°-202° C (visual capillary, Büchi 510) (decomposes)	No literature value found
b. Appearance:	Colorless powder	White, crystalline powder (USP, 1975)
c. Specific rotation:	$[\alpha]_D^{26}$: 251.2° (water)	$[\alpha]_D^{23}$: 287.9° (water) (Merck Index, 1976) for anhydrous ampicillin and equivalent to 249.4° for the trihydrate
2. Spectral data		
a. Infrared		
Instrument:	Beckman IR-12	
Phase:	1% potassium bromide	
Results:	See Figure 5	Identical to a supplied spectrum of USP standard ampicillin trihydrate
b. Ultraviolet/visible		
Instrument:	Cary 118	
Solvent:	0.1 N hydrochloric acid	
Results:		USP Standard Ampicillin Trihydrate

λ_{max} (nm)	$\varepsilon \times 10^{-2}$	λ_{max} (nm)	$\varepsilon \times 10^{-2}$
268	2.29 ± 0.02(δ)	268	2.18 ± 0.03(δ)
262	3.14 ± 0.02(δ)	262	3.06 ± 0.04(δ)
257	3.30 ± 0.02(δ)	257	3.30 ± 0.04(δ)

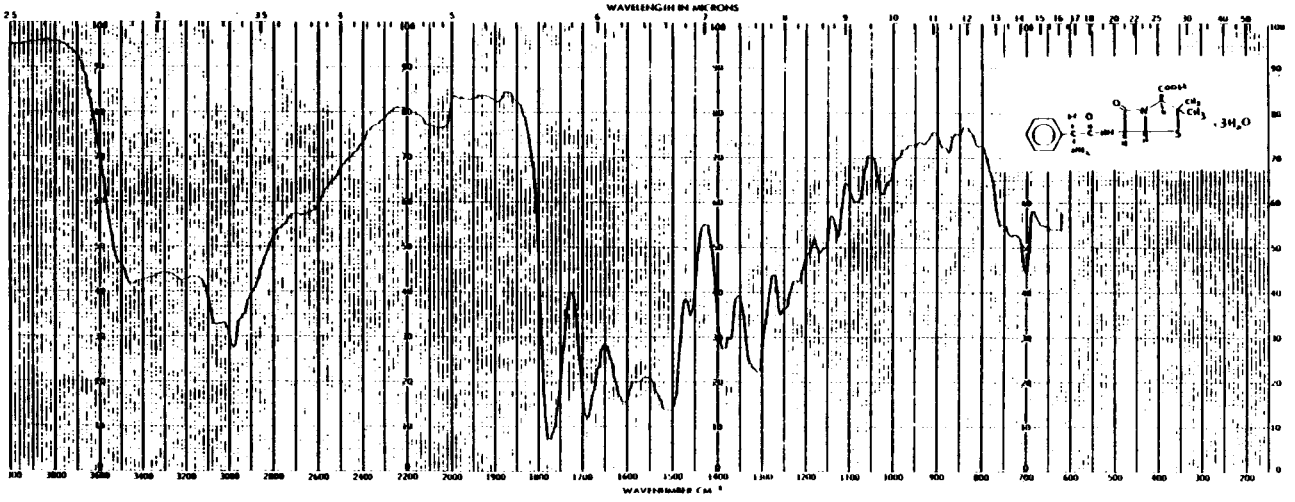


FIGURE 5. INFRARED ABSORPTION SPECTRUM OF AMPICILLIN TRIHYDRATE (LOT NO. 61849K)

	Determined	Literature Values
c. Nuclear magnetic resonance		
Instrument:	Varian EM-360A	
Solvent		
System a:	DMSO d_6 with tetramethyl silane internal standard	
System b:	DMSO d_6 plus D_2O with tetramethyl silane internal standard	
Assignments:	See Figures 6 and 7	
Chemical shift (δ):	**System a** a s, 1.30 ppm b s, 142 ppm c s, 3.96 ppm d s, 4.77 ppm e m, 5.18-5.41 ppm f m, 7.14-7.43 ppm g HDO and exchangeable protons 4.08-4.50 ppm h DMSO, 2.36-2.60 ppm i impurity, 1.2 ppm j impurity, 2.08 ppm k impurity, 4.6-4.75 ppm	
	System b a s, 134 ppm b s, 1.42 ppm c s, 3.88-4.05 ppm d s, 4.96 ppm e dd, 5.20-5.48 ppm J_{ce} = 7Hz f s, 7.42 ppm g HDO and exchangeable protons, 3.88-4.05 ppm h DMSO, 2.36-2.62 ppm i impurity, 1.2 j impurity, 2.1	Consistent with a literature spectrum (Wilson, 1974)

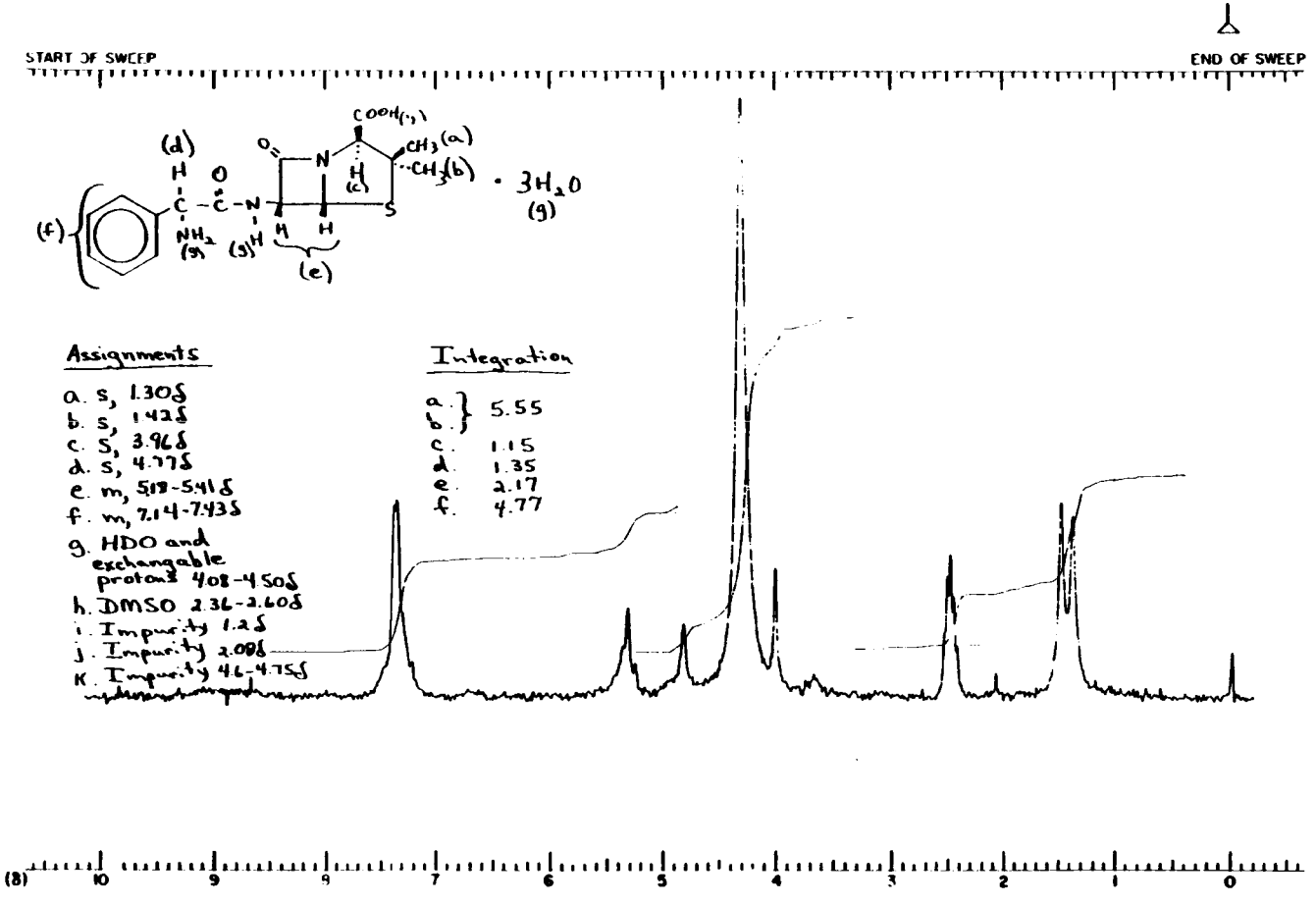


FIGURE 6. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF AMPICILLIN TRIHYDRATE (LOT NO. 61849K)

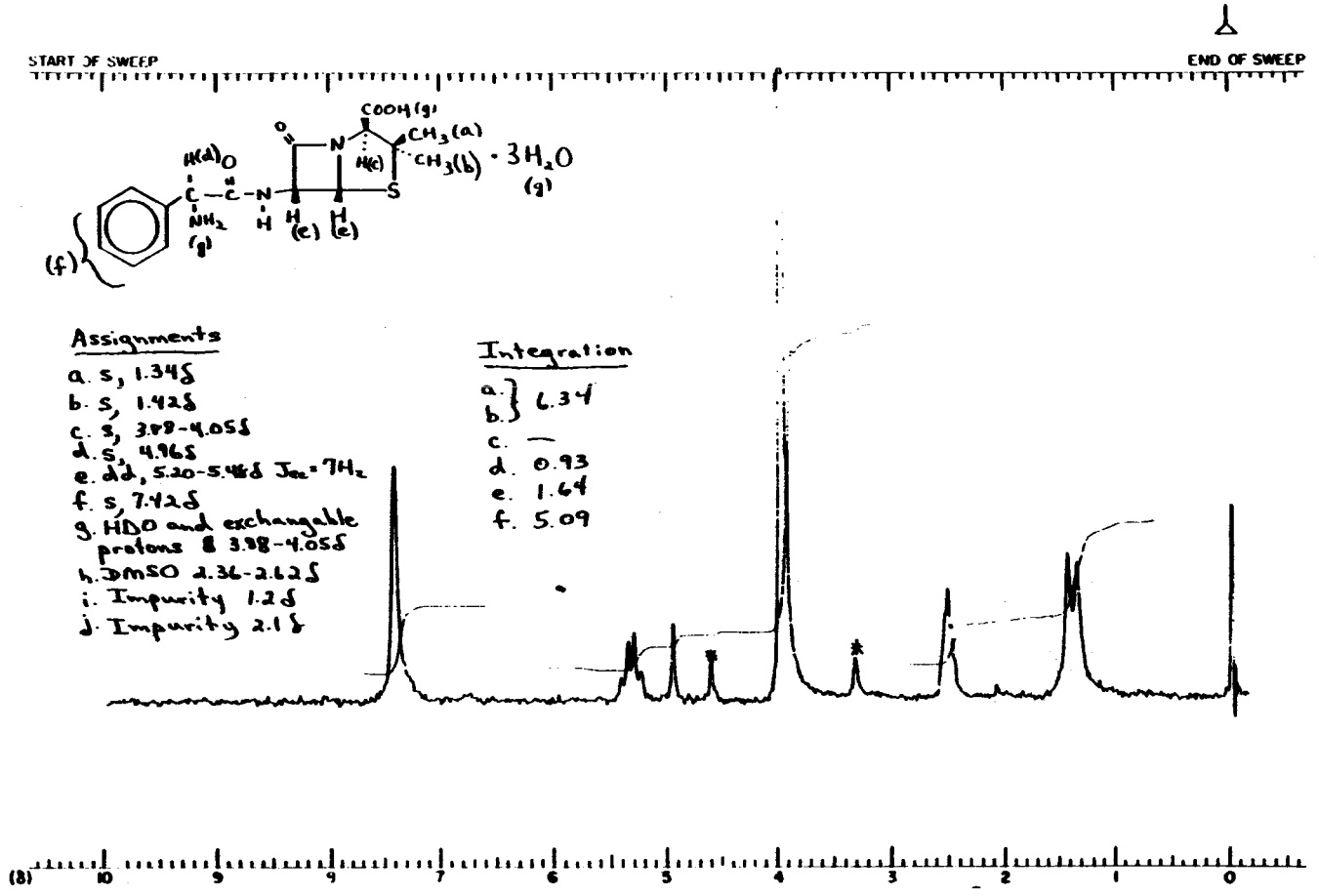


FIGURE 7. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF AMPICILLIN TRIHYDRATE WITH DEUTERATED WATER (LOT NO. 61849K)

Integration ratios:

System a	
a, b	5.55
c	1.15
d	1.35
e	2.17
f	4.77
System b	
a, b	6.34
c	--
d	0.93
e	1.64
f	5.09

3. **Water analysis (Karl Fischer):** 14.3% ± 0.3 (δ)% (theoretical for trihydrate 13.40%)

4. **Elemental analysis**

Element	C	H	N	S	O
Theory percent (T)	47.63	6.25	10.41	7.95	27.76
Determined percent (D)	47.40	6.32	10.25	7.72	27.65
	47.52	6.17	10.18	7.79	27.58
Percent D/T	99.6	100.0	98.1	97.5	99.5

5. **Titration**

   a. **Iodometric**

   Procedure: As outlined for potency in §436.204 of the Code of Federal Regulations (CFR, 1977)

   Results: A potency of 856.2 ± 4.4 µg/mg relative to a USP sample of ampicillin trihydrate

   b. **Carboxylic acid function**

   Procedure: The compound was dissolved in dimethyl sulfoxide:methanol (2:3) and titrated potentiometrically with 0.1 N sodium methoxide in methanol.

   Results: 100.4% ± 0.2(δ)%

c. Amine function

Procedure: The compound was dissolved in glacial acetic acid and titrated potentiometrically with 0.1 N perchloric acid in glacial acetic acid.

Results: 96.7% ± 0.2 (δ)%

6. Chromatographic analysis

a. Thin-layer chromatography

Plates: Silica Gel 60 F-254, 0.25 mm
Amount spotted: 1, 10, and 30 µl of a 2 mg/ml solution (methanol:water, 8:2), 2 µg of the reference standard, and 20 µg of USP standard ampicillin trihydrate
Reference standard: L-cysteine hydrochloride
Visualization: Short- and long-wave ultraviolet and chloroplatinic acid spray reagent (Pokorny et al., 1973)

System 1: *n*-Butanol:water:glacial acetic acid (60:25:15), equilibrated

	Sample	USP Standard
R_f:	0.44 (major)	0.43 (major)
	0.26 (minor)	0.26 (minor)
	0.50 (trace)	0.14 (reference standard)
	0.14 (reference standard)	
R_{st}:	3.14 (major)	3.07 (major)
	1.86 (minor)	1.86 (minor)
	3.57 (trace)	

System 2: Ethyl acetate:water:glacial acetic acid:methanol (70:10:10:10), equilibrated

	Sample	USP Standard
R_f:	0.18 (major)	0.18 (major)
	0.28 (minor)	0.28 (minor)
	0.03 (trace)	0.03 (trace)
	0.07 (reference standard)	0.07 (reference standard)
R_{st}:	2.6 (major)	2.6 (major)
	4.0 (minor)	4.0 (minor)
	0.43 (trace)	0.43 (trace)

b. High-performance liquid chromatography

Instrumental system
Pump: Waters 6000A
Programmer: Waters 660
Detector: Waters 440
Injector: Waters U6K
Detection: Ultraviolet, 254 nm
Column: μBondapak C_{18}, 300 × 3.9 mm ID, with a CO:PELL ODS 72 × 2.3 mm ID guard column
Solvent system: A: Water containing 5 mM heptanesulfonic acid, sodium salt, 1% acetic acid
B: Methanol containing 5 mM heptanesulfonic acid, sodium salt, 1% acetic acid
Flow rate: 1 ml/min
Sample injected
System 1: 15 μl of a 2.0 mg/ml pH 7.4 phosphate buffer solution of the compound
System 2: 15 μl of a 1.8 mg/ml pH 7.4 phosphate buffer solution of the compound and a 2.2 mg/ml pH 7.4 phosphate buffer solution of a USP standard
System 3: 15 μl of a 2.0 mg/ml pH 7.4 phosphate buffer solution of the compound
Program: System 1: 30% B, isocratic
System 2: 50% B, isocratic
System 3: 60% B, isocratic

Results

System 1: A major peak preceded by one impurity with a relative area of 0.11% was detected.

Peak No.	Retention Volume (ml)	Retention Volume Relative to Major Peak	Area (percent of major peak)
1	4.0	0.15	0.11
2	27.1	1.00	100.0

System 2: For the sample, a major peak, preceded by two peaks, the first (single component) with a relative area of 0.12% and the second (multicomponent) with a relative area of 0.43%, and followed by two impurities with relative areas of 0.26% and 0.24% was detected. For the USP standard, a major peak, preceded by a multicomponent peak with a relative area of 0.25% and followed by two impurities with relative areas of 0.86% and 0.44% was detected.

Peak No.	Retention Volume (ml)	Retention Volume Relative to Major Peak	Area (percent of major peak)
Sample			
1	3.7	0.65	0.12
2 (multicomponent)	~ 4.6	~ 0.81	0.43
3	5.7	1.00	100.0
4	8.0	1.40	0.26
5	10.7	1.88	0.24
USP Standard			
1 (multicomponent)	4.6	0.81	0.25
2	5.7	1.00	100.0
3	9.5	1.67	0.86
4	11.4	2.00	0.44

System 3: A major peak, followed by one impurity with a relative area of 0.24%

Peak No.	Retention Volume (ml)	Retention Volume Relative to Major Peak	Area (percent of major peak)
1	4.1	1.00	100.0
2	6.7	1.63	0.24

Summary: Peak number 1 in system 1 probably corresponds to peak 1 in system 2. No other correspondence was indicated between the systems. Therefore, two minor peaks, one being multicomponent, with a total relative area of 0.55% were detected preceding the major peak in the compound. A possible total of three impurities, representing up to 0.74% relative area, were detected following the major peak. Comparison of the compound with a USP standard in one system indicated the two to be of approximately equivalent purity.

7. **Conclusions:** The results of elemental analysis for carbon, hydrogen, and oxygen were in agreement with theoretical values; those for nitrogen and sulfur were slightly low. The water content by Karl Fischer titrimetry was 14.3% ± 0.3(δ)% (theoretical is 13.4%). A potency of 856.2 ± 4.4 µg/mg, relative to a USP standard, was indicated by iodometric titration. Nonaqueous, potentiometric titrations of the carboxylic acid and amine functional groups indicated purities of 100.4% ± 0.2(δ)% and 96.7% ± 0.2(δ)%, respectively. Thin-layer chromatography indicated a minor and a trace impurity by two solvent systems.

A USP standard material chromatographed simultaneously indicated a minor impurity by one system and a minor and a trace impurity by the other. Reverse-phase high-performance liquid chromatography (HPLC) detected two minor peaks, one being non-homogenous, preceding the major peak and a total of three impurities following the major peak. The total relative area of all impurities was approximately 1.4%. A USP standard material chromatographed in one of the three HPLC systems was similar in composition and relative area of the impurities. The infrared spectrum was identical to a spectrum of USP standard material. The ultraviolet spectrum was identical in appearance and similar with respect to ε_{max} values to a spectrum of the USP material. The nuclear magnetic resonance spectrum was consistent with a literature spectrum. Specific rotation was in agreement with a literature value.

B. Lot No. 33564-550

	Determined	Literature Value
1. Physical properties		
a. Appearance:	White, microcrystalline powder	
b. Specific rotation	$[\alpha]_D^{25}$: +247.9 ± 4.8°(δ) (water)	$[\alpha]_D^{23}$: 287.9° (water) For anhydrous ampicillin and equivalent to 249.4° for the trihydrate (Merck Index, 1976)
2. Spectral data		
a. Infrared		
Instrument:	Perkin-Elmer 283	
Phase:	1.5% in potassium bromide	
Results:	See Figure 8	Consistent with literature reference (Florey, 1973)
b. Ultraviolet/visible		
Instrument:	Cary 219	
Solvent:	0.1 N hydrochloric acid	pH 5.3 phosphate buffer
Results:	No absorbances were observed from 800 to 350 nm at a concentration of 0.1% (w/v)	

λ_{max} (nm)	$\varepsilon \times 10^{-2}$	λ_{max} (nm)	$\varepsilon \times 10^{-2}$
316 (shoulder)	0.218 ± 0.005(δ)	268	2.26
289 (shoulder)	0.268 ± 0.008(δ)	262	3.15
267	2.00 ± 0.01(δ)	257	3.51
261	2.90 ± 0.01(δ)		
256	3.22 ± 0.01(δ)		
250 (shoulder)	3.49 ± 0.01(δ)	(Florey, 1973)	

USP Reference

316 (shoulder)	0.272 ± 0.004(δ)
289 (shoulder)	0.279 ± 0.004(δ)
267	2.04 ± 0.02(δ)
261	2.95 ± 0.02(δ)
256	3.28 ± 0.02(δ)
250 (shoulder)	3.56 ± 0.04(δ)

Note: Shoulders were observed at 317, 288, and 251 nm for lot no. 61849K but were not reported.

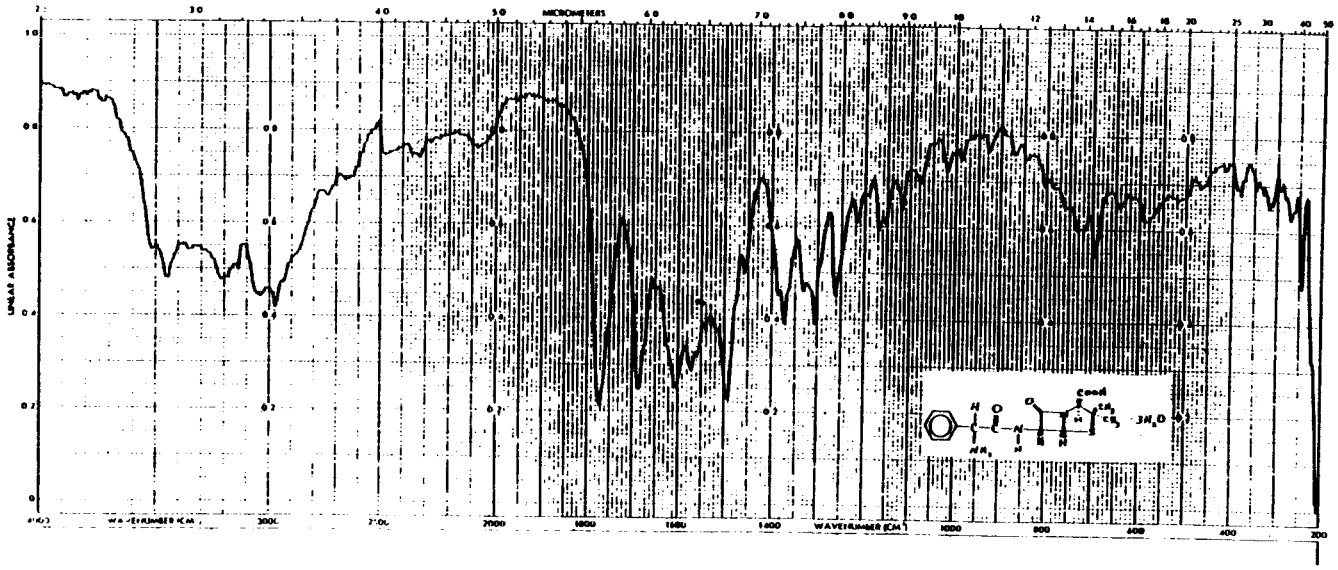


FIGURE 8. INFRARED ABSORPTION SPECTRUM OF AMPICILLIN TRIHYDRATE (LOT NO. 33564-550)

	Determined	Literature Values
c. Nuclear magnetic resonance		
Instrument:	Varian EM-360A	
Solvent:	Deuterated dimethyl sulfoxide with tetramethylsilane internal standard. Sample was exchanged with one drop of deuterium oxide.	Spectrum consistent with literature reference (Wilson, 1974)
Assignments:	See Figure 9	
Chemical shift (δ):	a s, 1.36 ppm b s, 1.47 ppm c s, 3.99 ppm d s, 4.96 ppm e m, 5.22-5.58 ppm f m, 7.13-7.67 ppm g unresolved m, 9.11 ppm h s, 4.56 ppm HDO	
Integration ratios:	a, b } 5.96 c 0.94 d 0.96 e 2.06 f 5.08 g 0.71 h HDO	

3. **Water analysis (Karl Fischer):** 13.24% ± 0.01(δ)% (theoretical percent water for trihydrate: 13.4%)

4. **Elemental analysis**

Element	C	H	N	S
Theory percent (T)	47.63	6.24	10.42	7.95
Determined percent	47.64	6.28	10.37	7.96
(D)	47.57	6.32	10.35	7.82
Percent D/T	99.95	101.0	99.42	99.24

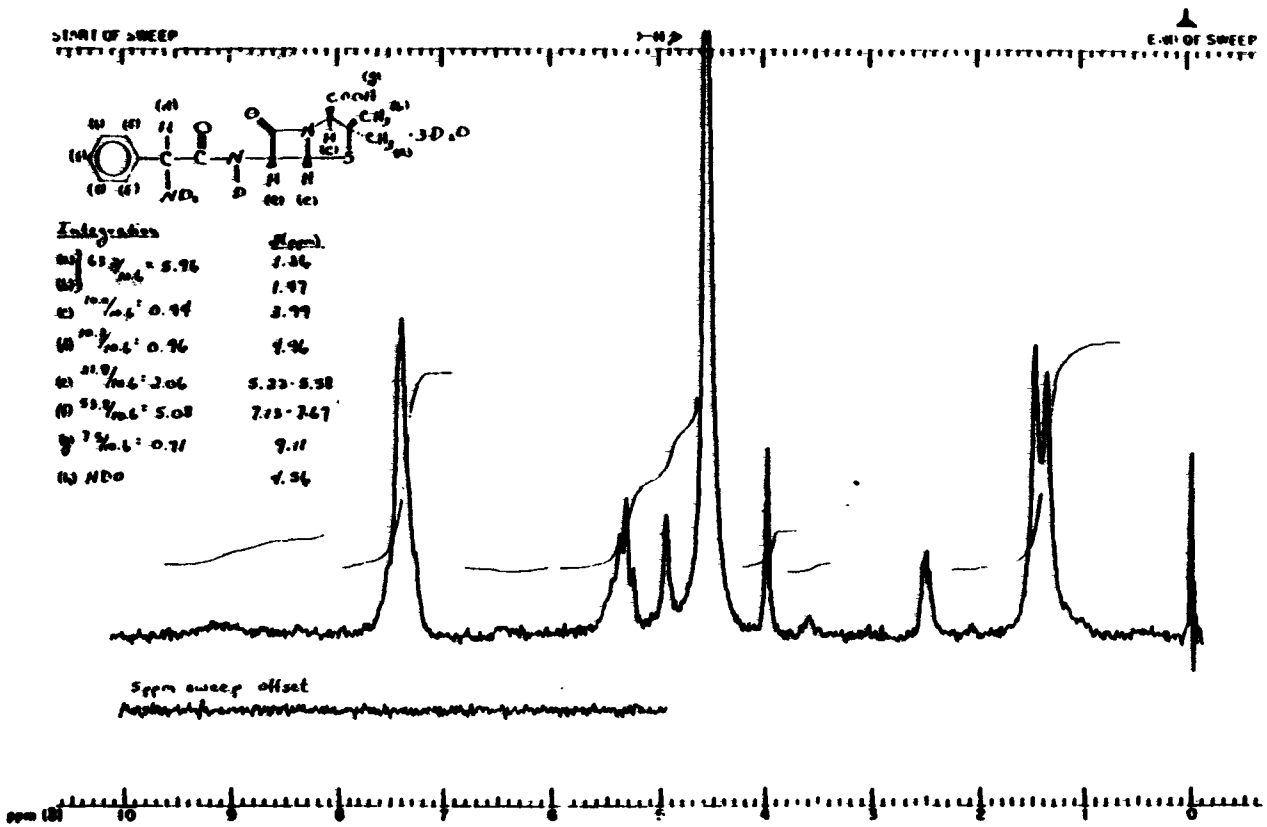


FIGURE 9. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF AMPICILLIN TRIHYDRATE (LOT NO. 33564-550)

5. **Titration**

   a. **Iodometric**

   Procedure: As outlined in §436.204 of the Code of Federal Regulations

   Results: A potency of 817 ± 2(δ) µg/mg

   b. **Carboxylic acid function**

   Procedure: Samples were dissolved in dimethyl sulfoxide:methanol (2:3) and titrated with 0.1 N sodium methoxide in methanol. Titrations were monitored potentiometrically with a combination pH/mV electrode filled with saturated methanolic potassium chloride.

   Results: 100.9% ± 0.5(δ)%

   c. **Amine titration**

   Procedure: Samples were dissolved in glacial acetic acid and titrated with 0.1 N perchloric acid in glacial acetic acid. Titrations were monitored potentiometrically with a combination pH/mV electrode filled with 4 M aqueous potassium chloride.

   Results: 97.8% ± 0.4(δ)%

6. **Chromatographic analysis**

   a. **Thin-layer chromatography**

   Plates: Silica Gel 60 F-254, 0.25 mm layer
   Amount spotted: 2, 20, 60 µg (1, 10, 30 µl of a 2 µg/µl solution in methanol:water [8:2])
   Reference standard: L(+)-Cysteine hydrochloride, 2 µg (1 µl of a 2 µg/µl solution in methanol:water [8:2])
   Visualization: Ultraviolet light (254 and 366 nm) and spray of iodoplatinate reagent (Pokorny et al., 1973)

   Note: Tanks and solvent systems were allowed to equilibrate overnight.

   System 1: *n*-Butanol:water:glacial acetic acid (60:25:15)

Spot Intensity	R_f	R_{st}
Minor	0.47	4.7
Major	0.29	2.9
Reference	0.10	--

System 2: Ethyl acetate:water:glacial acetic acid:methanol (70:10:10:10)

Spot Intensity	R_f	R_{st}
Minor	0.35	5.8
Major	0.21	3.5
Minor	0.02	0.33
Reference	0.06	--

b. High-performance liquid chromatography

Impurity profile

Instrumental system
Pump: Waters M6000A
Programmer: Waters 660
Detector: Waters 440
Injector: Waters U6K
Detection: Ultraviolet, 254 nm
Column: Waters μBondapak C_{18}, 300 × 3.9 mm ID
Guard column: Whatman CO:PELL ODS, 72 × 2.3 mm ID
Solvent system
A: Water containing 5 mM heptanesulfonic acid, sodium salt, and 1% (v/v) glacial acetic acid
B: Methanol containing 5 mM heptanesulfonic acid, sodium salt, and 1% (v/v) glacial acetic acid
Solvent ratio: A:B, 55:45
Flow rate: 1.0 ml/min
Sample injected: Solution containing 2.038 mg/ml ampicillin trihydrate in aqueous pH 7.4 buffer (Fischer pH 7.4 Dry Buffer Salts, monobasic potassium phosphate and disodium phosphate), filtered into amber septum vials and kept on ice in the dark
Volume injected: 15 μl

Results: A major peak and five impurities were observed. The major peak eluted at 6.8 minutes. Two impurities eluted before, and three eluted after, the major peak. All of the impurities had areas of less than 1.0% relative to the major peak area. The area percentages of peaks 1 and 2 were obtained by subtracting the area of the solvent blank, which contained small peaks at early retention times, from the impurity profile.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak) (a)
1	3.8	0.55	0.8
2	5.0	0.74	0.6
3	6.8	1.00	100
4	9.4	1.38	0.10
5	10.8	1.59	0.45
6	16.6	2.44	0.31

(a) Detector response is very dependent upon the absorbance of a substance at the detection wavelength used. The values reported are absolute areas expressed as percentages of the area of the major peak and do not take into account the different ε values of the compound and its impurities. Therefore, the areas reported do not necessarily reflect the actual weight percentages of the impurities in the sample.

When injections of an ampicillin trihydrate solution of similar concentration were made at 100%, 90%, 70%, 50%, 40%, and 30% B on the HPLC system described above, no additional impurities with areas greater than 1% relative to the major peak were seen.

Impurity profile comparison of lot no. 61849K and lot no. 33564-550: Injections of a solution of lot no. 61849K of similar concentration gave an impurity profile comparable to the impurity profile of lot no. 33564-550, although two differences were noted. The peak in lot no. 33564-550 at 3.8 minutes was seen in lot no. 61849K but at approximately one-ninth the size. In lot no. 61849K, an impurity peak (0.46%) was seen at 4.4 minutes and a trace impurity (<0.1%) at 5.0 minutes. The peak at 5.0 minutes in lot no. 33564-550 was broader and more diffuse and is not thought to be identical to that in lot no. 61849K.

Major peak lot comparison: Solutions of lot no. 61849K, lot no. 33564-550, and the USP standard, containing an internal standard (acetanilide), were analyzed by HPLC. The major peak areas were compared with internal standard peak areas, and the ampicillin content of lot no. 61849K and lot no. 33564-550, relative to the USP reference standard, was calculated. The instrument parameters listed in Section I.B.6.b.were used to analyze samples as follows:

Sample injected: Accurately weighed solutions containing approximately 1.4 mg/ml ampicillin trihydrate and 0.02 mg/ml acetanilide in aqueous pH 7.4 buffer, filtered and kept on ice in amber septum vials

Retention time: Acetanilide (internal standard): 5.0 min
Ampicillin trihydrate: 6.7 min

Results

Sample	Percent Ampicillin Trihydrate Compared with USP Reference (a)
USP Reference	100.0 ± 3.0(δ)
Lot No. 61849K	102.2 ± 2.4(δ)
Lot No. 33564-550	101.0 ± 2.4(δ)

(a) Pooled standard deviation: ± 2.6%

c. High-resolution gas chromatography

Capillary column gas chromatography was performed to determine the presence of N,N-dimethylaniline, a potential contaminant from the synthesis of ampicillin trihydrate. Aqueous solutions (0.8% w/v) of both study lots were extracted with methylene chloride. The extract was concentrated and analyzed by gas chromatography with a flame ionization detector (250° C). A fused silica DB-5 capillary column (15 m × 0.25 mm, 0.25 μm) was temperature programmed from 50° C to 250° C at 10° C/minute. Solutions of both lots spiked with 1 ppm (w/w relative to ampicillin trihydrate) N,N-dimethylaniline were concomitantly prepared and analyzed with the samples, as was a standard solution of N,N-dimethylaniline.

N,N-dimethylaniline was not detected in either lot of ampicillin trihydrate at a concentration of 1 ppm (w/w) or greater.

7. **Conclusions:** The results of the elemental analysis for carbon, hydrogen, nitrogen, and sulfur were in agreement with the theoretical values. Karl Fischer analysis indicated a water content of 13.24% ± 0.01(δ)%. Iodometric titration indicated a potency of 817 ± 2(δ) μg/mg. Nonaqueous titrations of the carboxylic acid and amine functional groups indicated purities of 100.9% ± 0.5(δ)% and 97.8% ± 0.4(δ)%, respectively. Thin-layer chromatography by one system indicated a major spot and one minor impurity. A second thin-layer chromatographic system indicated a major spot and two minor impurities. High-performance liquid chromatography indicated a major peak and five impurities, two eluting before and three eluting after the major peak. The total area of the impurities was 2.22% relative to the major peak. The concomitant HPLC analysis of lot nos. 61849K and 33564-550 indicated similar impurity profiles, and the results of the previous and current analysis of lot no. 61849K were consistent. Infrared, ultraviolet/visible, and nuclear magnetic resonance spectra were consistent with the structure of ampicillin trihydrate.

II. Chemical Stability Study of Ampicillin Trihydrate Lot No. 61849K Performed by the Analytical Chemistry Laboratory

A. Sample storage: Samples of the bulk compound were stored in the dark in glass vials with Teflon®-lined caps for 2 weeks at temperatures of −20°, 5°, 25°, or 60° C.

B. Analytical method: Duplicate samples from each storage temperature were prepared by dissolving approximately 150 mg of the compound in 50 ml of pH 7.4 phosphate buffer containing sufficient propriophenone, the internal standard, to yield a final concentration of 0.045 mg/ml. These samples were analyzed by the high-performance liquid chromatographic system described in I.A.6.b. with a 50% B isocratic program and a flow rate of 2 ml/minute.

C. Results

Storage Temperature	Percent Compound (normalized to −20° C sample)
−20° C	100.0 ± 0.8(δ)
5° C	99.9 ± 0.8(δ)
25° C	99.7 ± 0.8(δ)
60° C	99.4 ± 0.8(δ)

D. Conclusions: Ampicillin trihydrate is stable as the bulk chemical when stored in the dark for 2 weeks at temperatures of up to 60° C within the stated limits of error of the analysis. However, the decreasing purity from −20° C to 60° C could indicate a real decomposition because the compound has been reported to decompose from 6.8% to 12.5% when stored at 55° C for 1 month (Tsuji and Robertson, 1975).

III. Chemical Stability Study of Ampicillin Trihydrate Performed by the Study Laboratory

A. Storage conditions

Bulk: Approximately 4° C
Reference: −20° C

B. Analytical methods

1. Infrared spectroscopy

Lot no. 61849K analyzed on 6/13/80 and 8/18/80, lot no. 33564-550 analyzed on 11/05/81
Instrument: Perkin-Elmer 267
Phase: Potassium bromide pellet

2. Titration

a. Study chemical

About 125 mg of the compound was accurately weighed into a 100-ml flask and diluted to the mark with distilled water. Two milliliters of this solution was pipetted into a 50-ml glass-stoppered Erlenmeyer flask. Two milliliters of 1.0 N aqueous sodium hydroxide was added, stoppered, and allowed to stand for 15 minutes. Two milliliters of 1.2 N aqueous hydrochloric acid was added. From a buret, 10.0 ml of a 0.01 N iodine solution was added, the flask was stoppered, and the solution was allowed to stand for 15 minutes. The excess iodine was titrated with 0.01 N sodium thiosulfate (2.48 g of $Na_2S_2O_3$ and 125 mg Na_2CO_3 per liter). Toward the end of the titration (i.e., when the solution was straw colored), one drop of starch iodide paste was added. The titration was finished by taking the disappearance of the blue color as the endpoint.

b. Blanks

Two milliliters of the compound solution was pipetted into a 50-ml glass-stoppered Erlenmeyer flask, and 10.0 ml of a 0.01 N iodine solution was added. The solution was titrated immediately as directed above for the study chemical.

c. Calculations

The potency of the study material was calculated as follows:

$$\text{Potency} = \frac{(\text{volume of } Na_2S_2O_3 \text{ blank} - \text{volume of } Na_2S_2O_3 \text{ study material}) \text{ milliliters} \times F}{\text{weight of study material in milligrams}}$$

$$\text{Where } F = \frac{\text{weight of reference material in milligrams} \times 856.2}{(\text{volume of blank} - \text{volume of } Na_2S_2O_3 \text{ reference material})}$$

3. High-performance liquid chromatography

A solution of propiophenone, the internal standard, was prepared by weighing approximately 100 mg, quantitatively transferring to a 100-ml volumetric flask, and diluting to the mark with methanol. Approximately 300 mg of the compound was weighed and transferred quantitatively to a 100-ml volumetric flask.

With a volumetric pipette, 5 ml of the internal standard solution was placed in the flask containing the compound. The flask was filled to the mark with aqueous pH 7.4 phosphate buffer and shaken well to mix. A blank solution was prepared by pipetting 5 ml of the internal standard solution into a 100-ml flask and diluting to the mark with aqueous pH 7.4 phosphate buffer. Samples were analyzed on the following HPLC system:

Instrument: Waters 440 or 204
Column: Waters μBondpak C_{18}, 4 mm × 30 cm
Detection: Ultraviolet 254 nm
Column guard: Waters Bondapak C_{18}/Corasil, 4 mm × 4.5 cm
Mobile phase: 50% (Water--5 mM heptanesulfonic acid; sodium salt, 1% acetic acid), 50% (methanol--5 mM heptanesulfonic acid, sodium salt, 1% acetic acid)
Flow rate: 1 ml/min
Compound solvent: Fisher pH 7.41 buffer

C. Results

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

2. **Titration**

Date of Analysis	Lot No.	Potency (μg/mg) (a) Bulk	Reference	Percent Purity Bulk
12/16/80	61849K	856.3	--	--
04/15/81		857.8	--	--
08/14/81		901.0	897.0	100.4
11/05/81	33564-550	886.4	--	--
12/11/81		860.1	865.8	99.3
04/13/82		884.0	898.8	98.4
09/09/82		836.8	841.4	99.5

(a) Results of duplicate analysis

3. **High-performance liquid chromatography**

Date of Analysis	Lot No.	Percent Purity Bulk	Reference
06/13/80	61849K	~100	~100
08/18/80		~100	~100
12/16/80		~100	~100
04/15/81		~100	~100
08/13/81		~100	~100
11/05/81	33564-550	~100	--
12/11/81		~100	~100
04/13/82		~100	~100
09/09/82		~ 99.4	~ 99.5

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

APPENDIX I

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

I. Stability Study of Ampicillin Trihydrate Corn Oil Gavage Formulations Conducted at the Analytical Chemistry Laboratory

A. Study parameters

Concentration: 100 mg/ml
Vehicle: Corn oil
Duration: 14 days
Temperature: Room temperature or 5° C
Analysis times: 25° C storage--0, 0 + 3 hours, 1, 2, 7, 13, or 14 days
5° C storage--0, 2, 7, or 14 days

B. Sample preparation and storage: A suspension of 10.00 ± 0.01 g of ampicillin trihydrate in 84.0 g of corn oil (91.7 ml) was prepared by adding the chemical in small increments to the oil while the oil was stirred vigorously on a magnetic stirrer.

Aliquots of the suspension (32, approximately 1.5 g each) were transferred to tared 60-ml screw-cap vials and weighed to the nearest 0.1 mg. Three of the vials were randomly chosen and set aside for analysis after 3-hour exposure open to air and light. Five of the vials were randomly chosen for the zero-time analyses and to confirm homogeneity of the suspension.

The remaining 24 vials were randomly subdivided into 8 groups of 3 vials each for storage in the dark at 5° C and 25° C. From this latter group, triplicate vials were analyzed after 1, 2, 7, 13, or 14 days' storage at 25° C and after 2, 7, or 14 days' storage at 5° C. The target concentration of ampicillin trihydrate in the suspension was 100.0 mg/ml (106.4 mg/g).

C. Analysis procedure

1. Special reagents

Extracting solvent: 800 ml of reagent-grade methanol was diluted to 1 liter with 0.01 M sodium dihydrogen phosphate (1.38 g of $NaH_2PO_4 \cdot H_2O$ per liter of water).

Internal standard solution: 73.04 mg of acetanilide was dissolved in 250 ml of methanol; then 125 ml was diluted to 500 ml with 0.01 M aqueous sodium dihydrogen phosphate.

2. **Procedure:** On each analysis day, samples were extracted with 40 ml of the extracting solvent by being shaken vigorously for 1 minute and sonicated for 8 minutes. After the sample was clarified by centrifugation, a 5-ml aliquot from each upper layer was mixed with 5 ml of internal standard solution and diluted to 25 ml with aqueous 0.01 M sodium dihydrogen phosphate.

A few milliliters of each diluted sample solution was filtered through a 0.5-μ Millipore filter and sealed in a 5-ml septum vial. The concentration of ampicillin trihydrate in the solutions was determined by the high-performance liquid chromatographic system described below:

Instrument: Waters Associates Model 202 Liquid Chromatograph
Column: μBondapak C_{18}, 300 mm × 4 mm ID
Guard column: Whatman CO:PELL; 70 mm × 4 mm ID
Detector: Ultraviolet, 254 mm
Mobile phase: 65% aqueous 0.01 M sodium dihydrogen phosphate
35% methanol
Flow rate: 1 ml/min
Injection volume: 20 μl
Retention times: Study chemical, 5.3 min
Reference standard, 7.3 min

D. **Quality control protocols:** Analysis was performed by making single injections in a randomized order of sample solutions prepared in triplicate on each study day. All determinations were related to an internal standard incorporated into the sample solutions. Results were calculated from relative response factors (RRF) computed from peak height measurements of the calibration standards by the following equations:

$$RRF = \frac{\text{milligram per milliliter study chemical} \times \text{peak height of internal standard}}{\text{peak height of study chemical} \times \text{milligrams per milliliter of internal standard}}$$

then the milligrams per gram of chemical in the vehicle was calculated as

$$\frac{RRF \times \text{sample peak height} \times \text{milligrams per milliliter internal standard} \times DF}{\text{peak height internal standard} \times \text{grams of sample}}$$

where DF = dilution factor.

The linearity of the high-performance liquid chromatographic system was determined with standard solutions of ampicillin trihydrate at concentrations of 0.48, 0.80, and 0.96 mg/ml. The correlation coefficient was 0.99993. Homogeneity of the suspension determined on five weighings similar in size to that used for the samples showed a 0.4% maximum deviation from the mean concentration of 106.4 mg/g.

E. Results: Fourteen-day stability study

Storage Time (days)	Storage Temperature	Milligrams Ampicillin Trihydrate/ Gram Corn Oil (a)	Percent Recovery (b,c)
0		106.4	100.0 ± 0.4
0 ± 3 h	Room temperature (open to air and light)	106.3	99.9 ± 0.9
1	Room temperature	105.6	99.3 ± 0.5
2	Room temperature	107.1	100.6 ± 0.8
2	5° C	107.0	100.8 ± 0.2
7	Room temperature	107.1	100.7 ± 0.6
7	5° C	106.7	100.3 ± 0.5
13	Room temperature	107.7	101.2 ± 0.2
14	Room temperature	107.9	101.4 ± 0.9
14	5° C	107.4	101.0 ± 1.2

(a) Target concentration of ampicillin trihydrate in corn oil suspension was 106.4 mg/g.
(b) Zero-time recovery yield, 99.0% ± 0.4%
(c) The error values in this table are maximum deviations from the mean.

F. Conclusions: Ampicillin trihydrate in a 100 mg/ml corn oil suspension showed no instability after 14 days' storage in the dark at 5° C or 25° C. Samples exposed 3 hours to air or light at room temperature also showed no loss within the limits of the study errors (± 0.9%).

II. Homogeneity Study of Ampicillin Trihydrate in Feed Conducted at the Analytical Chemistry Laboratory

A. Premix preparation: Ampicillin trihydrate (14.97 ± 0.01 g) was transferred to a tared 600-ml beaker and mixed by spatula with approximately 15 g of feed. An additional 30 g and 60 g of feed were added and blended in the same manner; then a final portion of feed was incorporated to bring the total weight of the premix to 200 g.

B. Bulk mixing and sampling: A 600-g quantity of feed was layered evenly in the blender; then the 200-g premix was added in roughly equal amounts to both sides of the blender. The fine material adhering to the beaker walls was taken up by briefly stirring 100 g of feed in the beaker and then adding it to the blender. After an additional 600 g of feed was layered over the premix, the blender ports were sealed, and the contents were blended for 15 minutes, with the intensifier bar turned on for the first 5 minutes. During the mixing operation, the blender shells were periodically tapped with a block of wood to knock loose any feed that may have become packed in the corners of the blender.

At the end of the 15-minute mixing period, approximately 40 g of the feed was sampled from the upper left and right shells and from the bottom discharge port. Triplicate 10.0-g portions of each sample were transferred to 200-ml centrifuge bottles for analysis. The target concentration of ampicillin trihydrate in the blend was 9,980 ppm.

C. Analysis

Special reagents: Extracting solution--200 ml of reagent-grade methanol was diluted to 1,000 ml with 0.01 M sodium dihydrogen phosphate (1.38 g of $NaH_2PO_4 \cdot H_2O$/liter in water).

Internal standard solution--reagent-grade acetanilide was dissolved in the extracting solution and diluted to a concentration of approximately 22 µg/ml.

Procedure: Samples (10 g) were extracted with 100 ml of extracting solution by shaking for 30 minutes on a Burrell Wrist-Action® shaker. The extracts were clarified by centrifugation. Five-milliliter aliquots were mixed with 5 ml of internal standard solution (D.2). A few milliliters of each mixture was filtered through a 0.5-µ Millipore filter and sealed in a 5-ml septum vial. The ampicillin trihydrate concentration of the solution was determined by the high-performance liquid chromatographic system described below.

Instrument: Waters Associates Model ALC-202 liquid chromatograph
Column: Waters Associates µBondapak C_{18} 300 mm × 4 mm, ID
Guard Column: Whatman CO:PELL, 70 mm × 4 mm ID
Detector: UV at 254 nm
Attenuation: 0.02 AU/Full scale
Mobile phase: Methanol (110 ml) diluted to 1,000 ml with aqueous 0.01 M sodium dihydrogen phosphate (D.1)
Flow rate: 1 ml/min
Injection volume: 15 µl
Retention times: Study chemical--12.2 min
Internal standard--14.9 min

D. Quality assurance measures: Analyses were performed in a random order on single injections of sample extracts prepared in triplicate. Results were not corrected because the mean recovery yield of eight zero-time analyses was 100.3% ± 1% of the target value. Results were calculated with two independently prepared external standard solutions injected four times throughout the chromatographic analysis. The linearity of the high-performance liquid chromatographic system was evaluated with standard solutions of ampicillin trihydrate in extracting solution at varying concentrations.

E. Feed homogeneity study results

Sampling Location	Ampicillin Trihydrate in Feed (ppm) (a)	Percent Recovery (b)
Right (c)	9,800	98
	10,300	103
	Av = 10,100	Av = 101 ± 2
Left	9,700	97
	10,200	102
	9,800	98
	Av = 9,900	Av = 99 ± 2
Bottom	9,200	92
	10,500	105
	10,500	105
	Av = 10,100	Av = 101 ± 6

(a) Target concentration of ampicillin trihydrate in feed was 9,980 ppm.
(b) Error values are average deviations from the mean and are the sum of the analytical method error plus feed blend variations.
(c) One sample was lost.

F. Conclusions: Ampicillin trihydrate was blended into rodent feed at 10,000 ppm and was sampled at three locations in the blender. The mean of triplicate analysis of the formulated diet from each sampling location varied by approximately 1% from the target concentration.

III. Stability Study of Ampicillin Trihydrate in Feed

A. Sample preparation and storage, analysis, and quality assurance: Four 12-oz size screw-cap jars were filled with approximately 250 g of formulated diet prepared as described in Section II. The jars were tightly sealed and stored in the dark at −20°, 5°, 25°, or 45° C for the 2-week stability study.

The analysis and quality assurance measures were the same as those described in Section II.

B. Results

Storage Temperature	Ampicillin Trihydrate in Feed (ppm) (a)	Percent Recovery (b)
−20° C	9,600	96
	9,400	94
	9,600	96
	Av = 9,500	Av = 95 ± 1
5° C	9,400	94
	9,000	90
	9,000	90
	Av = 9,100	91 ± 3
25° C	8,600	86
	9,100	91
	8,800	88
	Av = 8,800	Av = 88 ± 3
45° C	6,100	61
	6,000	60
	5,900	59
	Av = 6,000	Av = 60 ± 1

(a) Target concentration of ampicillin trihydrate in feed was 10,000 ppm.
(b) Error values are maximum deviations from the mean and represent the sum of the analytical method error plus feed blend variations.

C. Conclusions: Ampicillin trihydrate was blended into rodent feed at 10,000 ppm and was unstable during storage. Recovery of the chemical after storage for 2 weeks in the dark was 88% at 25° C.

APPENDIX J

METHODS OF ANALYSIS OF DOSE MIXTURES

APPENDIX J. METHODS OF ANALYSIS

I. Study Laboratory

Duplicate 2-g samples of the dosing solutions were diluted to 100 or 200 ml with extraction solvent (200 ml of 0.01 M sodium dihydrogen phosphate diluted to 1,000 ml with spectrograde methanol). The density of each was also determined.

All samples were shaken and then sonicated for 15 minutes. Approximately 10 ml of each was centrifuged at 12,000 rpm for 15 minutes, and 3 ml of each was diluted to a final volume of 25 ml. The absorption of each was determined at 263 nm against extraction solvent, and the concentration was determined from a standard curve of ampicillin trihydrate dissolved in extraction solvent.

II. Analytical Chemistry Laboratory

A. Preparation of spiked corn oil standards: Two standard solutions of ampicillin trihydrate in 0.1 N hydrochloric acid were prepared independently. These solutions were diluted with 0.1 N hydrochloric acid to make four additional standards. Aliquots (40 ml) of the six standard solutions were pipetted into individual 60-ml septum vials containing 2 g of undosed corn oil to make spiked corn oil standards bracketing the specified concentration range of the referee sample. Two grams of undosed corn oil in a 60-ml septum vial was treated with 40 ml of 0.1 N hydrochloric acid for use as a blank. After the vials were sealed, the spiked corn oil samples and the corn oil blank were used in the analysis procedure described below.

B. Preparation of referee sample: Three portions (approximately 2 g each) of the referee corn oil suspension were transferred to individually tared 60-ml septum vials and were weighed to the nearest 0.001 g. A 40-ml volume of 0.1 N hydrochloric acid was pipetted into each vial; then the referee samples were sealed and analyzed immediately by the procedure below.

C. Analysis: Vials containing the samples, standards, and the blank were agitated on a vortex mixer for 30 seconds and then shaken at maximum stroke on a Burrell Model 75 Wrist-Action® Shaker for 25 minutes. After being centrifuged for 3-5 minutes, the upper corn oil layer was aspirated off, and a 5-ml aliquot of the lower acid layer was diluted to 100 or 200 ml with 0.1 N hydrochloric acid. The solutions were thoroughly mixed, and the absorbance of each solution was measured versus 0.1 N hydrochloric acid in 1-cm quartz cells at 256 or 257 nm on a Cary 118 or Cary 219 spectrophotometer.

The total amount of ampicillin trihydrate in the referee corn oil samples was determined from a linear regression equation obtained from the standard data, relating the absorbance of each spiked corn oil sample and corn oil blank to the amount of chemical in the respective spiked corn oil standard.

D. Quality assurance measures: The referee corn oil suspension was analyzed in triplicate, and the corn oil blank sample was analyzed once. Individually spiked portions of undosed corn oil (six levels bracketing the specified concentration range of the sample) were prepared from two independently weighed standards and treated like the referee sample to obtain standard data.

APPENDIX K

RESULTS OF ANALYSIS OF DOSE MIXTURES

TABLE K1. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF AMPICILLIN TRIHYDRATE

Date Mixed	Concentration of Ampicillin Trihydrate in Corn Oil (percent, w/v) (a)		Determined as a Percent of Target
	Target	Determined	
01/26/80	30	32.0	107
	20	21.2	106
	15	13.68	91
	(b) 10	9.46	95
	7.5	6.73	90
	5.0	4.79	96
	3.75	3.62	97
	2.5	2.56	102

(a) Results of duplicate analysis unless otherwise specified
(b) Result of a single analysis

TABLE K2. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF AMPICILLIN TRIHYDRATE

Date Mixed	Concentration of Ampicillin Trihydrate in Corn Oil for Target Concentration (percent, w/v) (a)	
	15	30
08/22/80	15.3	28.9
08/26/80	(b,c) 12.3	(b,c) 26.6
09/17/80	(b) 14.7	(b) 28.0
12/19/80	(c) 17.9	32.1
02/13/81	15.6	28.9
04/07/81	15.7	28.3
06/05/81	14.6	27.9
07/31/81	15.3	29.5
09/23/81	15.1	29.5
11/18/81	14.4	30.0
01/14/82	14.9	30.4
03/10/82	14.9	29.8
05/05/82	15.0	30.7
06/30/82	14.5	29.4
08/11/82	14.3	29.6
Mean (percent, w/v)	15.0	29.3
Range (percent, w/v)	12.3-17.9	26.6-32.1
Standard deviation	1.14	1.31
Coefficient of variation (percent)	7.6	4.5
Number of samples	15	15

(a) Results of duplicate analysis unless otherwise specified
(b) Result of a single analysis
(c) Out of specifications

TABLE K3. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF AMPICILLIN TRIHYDRATE

Date Mixed	Lot Number	Target Concentration (percent, w/v)	Determined Concentration	
			Study Laboratory (a)	Referee Laboratory (b)
09/17/80	61849K	30	28.0	30.65
02/13/81		15	15.6	14.14
07/31/81		30	29.5	31.2
01/14/82	33564-550	15	14.9	15.2
08/11/82		30	29.6	33.1

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

APPENDIX L

SENTINEL ANIMAL PROGRAM

APPENDIX L. SENTINEL ANIMAL PROGRAM

I. Methods

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

Fifteen $B6C3F_1$ mice and 15 F344/N rats of each sex are selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group are killed at 6, 12, and 18 months on study. The blood from each animal is collected and clotted, and the serum is separated. The serum is cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests are performed:

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	PVM (pneumonia virus of mice) Reo 3 (reovirus type 3) GDVII (Theiler's encephalomyelitis virus) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia) Sendai	M.Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) MHV (mouse hepatitis virus) (6 mo)	MHV (mouse hepatitis virus) (12, 18 mo)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai (6, 12, 18 mo)	RCV (rat coronavirus)	

II. Results

TABLE L1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF AMPICILLIN TRIHYDRATE (a)

	Interval (months)	Number of Animals	Positive Serologic Reaction for
Rats	5	--	None positive
	14	10/10	PVM
	18	10/10	PVM
Mice	5	--	None positive
	14	6/9	PVM
		1/9	MHV
	18	2/6	PVM

(a) Blood samples were taken from sentinel animals at 5, 14, and 18 months after the start of dosing; samples were sent to Microbiological Associates, Inc. (Bethesda, MD) for the Animal Disease Screening Program.

APPENDIX M

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

Pelleted Diet: June 1980 to July 1982

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

TABLE M1. INGREDIENTS OF NIH 07 RAT AND MOUSE RATION (a)

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

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

TABLE M2. VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION (a)

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

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

TABLE M3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	24.04 ± 0.75	22.7-25.1	24
Crude fat (percent by weight)	4.84 ± 0.80	4.1-5.7	24
Crude fiber (percent by weight)	3.40 ± 0.29	2.9-4.3	24
Ash (percent by weight)	6.56 ± 0.50	5.7-7.43	24
Essential Amino Acids (percent of total diet)			
Arginine	1.260	1.21-1.31	2
Cystine	0.395	0.39-0.40	2
Glycine	1.175	1.15-1.20	2
Histidine	0.553	0.530-0.576	2
Isoleucine	0.908	0.881-0.934	2
Leucine	1.905	1.85-1.96	2
Lysine	1.250	1.20-1.30	2
Methionine	0.310	0.306-0.314	2
Phenylalanine	0.967	0.960-0.974	2
Threonine	0.834	0.827-0.840	2
Tryptophan	0.175	0.171-0.178	2
Tyrosine	0.587	0.566-0.607	2
Valine	1.085	1.05-1.12	2
Essential Fatty Acids (percent of total diet)			
Linoleic	2.37		1
Linolenic	0.308		1
Arachidonic	0.008		1
Vitamins			
Vitamin A (IU/kg)	11,146 ± 2,291	7,200-17,000	24
Vitamin D (IU/kg)	6,300		1
α-Tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm)	17.6 ± 3.3	7.4-27.0	(b) 23
Riboflavin (ppm)	6.9	6.1-7.4	2
Niacin (ppm)	75	65-85	2
Pantothenic acid (ppm)	30.2	29.8-30.5	2
Pyridoxine (ppm)	7.2	5.6-8.8	2
Folic acid (ppm)	2.1	1.8-2.4	2
Biotin (ppm)	0.24	0.21-0.27	2
Vitamin B_{12} (ppb)	12.8	10.6-15.0	2
Choline (ppm)	3,315	3,200-3,430	2
Minerals			
Calcium (percent)	1.29 ± 0.21	0.81-1.69	24
Phosphorus (percent)	1.00 ± 0.07	0.86-1.10	24
Potassium (percent)	0.809	0.772-0.846	2
Chloride (percent)	0.557	0.479-0.635	2
Sodium (percent)	0.304	0.258-0.349	2
Magnesium (percent)	0.172	0.166-0.177	2
Sulfur (percent)	0.278	0.270-0.285	2
Iron (ppm)	418	409-426	2
Manganese (ppm)	90.8	86.0-95.5	2
Zinc (ppm)	55.1	54.2-56.0	2
Copper (ppm)	12.68	9.65-15.70	2
Iodine (ppm)	2.58	1.52-3.64	2
Chromium (ppm)	1.86	1.79-1.93	2
Cobalt (ppm)	0.57	0.49-0.65	2

(a) One or two batches of feed analyzed for nutrients reported in this table were manufactured in January and/or April 1983.
(b) One batch (July 22, 1981) was not analyzed for thiamine.

TABLE M4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminant	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.42 ± 0.21	<0.05-1.06	24
Cadmium (ppm)	0.09 ± 0.02	<0.05-0.10	24
Lead (ppm)	0.99 ± 0.72	0.42-3.37	24
Mercury (ppm) (a)	< 0.05		24
Selenium (ppm)	0.31 ± 0.08	0.14-0.52	24
Aflatoxins (ppb) (a,b)	<10	<5.0-<10.0	24
Nitrate nitrogen (ppm) (c)	8.15 ± 3.65	2.1-17.0	24
Nitrite nitrogen (ppm) (c)	2.23 ± 1.59	0.4-6.9	24
BHA (ppm) (d,e)	4.55 ± 3.59	<0.4-13.0	24
BHT (ppm) (d)	2.55 ± 1.40	0.8-5.9	24
Aerobic plate count (CFU/g)	40,592 ± 32,056	4,900-120,000	24
Coliform (MPN/g) (f)	30.3 ± 53.2	<3-240	23
Coliform (MPN/g) (g)	74.8 ± 224.5	<3-1,100	24
E. coli (MPN/g)	<3		24
Total nitrosamines (ppb) (h,i)	7.20 ± 7.04	0.8-24.5	21
Total nitrosamines (ppb) (i, j)	29.40 ± 64.76	0.8-273.2	24
N-Nitrosodimethylamine (ppb) (h,i)	5.67 ± 6.49	0.8-20.0	21
N-Nitrosodimethylamine (ppb) (i, j)	27.67 ± 64.38	0.8-272	24
N-Nitrosopyrrolidine (ppb)	1.35 ± 0.92	0-3.5	24
Pesticides (ppm)			
α-BHC (a,k)	<0.01		24
β-BHC (a)	<0.02		24
γ-BHC-Lindane (a)	<0.01		24
δ-BHC (a)	<0.01		24
Heptachlor (a)	<0.01		24
Aldrin (a)	<0.01		24
Heptachlor epoxide (a)	<0.01		24
DDE (a)	<0.01		24
DDD (a)	<0.01		24
DDT (a)	<0.01		24
HCB (a)	<0.01		24
Mirex (a)	<0.01		24
Methoxychlor (l)	<0.05	0.09 (8/26/81)	24
Dieldrin (a)	<0.01		24
Endrin (a)	<0.01		24
Telodrin (a)	<0.01		24
Chlordane (a)	<0.05		24
Toxaphene (a)	<0.1		24
Estimated PCBs (a)	<0.2		24
Ronnel (a)	<0.01		24
Ethion (a)	<0.02		24
Trithion (a)	<0.05		24
Diazinon (l)	<0.1	0.2 (4/27/81)	24
Methyl parathion (a)	<0.02		24
Ethyl parathion (a)	<0.02		24
Malathion (m)	0.09 ± 0.06	<0.05-0.27	24
Endosulfan I (a)	<0.01		24
Endosulfan II (a)	<0.01		24
Endosulfan sulfate (a)	<0.03		24

TABLE M4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) All values were less than the detection limit, which is given in the table as the mean.
(b) Detection limit was reduced from 10 ppb to 5 ppb after 7/81.
(c) Source of contamination: Alfalfa, grains, and fish meal
(d) Source of contamination: Soy oil and fish meal
(e) Two batches contained less than 0.5 ppm.
(f) Mean, standard deviation, and range exclude one very high value of 1,100 obtained for the batch produced on 12/16/80.
MPN = most probable number.
(g) Mean, standard deviation, and range include the high value listed in footnote (f).
(h) Mean, standard deviation, and range exclude three very high values in the range of 115-273.2 ppb obtained for batches produced on 1/26/81, 2/23/81, and 4/27/81.
(i) All values were corrected for percent recovery.
(j) Mean, standard deviation, and range include the extreme values given in footnote h.
(k) BHC = hexachlorocyclohexane or benzene hexachloride
(l) One observation was above the detection limit. The value and the date it was obtained are listed under the range.
(m) Eleven batches contained more than 0.05 ppm.

APPENDIX N

DATA AUDIT SUMMARY

APPENDIX N. DATA AUDIT SUMMARY

The experimental data and tables of the draft NTP Technical Report on the toxicology and carcinogenesis studies of ampicillin trihydrate in F344/N rats and B6C3F$_1$ mice were examined for completeness, consistency, and accuracy and for procedures consistent with Good Laboratory Practice requirements. The audit was conducted at the NTP Archives from April to November 1985 by ImmuQuest Laboratories, Inc. (L. Brennecke, D.V.M., ACVP; S. Corson, HT, ASCP; P. Errico, M.A.; C. Reese; K. Witkin, Ph.D.), Pathco, Inc. (J. Seely, D.V.M., ACVP), and Dynamac Corporation (E. Zurek; L. Plankenhorn). The 2-year studies in rats and mice were conducted from September 1980 to September 1982 at Springborn Institute for Bioresearch, Inc., Spencerville, Ohio.

The full report of the audit is on file at the NTP, NIEHS. The audit included, but was not limited to, a review of the records of the inlife portion of the studies for 10% of the animals (body weight, clinical observations, palpation, dosing records); all records containing environmental data, mortality data, dose preparation data, chemical inventory and analyses, and corn oil analyses; a slide/block match for 100% of the high dose and vehicle control animals; all Individual Animal Data Records containing necropsy and histopathologic findings; and a 100% wet tissue review for animal/carcass identification. An audit was performed on inlife data (including dosing records, clinical observations, and body weights) for animals for which there were questions about identification.

Animal/carcass identification discrepancies were noted in rats and mice. Animals were identified by a combination of ear punches and toe clips to provide a unique cage-sequential animal number for each sex and species. In rats, the most common problem was that the animal identity was legible but did not agree with the bag number. Many of these problems were due to failure to clip the animal toes correctly. In mice, the most common problem was that the animal identity was illegible due to an opened ear hole. In most cases for which there was an identification problem, there was no indication that the animals had been interchanged. For example, one animal in a cage of five might be correctly labeled for cage number but not for animal number. A total of 36 male rats (15 vehicle control, 10 low dose, and 11 high dose); 29 female rats (4 vehicle control, 15 low dose, and 10 high dose); 36 male mice (14 vehicle control, 10 low dose, and 12 high dose); and 11 female mice (4 vehicle control, 2 low dose, and 5 high dose) had potential identification problems. The inlife data for these animals were reviewed, and there was no indication that animals had been interchanged between groups.

Observations during the inlife phase of the studies indicated that animals were occasionally misdosed, primarily due to miscalculations of body weight. Two mice were noted as being in the wrong cage but were replaced in the correct cage.

Not all chemical records and standard operation procedures were documented in the raw data, but referee analyses performed throughout the studies indicated that the doses were accurately prepared. Pathology findings were consistent with results reported in the Technical Report. There were a few miscellaneous lesions in nontarget organs that were not examined.

In conclusion, the data examined during this audit are considered adequate to support the contents of the Technical Report.

*U. S. GOVERNMENT PRINTING OFFICE:1987- 181-296:41324