NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 336

TOXICOLOGY AND CARCINOGENESIS STUDIES OF PENICILLIN VK

(CAS NO. 132-98-9)

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF PENICILLIN VK

(CAS NO. 132-98-9)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

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

June 1988

NTP TR 336

NIH Publication No. 88-2592

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

NOTE TO THE READER

This study was performed under the direction of the National Institute of Environmental Health Sciences as a function of the 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 public peer review.

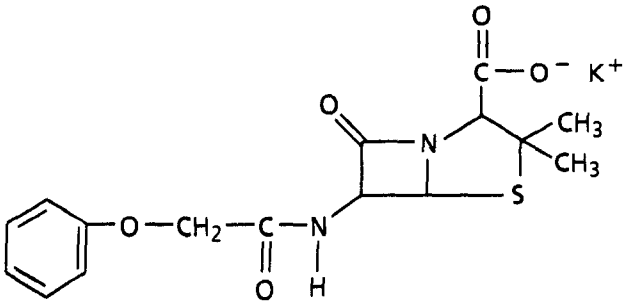
Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to identify any mistakes so that corrective action may be taken. Further, anyone who is aware of related ongoing or published studies not mentioned in this report is encouraged 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

CONTENTS (Continued)

APPENDIXES



PENICILLIN VK

4-Thia-1-azabicyclo(3.2.0)heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenoxy-acetamido)-, monopotassium salt

CAS No. 132-98-9

$C_{16}H_{17}KN_2O_5S$ Molecular weight 388.5

Synonyms:

Penicillin V potassium	D-α-Phenoxymethylpenicillinate K salt	PVK
Penicillin V potassium salt	Phenoxymethylpenicillin potassium	

Trade Names:

Antibiocin	Cliacil	Ispenoral	Pen-Vee K	Stabillin VK Syrup 125
Apsin VK	Compocillin VK	Ledercillin VK	Pen-V-K powder	Stabillin VK Syrup 62.5
Arcacil	Distakaps V-K	Megacillin oral	Penvikal	Sumapen VK
Arcasin	Distaquaine V-K	Oracil-VK	Pfizerpen VK	Suspen
Aspin VK	Dowpen V-K	Orapen	Qidpen VK	Uticillin VK
Beromycin	DQV-K	Ospeneff	Robicillin VK	V-Cil-K
Beromycin 400	Fenoxypen	Pedipen	Rocillin-VK	V-Cillin K
Betapen VK	Icipen	Penagen	Roscopenin	Veetids
Calciopen K	Isocillin	Pencompren	SK-Penicillin VK	Vepen

ABSTRACT

Penicillin VK, a widely used antibiotic for treatment of gram-positive coccal infections, was nominated for study by the National Cancer Institute because rodent carcinogenicity studies for this drug had not been performed. The chemical (94% or 98% pure, USP grade) was administered orally (by gavage in corn oil) because oral administration is the primary route used to treat infections in humans. Fourteen-day, 13-week, and 2-year studies were conducted in F344/N rats and B6C3F$_1$ mice. Additional studies were performed to evaluate the potential for genetic damage in bacteria and mammalian cells.

Fourteen-Day and Thirteen-Week Studies: In the 14-day studies, penicillin VK was administered at doses of 150-2,400 mg/kg. No compound-related deaths or dose-related histopathologic lesions were seen in rats or mice. Final mean body weights of dosed male rats were 5%-17% lower than that of controls; weights of dosed and control female rats were comparable. Final mean body weights of dosed mice were 5%-9% lower than those of controls. Diarrhea was observed in all dosed groups of rats and mice.

In the 13-week studies, male and female rats received doses of 180-3,000 mg/kg and male and female mice received doses of 250-3,000 mg/kg. No compound-related deaths were seen in rats or mice. Final mean body weights of rats that received 3,000 mg/kg were 11% lower than those of the vehicle controls for males and 6% lower for females. For mice, mean body weights were comparable. Diarrhea

occurred in male rats at doses of 750 mg/kg and above and in female rats at doses of 1,500 and 3,000 mg/kg. Mucous cell metaplasia of the glandular stomach was observed in male and female rats receiving 1,500 and 3,000 mg/kg. Lesions of the glandular stomach (inflammation, mucous cell metaplasia, and eosinophilic cytoplasmic change) and the forestomach (papillary hyperplasia and hyperkeratosis) were seen in all groups of dosed mice. The severity of lesions at 1,000 mg/kg or below was considered minimal. Based on these results, doses selected for rats and mice in the 2-year studies were 0, 500, or 1,000 mg/kg.

Body Weight and Survival in the Two-Year Studies: Mean body weights of dosed and vehicle control male and female rats and male mice were comparable. Mean body weights of dosed female mice were 4%-16% lower than those of the vehicle controls from week 28 to the end of the study. Diarrhea was observed for dosed male and female rats and for dosed male mice. Survival of low and high dose male rats and high dose female rats was reduced (male rats: vehicle control, 34/50; low dose, 19/50; high dose, 16/50; female rats: 29/50; 26/50; 16/50). Survival of male and female mice was comparable to that of the vehicle controls (male mice: 24/50; 36/50; 26/50; female mice: 36/50; 32/50; 32/50).

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: Nonneoplastic lesions occurred at low incidences in the nasal mucosa, lung, and forestomach of dosed male rats and in the nasal mucosa and lung of dosed female rats. Congestion and aspiration pneumonia occurring in dosed rats dying before week 104 was the principal cause of death in these animals.

Nonneoplastic lesions of the gastric fundal gland (eosinophilic cytoplasmic change and dilatation) and glandular stomach (cyst, chronic focal inflammation, hyperplasia, fibrosis, and squamous metaplasia) were seen in dosed male and female mice, and lesions of the gallbladder (eosinophilic cytoplasmic change) were seen in male mice.

Slight increases in the incidences of adenomas of the pituitary gland in high dose male rats and of fibroadenomas or adenomas (combined) of the mammary gland in low dose female rats were observed. These were not considered to be compound-related lesions.

The incidence of hepatocellular adenomas was decreased in high dose male mice (14/50; 15/49; 4/49). No compound-related neoplasms were seen in female mice.

Genetic Toxicology: Penicillin VK was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 with or without exogenous metabolic activation. The chemical was mutagenic only with activation in the mouse lymphoma L5178Y/TK$^{+/-}$ forward mutation assay. Incubation of Chinese hamster ovary cells with penicillin VK resulted in increased frequencies of sister chromatid exchanges and chromosomal aberrations in the absence of metabolic activation under conditions of delayed harvest to compensate for chemical-induced cell cycle delay; no effects from penicillin VK exposure were observed in these cells in the presence of S9.

Audit: The data, documents, and pathology materials from the 2-year studies of penicillin VK were audited. The audit findings show that the conduct of the studies is documented and support the data and results given in this Technical Report.

Conclusions: Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of penicillin VK for F344/N rats or for B6C3F$_1$ mice administered 500 or 1,000 mg/kg penicillin VK in corn oil by gavage, 5 days per week for 2 years. Nonneoplastic lesions were seen in the glandular stomach of dosed mice. Decreased survival of low and high dose male rats and of high dose female rats reduced the sensitivity of the studies for determining the presence or absence of a carcinogenic response in this species.

SUMMARY OF THE TWO-YEAR GAVAGE AND GENETIC TOXICOLOGY STUDIES OF PENICILLIN VK

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Dose			
0, 500, or 1,000 mg/kg penicillin VK in corn oil, 5 d/wk	0, 500, or 1,000 mg/kg penicillin VK in corn oil, 5 d/wk	0, 500, or 1,000 mg/kg penicillin VK in corn oil, 5 d/wk	0, 500, or 1,000 mg/kg penicillin VK in corn oil, 5 d/wk
Survival rates in the 2-year study			
34/50; 19/50; 16/50	29/50; 26/50; 16/50	24/50; 36/50; 26/50	36/50; 32/50; 32/50
Nonneoplastic effects			
None	None	Gastric fundal gland--eosinophilic cytoplasmic change and dilatation; glandular stomach--cysts, chronic focal inflammation, epithelial hyperplasia, fibrosis, and squamous metaplasia; gallbladder--eosinophilic cytoplasmic change	Gastric fundal gland--eosinophilic cytoplasmic change and dilatation; glandular stomach--cysts, chronic focal inflammation, epithelial hyperplasia, fibrosis, and squamous metaplasia
Neoplastic effects			
None	None	None	None
Level of evidence of carcinogenic activity			
No evidence	No evidence	No evidence	No evidence
Other considerations			
Decreased survival in low and high dose groups	Decreased survival in high dose group	None	Decreased body weight in dosed female groups
Genetic toxicology			
Not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537; mutagenic with but not without activation in mouse lymphoma assay; increased sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells in absence of S9.			

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 8.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 11.

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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 NTP toxicology and carcinogenesis studies 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 study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans.

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence including: animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results ("Clear Evidence" and "Some Evidence"); one category for uncertain findings ("Equivocal Evidence"); one category for no observable effects ("No Evidence"); and one category for experiments that because of major flaws cannot be evaluated ("Inadequate Study"). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Reports series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following quintet is 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 Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related.
- **No Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.
- **Inadequate Study of Carcinogenic Activity** is demonstrated by studies that because of major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. This should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- The adequacy of the experimental design and conduct;
- Occurrence of common versus uncommon neoplasia;
- Progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic lesions;
- Some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- Combining benign and malignant tumor incidences known or thought to represent stages of progression in the same organ or tissue;
- Latency in tumor induction;
- Multiplicity in site-specific neoplasia;
- Metastases;
- Supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- The presence or absence of dose relationships;
- The statistical significance of the observed tumor increase;
- The concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- Survival-adjusted analyses and false positive or false negative concerns;
- Structure-activity correlations; and
- In some cases, genetic toxicology.

These considerations together with the definitions as written should be used as composite guidelines for selecting one of the five categories. 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 induction by chemicals of more neoplasms than are generally found, or the earlier induction by chemicals of neoplasms that are commonly observed. 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.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Penicillin VK 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 November 1980 and ended in December 1982 at Springborn Institute for Bioresearch, Inc.

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

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

John Bucher, Ph.D.
Scot L. Eustis, D.V.M., Ph.D.
Joseph K. Haseman, Ph.D.
James Huff, Ph.D.

(Discipline Leaders and Principal Contributors)

Jack Bishop, Ph.D.
Douglas Bristol, Ph.D.
R. Chhabra, 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.
M. Vernon, Ph.D.
Douglas Walters, Ph.D.

NTP Pathology Working Group
(Evaluated Slides and Prepared Pathology Report for Rats on 10/15/86)

Kunitoshi Mitsumori, D.V.M., Ph.D. (Chair) (NTP)
Gary Boorman, D.V.M., Ph.D. (NTP)
Michael Elwell, D.V.M., Ph.D. (NTP)
Scot L. Eustis, D.V.M., Ph.D. (NTP)
Bhola Gupta, B.V.Sc., Ph.D. (NTP)
Kevin Morgan, B.V.Sc., M.R.C.V.S., Ph.D.
Chemical Industry Institute of Technology

(Evaluated Slides and Prepared Pathology Report for Mice on 5/22/86)

Kunitoshi Mitsumori, D.V.M., Ph.D. (Chair) (NTP)
Gary Boorman, D.V.M., Ph.D. (NTP)
Michael Elwell, D.V.M., Ph.D. (NTP)
Scot L. Eustis, D.V.M., Ph.D. (NTP)
Charles Montgomery, D.V.M. (NTP)
Henk Solleveld, D.V.M., Ph.D.
IVEG, TNO, The Netherlands
Steven Stefanski, D.V.M., M.S. (NTP)

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

R. Hiles, Ph.D.
C. Chrisp, D.V.M.
J. Boyce, D.V.M.

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

J. Gauchat
J. Hardisty, D.V.M.
P. Millar, M.V.M., M.R.C.V.S.

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

William D. Theriault, Ph.D.
Abigail C. Jacobs, Ph.D.
John Warner, M.S.

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on penicillin VK on July 14, 1987, 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

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

Michael A. Gallo, Ph.D.
Associate Professor, Director of Toxicology
Department of Environmental and Community Medicine, UMDNJ - Rutgers Medical School
Piscataway, New Jersey

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

Ad Hoc Subcommittee Panel of Experts

John Ashby, Ph.D.
Imperial Chemical Industries, PLC
Central Toxicology Laboratory
Alderley Park, England

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

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

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

Donald H. Hughes, Ph.D.*
Scientific Coordinator, Regulatory Services Division, The Procter and Gamble Company
Cincinnati, Ohio

William Lijinsky, Ph.D.*
Director, Chemical Carcinogenesis
Frederick Cancer Research Facility
Frederick, Maryland

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

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

Andrew Sivak, Ph.D. (Principal Reviewer)
Vice President, Biomedical Science
Arthur D. Little, Inc.
Cambridge, Massachusetts

*Unable to attend

SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF PENICILLIN VK

On July 14, 1987, the draft Technical Report on the toxicology and carcinogenesis studies of penicillin VK received public 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.K. Dunnick, NIEHS, introduced the studies by reviewing the experimental design, results, and proposed conclusions (no evidence of carcinogenic activity for male or female rats or male or female mice).

Dr. Capen, a principal reviewer, agreed with the conclusions. He asked for clarification of the significance of the eosinophilic cytoplasmic changes reported in the fundus of the stomach. Dr. S. Eustis, NIEHS, responded that the eosinophilic changes are believed to represent a potential secretory material in the epithelial cells lining the glandular stomach.

As a second principal reviewer, Dr. Sivak agreed with the conclusions. He expressed concern about the selection of corn oil as the vehicle for a water soluble substance, as this might influence the pharmacokinetics in relation to humans. Dr. Dunnick commented that at the time these studies were designed, ampicillin was also selected and because it was less water soluble, the vehicle chosen for both studies was corn oil. She said that an aqueous gavage solution would have been appropriate and noted that NTP is monitoring blood levels on some of the newer studies on drugs.

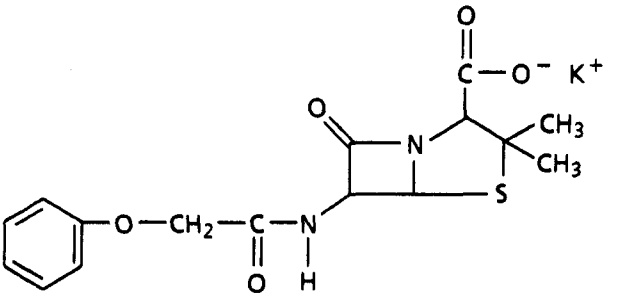
As a third principal reviewer, Dr. Popp agreed with the conclusions.

Dr. Capen moved that the Technical Report on penicillin VK be accepted with revisions discussed and with the conclusions as written for male and female rats and mice, no evidence of carcinogenic activity. Dr. Sivak seconded the motion, which was approved unanimously with eight votes.

I. INTRODUCTION

Production, Use, and Human Exposure
Toxicity
Reproductive and Teratogenic Effects
Absorption, Distribution, and Metabolism
Genetic Toxicity
Study Rationale

I. INTRODUCTION



PENICILLIN VK
4-Thia-1-azabicyclo(3.2.0)heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-(2-phenoxy- acetamido)-, monopotassium salt

CAS No. 132-98-9

$C_{16}H_{17}KN_2O_5S$ Molecular weight 388.5

Synonyms:

Penicillin V potassium	D-α-Phenoxymethylpenicillinate K salt	PVK
Penicillin V potassium salt	Phenoxymethylpenicillin potassium	

Trade Names:

Antibiocin	Cliacil	Ispenoral	Pen-Vee K	Stabillin VK Syrup 125
Apsin VK	Compocillin VK	Ledercillin VK	Pen-V-K powder	Stabillin VK Syrup 62.5
Arcacil	Distakaps V-K	Megacillin oral	Penvikal	Sumapen VK
Arcasin	Distaquaine V-K	Oracil-VK	Pfizerpen VK	Suspen
Aspin VK	Dowpen V-K	Orapen	Qidpen VK	Uticillin VK
Beromycin	DQV-K	Ospeneff	Robicillin VK	V-Cil-K
Beromycin 400	Fenoxypen	Pedipen	Rocillin-VK	V-Cillin K
Betapen VK	Icipen	Penagen	Roscopenin	Veetids
Calciopen K	Isocillin	Pencompren	SK-Penicillin VK	Vepen

Production, Use, and Human Exposure

Penicillin VK (phenoxymethylpenicillin, potassium salt) was first introduced in the United States for use as an antibiotic in 1955 (personal communication to Dr. J. Dunnick from V. Glocklin, Food and Drug Administration [FDA], March 7, 1983). It is one of the most widely used drugs in the United States, with approximately 23 million prescriptions being written per year for penicillin V or VK (FDA, 1986). The parent compound penicillin V was first prepared in 1948 (Behrens, 1948) and became clinically important when it was demonstrated to retain its antibiotic effects at low pH (Brandl et al., 1953). Penicillin VK became the preferred form of the drug for oral administration because higher serum levels were obtained when the salt (penicillin VK) rather than the free acid (penicillin V) was used (Kaipainen and Harkonen, 1956; Colquhoun et al., 1957).

Like that of the other penicillins, the structure of penicillin VK consists of a thiazolidine ring connected to a β-lactam ring. Penicillin VK has a unique side chain that differentiates it from the other penicillin antibiotics. Penicillin VK is a white, odorless, crystalline powder (Dunham, 1972). β-Lactam antibiotics may be inactivated by β-lactamases (penicillinases) that open the β-lactam ring or by amidases that split the side chain (Mandell and Sande, 1985; Herzberg and Moult, 1987). In the United States, penicillin V is produced by fermentation from cultures of *Penicillin chrysogenum* by adding phenoxyacetic acid to the medium (AICE, 1970; Selwyn, 1980). One milligram of penicillin VK is equivalent to 1,530 international units (IU) (Dunham, 1972),

an IU being the specific activity contained in 0.6 µg of crystalline sodium salt of penicillin G (Mandell and Sande, 1985).

Penicillin VK is administered to patients as a solution or in tablet form for oral use. It is usually given four times per day for the treatment of gram-positive cocci including streptococcal, pneumococcal, staphylococcal, and fusospirochetosis infections (Aronoff et al., 1984; Schwartz et al., 1981; PDR, 1986). Penicillin VK is not active against penicillinase-producing bacteria. The recommended dose for adults and children over 12 years of age is 125-250 mg (200,000-400,000 IU) every 6-8 hours for 10 days (USP, 1985; Remington's, 1985). Thus, a 70-kg man taking 1,000 mg of the drug per day receives a dose of approximately 14 mg/kg per day. The recommended dose for children under 12 years is 15-56 mg per day (PDR, 1986). Like the other β-lactam antibiotics, penicillin VK exerts its bactericidal effect by inhibiting the cross-linking step (transpeptidation) of bacterial cell wall biosynthesis (Waxman and Strominger, 1983; Mandell and Sande, 1985; Kelly et al., 1982).

Penicillin VK was evaluated for prophylactic use for the prevention of streptococcal infection in children with sickle cell anemia (Gaston et al., 1986), and the National Heart, Lung, and Blood Institute is planning a long-term followup study on the use of oral penicillin VK prophylaxis therapy in this population (personal communication to Dr. J. Dunnick from M. Gaston, March 1987). To date, no reports have associated penicillin use in humans with any carcinogenic effect, although other toxic responses have been reported as described below (PDR, 1986; personal communication to Dr. J. Dunnick from V. Glocklin, FDA, March 1983; Friedman and Ury, 1980).

Toxicity

The following LD_{50} values were reported for penicillin VK: 1,750 mg/kg in rats (strain unspecified) after intraperitoneal injection, and 1,000 mg/kg in mice (strain unspecified) after intravenous injection (Auhagen et al., 1962); 1,040 mg/kg in Charles River CD rats after oral administration (Goldenthal, 1971); and 1,351 mg/kg in mice (strain unspecified) after intraperitoneal injection (Drugs in Japan, 1982). At the time that this antibiotic was introduced into clinical use, comprehensive animal toxicity evaluation was not required or reported (personal communication to Dr. J. Dunnick from V. Glocklin, FDA, March 1983). Exposure of SPF (CD-1) mice to penicillin G in the drinking water at 500 U/ml reduces the number of anaerobic bacteria in the ceca (Berg, 1981).

The most common side effects reported after penicillin treatment in humans are anaphylactoid reactions. Other side effects reported (incidence not specified) include fever; gastrointestinal symptoms, such as nausea, vomiting, and diarrhea; skin rashes; and reversible effects on the hemic and lymphatic systems, including anemia, thrombocytopenia, and leukopenia (Erffmeyer, 1981; Norrby, 1986; Mandell and Sande, 1985; Alanis and Weinstein, 1983; Braver, 1983; Kitano et al., 1984). Penicillin and structurally related antibiotics elicit antibodies of all the major classes (IgE, IgA, IgM, IgG, IgD). A person with an allergy to one penicillin is assumed to be allergic to all penicillins (Erffmeyer, 1981). The prevalence of penicillin allergy in the U.S. population is estimated to be between 5% and 10% (Wendel et al., 1985).

Reproductive and Teratogenic Effects

The penicillins are frequently prescribed during pregnancy (Ledger, 1977). Reproductive toxicity or teratogenic effects after penicillin use have not been reported (Erffmeyer, 1981; Mandell and Sande, 1985; Jick et al., 1981). Penicillins have been reported to cross the placenta (Elek et al., 1972; Charles, 1954) and to be transmitted in human milk (Wilson et al., 1980).

Absorption, Distribution, and Metabolism

Penicillin VK is a biologically effective antibiotic because it is stable in acidic medium and is well absorbed from the gastrointestinal tract, with an estimated 80% of the drug absorbed after oral administration. Eighty percent of absorbed penicillin V is bound to serum protein (Neu, 1977), primarily albumin (Rolinson and Sutherland, 1965). The serum half-life of penicillin V is estimated to be 1 hour (McCracken et al., 1978).

After an oral dose of 266 mg penicillin VK was administered to humans, the serum level of the antibiotic was 4.2 IU/ml serum (Colquhoun et al., 1957). Peak serum or plasma levels of penicillin VK after oral administration were seen one-half hour after administration (Juncher and Raaschou, 1957; Colquhoun et al., 1957; Peck and Griffith, 1957-1958). After oral administration of 500 mg penicillin V to humans, 26% was recovered in the urine as penicillin and 35% as penicillic acid (Cole et al., 1973).

Recovery in the urine and bile 9 hours after intravenous administration of penicillin VK to male Wistar rats was 101% (43% penicillin V, 36% phenoxymethylpenicilloic acid, and 22% 6-aminopenicillanic acid and its corresponding penicilloic acid). The metabolic fate of penicillin VK is similar in a variety of animal species (Tsuji et al., 1983).

Genetic Toxicity

Published data on the mutagenicity of penicillin VK are very limited; however, several papers report results from tests with other or unspecified penicillins. For many studies, details of experimental conditions and complete data tables were not provided. Ostanina et al. (1977) reported that penicillin VK formed complexes in vitro with native and denatured *Escherichia coli* DNA and ribosomal RNA, inhibited nucleic acid synthesis in *Micrococcus lysodeikticus* and mouse lymphocytes, and blocked a DNA-dependent RNA polymerase system in vitro. When tested by the NTP, penicillin VK was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 with or without Aroclor 1254-induced Sprague Dawley rat or Syrian hamster liver S9 (Mortelmans et al., 1986; Appendix E, Table E1).

Penicillin VK was tested independently by two laboratories using the mouse lymphoma L5178Y/TK$^{+/-}$ forward mutation assay (Table E2). Neither laboratory reported mutagenic activity without S9, but test results at both laboratories were positive in the presence of S9 from Aroclor 1254-induced F344 rat liver. One of the laboratories also tested penicillin VK in mouse lymphoma cells with S9 from noninduced rat liver, and it was mutagenic under those conditions as well.

Treatment of Chinese hamster ovary cells with penicillin VK resulted in significantly increased frequencies of sister chromatid exchanges and chromosomal aberrations in the absence of metabolic activation under conditions of delayed harvest (to compensate for chemical-induced cell cycle delay); no effects from penicillin VK exposure were observed in these cells with S9 (Tables E3 and E4). Clastogenic effects by penicillin VK have also been reported by Parida (1972), who examined testicular tissue of the grasshopper *Phloeba antennala* after administration of 5 mg "Crystopen V" in feed; chromosomal aberrations were observed in 63% of the cells studied. The author stated that stickiness and despiralization, which he attributed to drug interaction with chromosomal proteins, were the most frequent abnormalities observed and that they hindered the assessment of other types of structural aberrations.

Literature reports on other penicillins indicate that these compounds do not inhibit growth due to DNA damage in *Bacillus subtilis* (Kada et al., 1972; Suter and Jaeger, 1982) or *E. coli* (Slater et al., 1971; Rosenkranz, 1981). Suter and Jaeger (1982) reported penicillin G-induced growth inhibition of *E. coli* rec/rec^{+} in the spot test but not when exposure occurred via the plate incorporation method. In an NTP mouse lymphoma L5178Y/TK$^{+/-}$ assay, treatment with penicillin V in the presence or absence of exogenous metabolic activation resulted in no significant increase in mutations (Table E2). Benzylpenicillin, sodium salt, has been reported to induce chromosomal aberrations in the meiotic cells of the grasshopper *Poecilocerus pictus* (Subramanyam and Reddy, 1975). A single injection of 50 mg/kg penicillin G induced chromosomal aberrations in mouse bone marrow cells (Manna and Bardhan, 1973), but doses of 200 or 800 mg/kg per day for 5 days to CFLP male mice did not produce increases in dominant lethal mutations in the offspring (James and Smith, 1982). No sperm head abnormalities were observed in male CBA × BALB/c mice administered penicillin (type unspecified) by intraperitoneal injection at doses up to 1,600 mg/kg per day for 5 days (Topham, 1980).

Study Rationale

Penicillin VK was selected for study as a representative of the penicillin G- and V-type antibiotics (antibiotics used in the treatment of gram-positive coccal infections) for which carcinogenicity data were not available. Penicillin VK was selected as the representative compound because it was water soluble and acid stable and could be administered orally, as opposed to other members of this antibiotic class, such as penicillin G, which are primarily administered intramuscularly. Corn oil was selected as the vehicle to allow for comparison of results with those of 2-year studies of ampicillin trihydrate (NTP, 1987) (a compound only slightly water soluble).

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF PENICILLIN VK

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 PENICILLIN VK

USP-grade, unformulated penicillin V potassium salt (penicillin VK) was obtained in two lots from Bristol Myers Company (Table 1). Purity, identity, and stability analyses were conducted at Midwest Research Institute (MRI) (Kansas City, Missouri). MRI reports on analyses performed in support of the penicillin VK studies are on file at NIEHS.

The infrared and nuclear magnetic resonance spectra for both lots (Figures 1 to 4) were consistent with those in the literature (Sadtler Pharmaceutical Spectra; Wilson et al., 1974). The ultraviolet/visible absorption maxima observed for both lots were consistent with those obtained for a USP standard.

Lot no. C9014 was obtained as a colorless, fluffy solid with an optical rotation $[\alpha]_D$ of $+219.9° \pm 1.0°$ at 26° C and a decomposition temperature of 197°-202° C with a sharp exotherm at 253.5°-260° C. Cumulative analytical chemistry data indicated that lot no. C9014 met all USP and Federal regulations requirements for potency and purity. The study material was determined to be approximately 94% pure. The results of elemental analyses of this lot were slightly high for oxygen, were low for sulfur, and agreed with the theoretical values for carbon, hydrogen, nitrogen, and potassium. Water content by Karl Fischer titration was 0.91%. This lot had a potency of 1,493 penicillin V units/mg relative to a USP standard as indicated by iodometric titration (CFR, 1977). Lot no. C9014 was 102.5% pure by titration of the carboxylate group with 0.1 N perchloric acid. Thin-layer chromatography on silica gel plates with either an *n*-butanol:water:glacial acetic acid (60:25:15) or a chloroform:acetone:glacial acetic acid (30:65:5) mobile phase and visualization by ultraviolet light (254 nm) and a chloroplatinic acid spray (Pokorny et al., 1973) detected one minor and one trace impurity in lot no. C9014, whereas the USP standard had a minor impurity only. Five impurities with a total peak area 5.4% that of the major peak were detected by high-performance liquid chromatography on a μBondapak C_{18} column with a 1% aqueous acetic acid:methanol containing 1% acetic acid (70:30) mobile phase at a flow rate of 2 ml/minute and ultraviolet detection at 254 nm. Six impurities with a total area 5.8% that of the major peak were detected by a similar system with a 60:40 solvent ratio. A single impurity with an area 0.2% that of the major peak was detected in a USP standard by this system. Major peak comparison of lot no. C9014 with a USP reference standard by high-performance liquid chromatography gave a value of 92.0% relative to the standard.

TABLE 1. IDENTITY AND SOURCE OF PENICILLIN VK USED IN THE GAVAGE STUDIES

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Lot Numbers		
C9014	C9014	C9014 and H1688
Date of Initial Use		
9/28/79	12/21/79	Lot no. C9014--12/80; lot no. H1688--12/81
Supplier		
Bristol Myers Co. (Syracuse, NY)	Bristol Myers Co. (Syracuse, NY)	Bristol Myers Co. (Syracuse, NY)

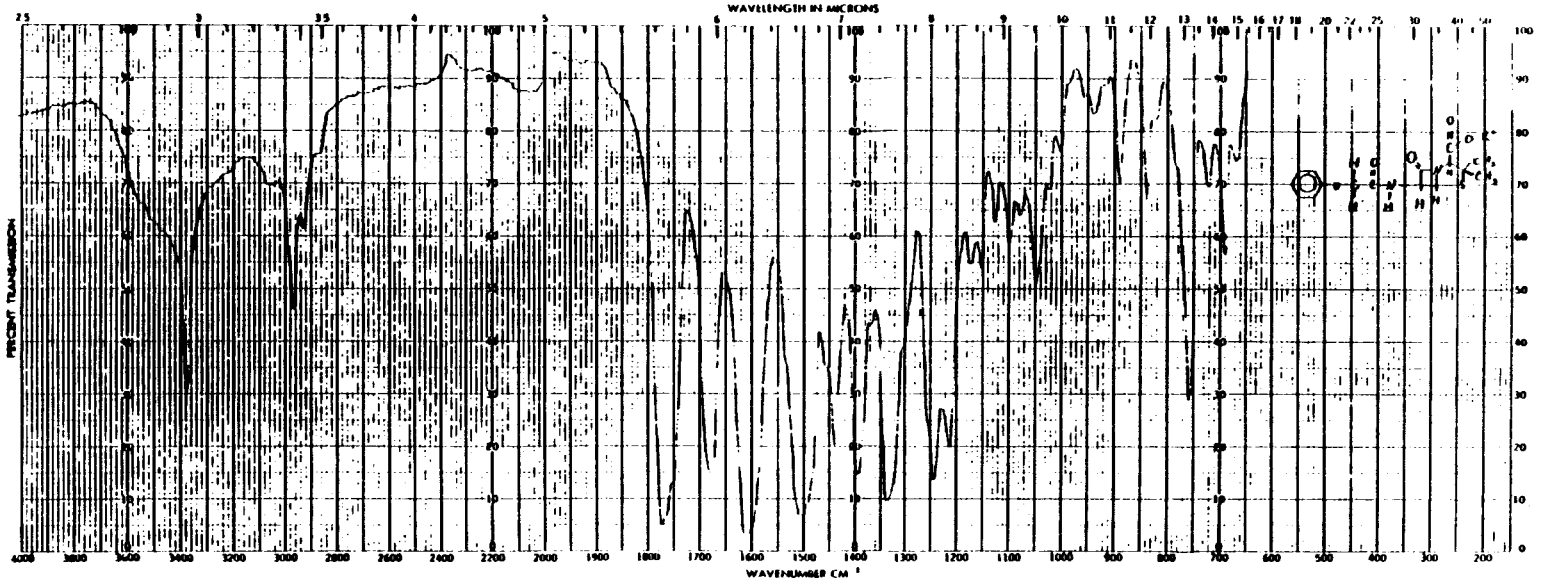


FIGURE 1. INFRARED ABSORPTION SPECTRUM OF PENICILLIN VK (LOT NO. C9014)

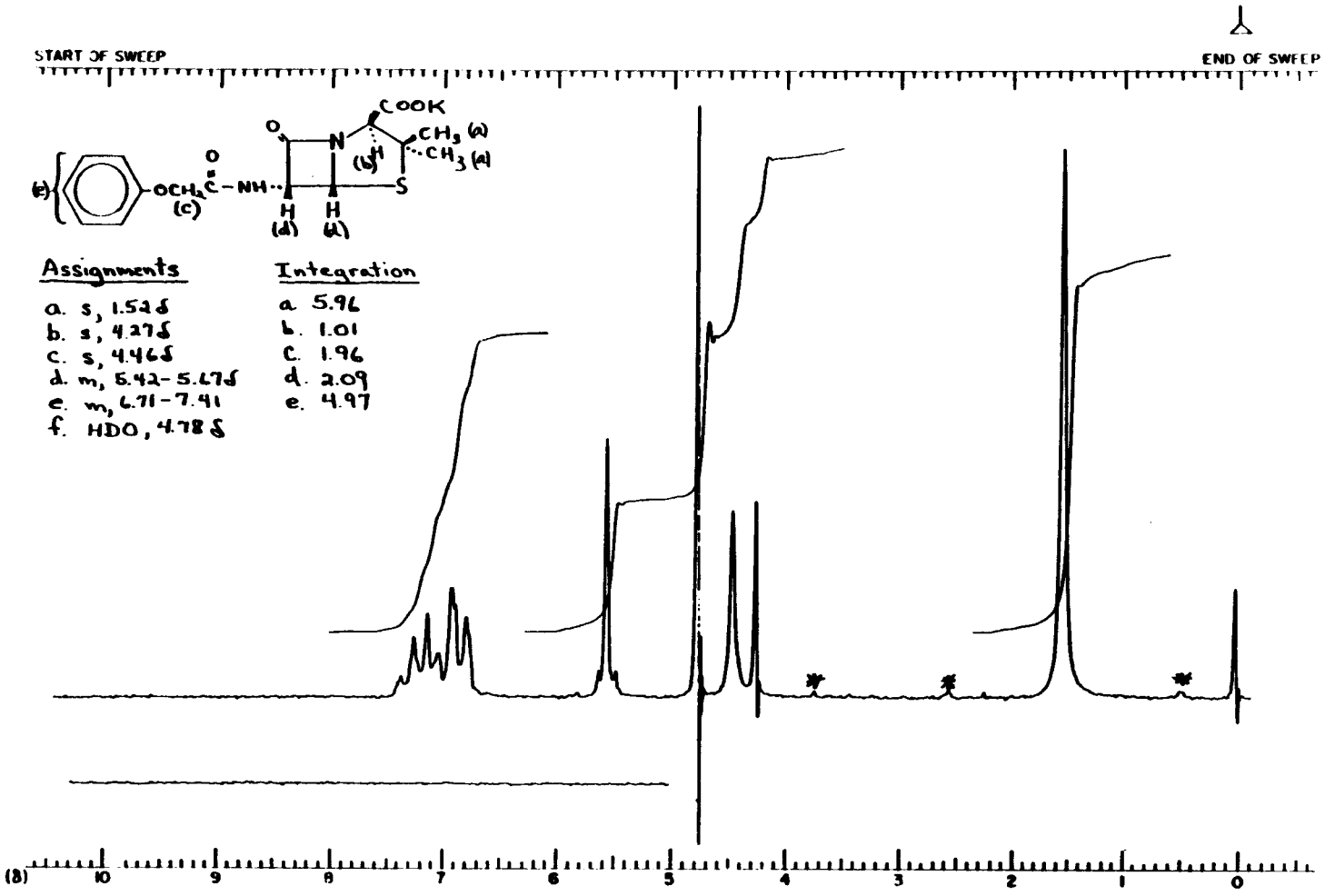


FIGURE 2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF PENICILLIN VK (LOT NO. C9014)

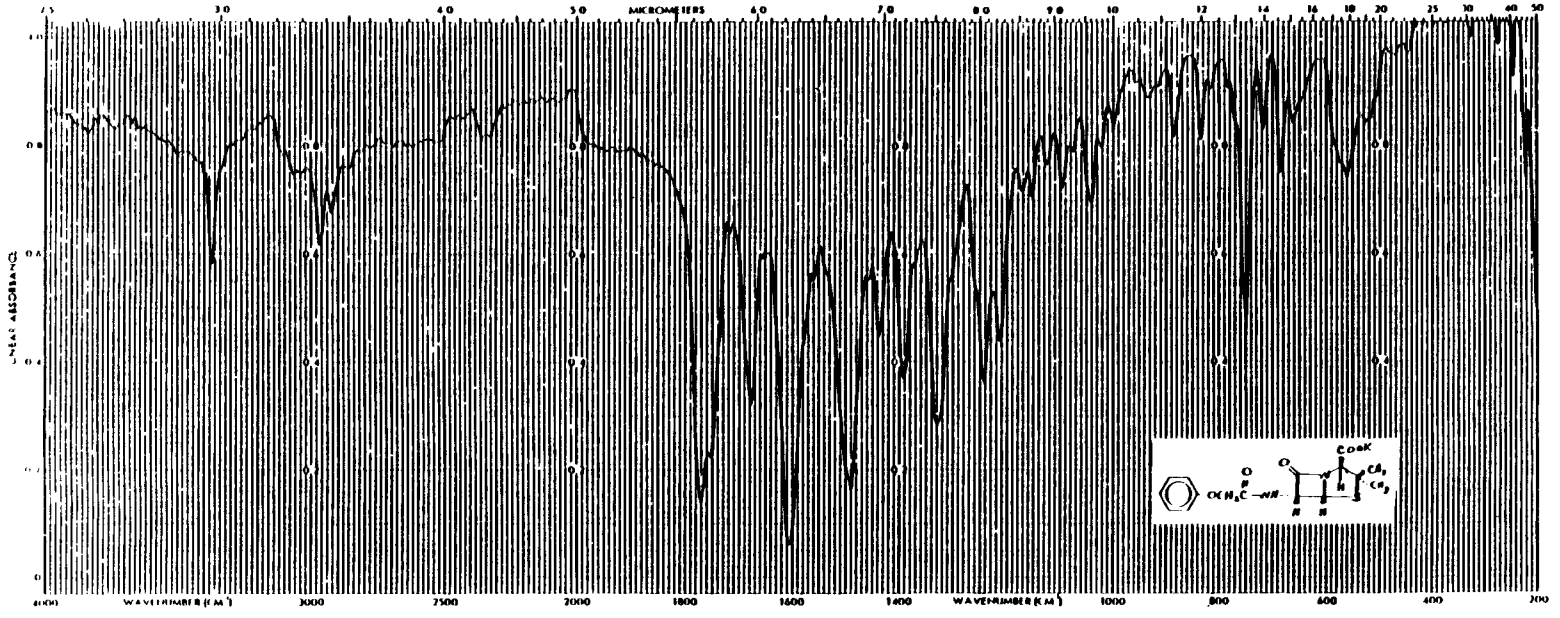


FIGURE 3. INFRARED ABSORPTION SPECTRUM OF PENICILLIN VK (LOT NO. H1688)

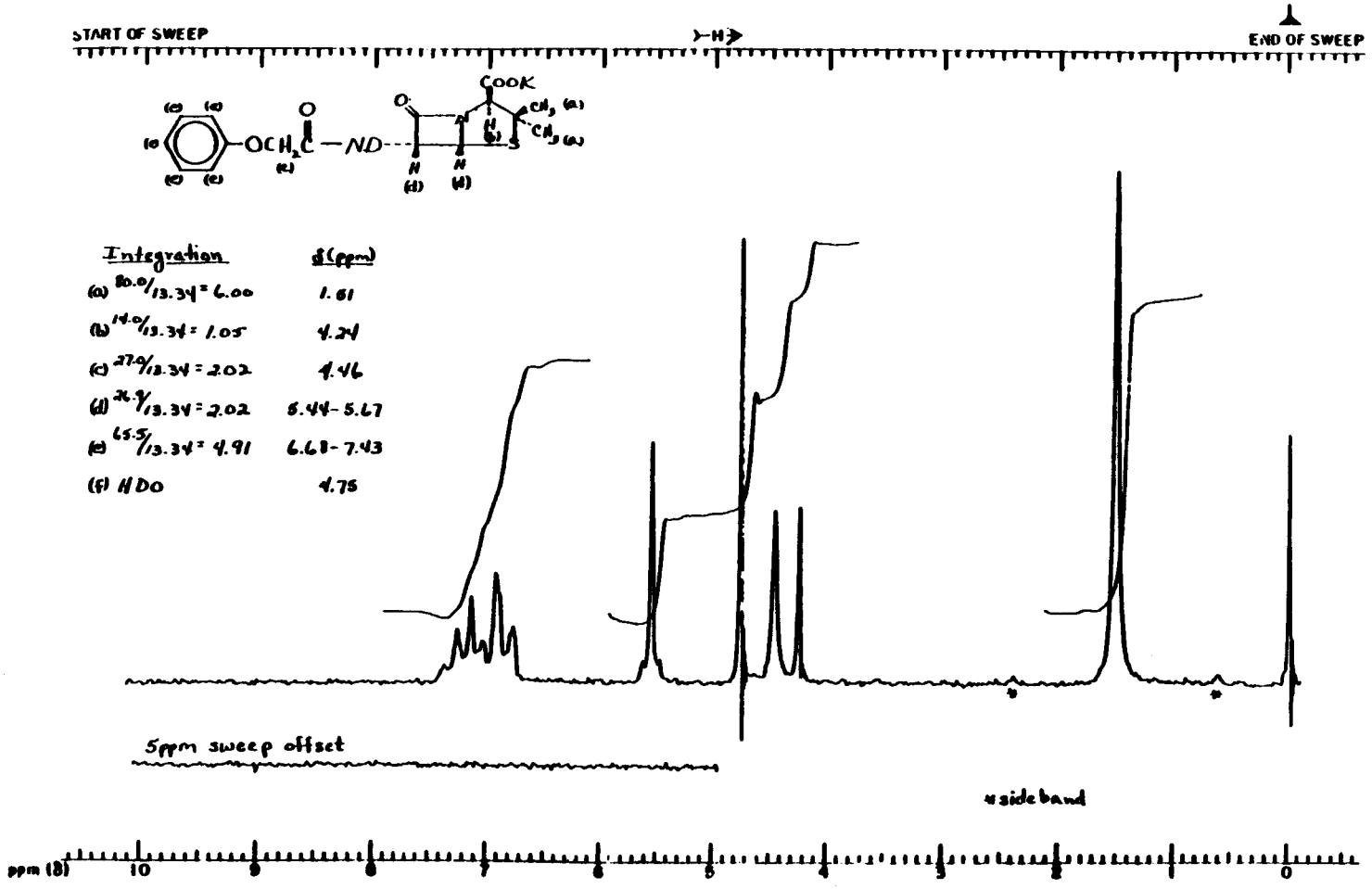


FIGURE 4. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF PENICILLIN VK (LOT NO. H1688)

Cumulative analytical chemistry data indicated that lot no. H1688 also met the USP requirements for potency and purity. The study material was determined to be approximately 98% pure. The results of elemental analysis agreed with the theoretical values. The water content was 0.07%. Iodometric titration indicated a potency of 1,505 penicillin V units/mg relative to a USP standard. Lot no. H1688 was 105% pure by titration of the carboxylate group. One trace impurity was detected by thin-layer chromatography by the same systems described for lot no. C9014 but with an iodoplatinate spray (Pokorny et al., 1973). One impurity with a total peak area 1.1% that of the major peak was detected by the high-performance liquid chromatographic system described for the previous lot but with a 67:33 solvent ratio and a flow rate of 1.5 ml/minute. Major peak comparison of lot no. H1688 with a USP reference standard by high-performance liquid chromatography gave a value of 96.8% relative to the standard.

Both lots of study material were analyzed for the presence of *N,N*-dimethylaniline by extraction of aqueous solutions of penicillin VK with methylene chloride followed by high-resolution gas chromatography with flame ionization detection. Results of these analyses indicated that *N,N*-dimethylaniline was not present in either lot of study material at a concentration of 1 ppm (w/w) or greater.

Stability studies performed with the same high-performance liquid chromatographic system with a 55:45 solvent ratio indicated that penicillin VK was stable in the dark for 2 weeks at temperatures up to 60° C. The study laboratory stored several portions at −40° C to serve as reference samples; the bulk chemical was stored at −4° C. Periodic reanalyses of the bulk chemical and reference samples were performed at the study laboratory. Iodometric titration with 0.01 N sodium thiosulfate and the high-performance liquid chromatographic system previously described except with a 60:40 solvent ratio indicated that no notable deterioration of the bulk chemical occurred over the course of the studies. Identity of the chemical at the study laboratory was confirmed by infrared spectroscopy.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

Stability studies of penicillin VK mixed with NIH 07 Rat and Mouse Ration indicated that penicillin VK at a concentration of 1,000 ppm was unstable when stored for 2 weeks at temperatures ranging from 5° C to 45° C. Recovery of penicillin VK after 2 weeks' storage, sealed and protected from air and light, was 85% at 5° C, 40% at 25° C, and 7% at 45° C. Because of the instability of penicillin VK mixed in rodent feed, corn oil was investigated as a possible vehicle for gavage studies.

Penicillin VK and corn oil were mixed to give the desired concentrations (Table 2). Stability studies of a 10 mg/ml dose mixture stored for 2 weeks at room temperature or 5° C were performed by extraction with 0.01 M sodium dihydrogen phosphate:methanol (1:4) and analysis by high-performance liquid chromatography on a Varian MicroPak C_{18} column with an aqueous 0.01 M sodium dihydrogen phosphate:methanol (52:48) mobile phase at a flow rate of 1 ml/minute and ultraviolet detection at 254 nm. The concentration of penicillin VK was calculated from an acetanilide internal standard.

Penicillin VK (10 mg/ml) in corn oil was found to be stable when stored at room temperature or 5° C for 14 days. In the 13-week and 2-year studies, dose mixtures were stored at 4° C for no longer than 2 weeks. Formulations of penicillin VK in corn oil were periodically selected at random at the study laboratory, extracted with the same extraction solvent listed above, and analyzed in duplicate by ultraviolet spectroscopy (269 nm) to estimate the accuracy with which formulations were prepared over the course of the studies. Dose mixtures were analyzed once during the 13-week studies; the results ranged from 94% to 107% of the target concentrations (Table 3). During the 2-year studies, the dose mixtures were analyzed once every 2 months,

TABLE 2. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF PENICILLIN VK

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation		
24% (w/v) stock suspension of penicillin VK in corn oil prepared every 2 d by blending at high speed in Waring micro-blender; blending repeated before dosing to obtain uniform suspension	30% and 20% suspensions prepared by mixing corn oil and weighed penicillin VK in Waring Blender until thoroughly blended. Mixture transferred to volumetric flask, brought to volume with corn oil, and thoroughly mixed with stir bar and magna-stirrer. Contents of volumetric flask further mixed in beaker with magna-stirrer. Lower concentrations prepared by serial dilution of next higher concentration	Weighed amounts of penicillin VK diluted to volume with corn oil to give 50, 100, or 200 mg/ml and mixed in a Waring Blender or a Tekmer SD-45 homogenizer. Stock suspensions divided into quantities needed for each day of dosing; on day of dosing, mixture warmed to room temperature, reblended, and mixed during dosing with magnetic stir bar
Maximum Storage Time		
1 d	2 wk	2 wk
Storage Conditions		
4° C	4° C	4° C

TABLE 3. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF PENICILLIN VK (a)

Target Concentration (mg/ml)	Determined Concentration (mg/ml) (b)	Determined as a Percent of Target
25	26.8	107.2
37.5	38.3	102.1
50	51.7	103.4
75	71.3	95.1
100	99.5	99.5
150	141.6	94.4
200	189.5	94.8
300	311	103.7

(a) Date mixed: 1/9/80
(b) Results of duplicate analysis

and concentrations ranged from 89% to 106% of the target values (Table 4). Because 40/41 dose mixtures analyzed were within ±10% of the target concentrations, the dose mixtures were estimated to have been within specifications 98% of the time throughout the 2-year studies. Referee analyses were periodically performed by the analytical chemistry laboratory. The penicillin VK concentrations in one referee sample were outside of specifications (Table 5).

TABLE 4. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF PENICILLIN VK

Date Mixed	Concentration of Penicillin VK in Corn Oil for Target Concentration (mg/ml) (a)		
	50	100	200
11/21/80		101	204
01/15/81	48	100	206
03/12/81	48	92	(b) 178
05/07/81	47	95	181
07/07/81	53	95	194
09/01/81	50.2	103.1	205.5
10/28/81	48.9	99.9	198.9
12/22/81	48.6	98.2	200
02/17/82	47	97	199
03/31/82	50	101	202
06/02/82	49	99	199
08/25/82	49.4	97	197
09/22/82	47	99	198
11/09/82	50.3	97.4	197
Mean (mg/ml)	49.0	98.2	197.1
Standard deviation	1.69	2.90	8.20
Coefficient of variation (percent)	3.4	3.0	4.2
Range (mg/ml)	47-53	92-103.1	178-206
Number of samples	13	14	14

(a) Results of duplicate analysis
(b) Out of specifications

TABLE 5. RESULTS OF REFEREE ANALYSIS IN THE TWO-YEAR GAVAGE STUDIES OF PENICILLIN VK

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (mg/ml)	
		Study Laboratory (a)	Referee Laboratory (b)
11/21/80	200	204	195
03/12/81	50	48	55
10/28/81	100	99.9	(c) 117.7
03/31/82	50	50	44.7
09/22/82	200	198	197

(a) Results of duplicate analysis
(b) Results of triplicate analysis
(c) Out of specifications

II. MATERIALS AND METHODS

FOURTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 14 days before the studies began. Doses selected for the 14-day studies were based on oral administration LD_{50} values for adult rats of 1,040 mg/kg penicillin VK (Goldenthal, 1971). The highest dose for the 14-day studies in rats was set at approximately two times the oral LD_{50} value. The highest dose for the 14-day studies in mice was also set at 2,400 mg/kg to allow expression of toxicity in rats and mice. Groups of five rats and five mice of each sex were administered 150, 300, 600, 1,200, or 2,400 mg/kg penicillin VK in corn oil by gavage for 14 consecutive days. The controls were untreated.

Animals were housed five per cage and received water and feed ad libitum. Details of animal maintenance are presented in Table 6. The rats and mice were observed two times per day and were weighed on days 0, 7, and 14. A necropsy was performed on all animals. Three males and three females of each species from the control and 2,400 mg/kg groups were examined histopathologically.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of penicillin VK and to determine the concentrations to be used in the 2-year studies.

Five-week-old male and female F344/N rats and 4- to 6-week-old male and female B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and were observed for 15 days before the studies began. Rats and mice were housed five per cage in polycarbonate cages. NIH 07 Rat and Mouse Ration pellets and water (half deionized/half tap) were available ad libitum.

Groups of 10 rats of each sex were administered 0, 180, 370, 750, 1,500, or 3,000 mg/kg penicillin VK in corn oil by gavage, 5 days per week for 13 weeks. The 3,000 mg/kg groups of rats were given two doses of 1,500 mg/kg, 5 hours apart. Groups of 10 mice of each sex received 0, 250, 500, 1,000, 2,000, or 3,000 mg/kg on the same schedule.

Animals were checked two times per day; moribund animals were killed. Individual animal weights were recorded weekly. At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Groups and tissues examined are listed in Table 6.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats and 50 mice of each sex were administered 0, 500, or 1,000 mg/kg penicillin VK in corn oil by gavage, 5 days per week for 103 weeks (rats) or 104 weeks (mice).

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. Rats were shipped to the study laboratory at 4 weeks of age and mice, at 4-5 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 were placed on study at 7 weeks of age and the mice, at 8 weeks of age. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix F).

TABLE 6. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF PENICILLIN VK

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		
150, 300, 600, 1,200, or 2,400 mg/kg penicillin VK in corn oil by gavage; dose vol: 10 ml/kg; controls were untreated	Rats--0, 180, 370, 750, 1,500, or 3,000 mg/kg penicillin VK in corn oil by gavage (3,000 mg/kg group received 1,500 mg/kg 2 × d, 5 h apart); mice--0, 250, 500, 1,000, 2,000, or 3,000 mg/kg; dose vol: rats--5 ml/kg; mice--10 ml/kg	0, 500, or 1,000 mg/kg penicillin VK in corn oil by gavage; dose vol: rats--5 ml/kg; mice--10 ml/kg
Date of First Dose		
9/28/79	12/21/79	Rats--12/1/80; mice--12/8/80
Date of Last Dose		
10/11/79	3/20/80	Rats--11/21/82; mice--12/6/82
Duration of Dosing		
14 consecutive d	5 d/wk for 13 wk	5 d/wk for 103 wk (rats) or 104 wk (mice)
Type and Frequency of Observation		
Observed 2 × d; weighed on d 0, 7, and 14	Observed 2 × d; weighed 1 × wk	Observed 2 × d; weighed 1 × wk for 12 wk, 1 × 4 wk through wk 88, and 1 × 2 wk thereafter; palpated for tumors 1 × 4 wk after wk 41
Necropsy and Histologic Examination		
Necropsy performed on all animals; tissues from 3 animals per sex in the control and 2,400 mg/kg groups examined histologically	Necropsy performed on all animals. Histologic exam performed on vehicle control and 3,000 mg/kg groups and on animals that died before the end of the studies; tissues examined include: adrenal glands, brain, esophagus, eyes (if grossly abnormal), gross lesions, heart, kidneys, large intestine, liver, lungs and mainstem bronchi, mammary gland, pancreas, parathyroids, pharynx (if grossly abnormal), pituitary gland, prostate/testes/epididymis or ovaries/uterus, salivary glands, skin, small intestine, spinal cord (if neurologic signs present), spleen, sternebrae or femur or vertebrae including marrow, stomach, thymus, thyroid gland, tissue masses, trachea, and urinary bladder	Necropsy and histologic exam performed on all animals; tissues examined include gallbladder (mice) and mandibular or mesenteric lymph nodes plus those tissues examined in the 13-week studies
ANIMALS AND ANIMAL MAINTENANCE		
Strain and Species		
F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice
Animal Source		
Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)

TABLE 6. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF PENICILLIN VK (Continued)

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Study Laboratory		
Springborn Institute for Bioresearch, Inc.	Springborn Institute for Bioresearch, Inc.	Springborn Institute for Bioresearch, Inc.
Method of Animal Identification		
Ear notch and toe clip	Ear notch and toe clip	Ear notch and toe clip
Time Held Before Study		
14 d	15 d	18 d
Age When Placed on Study		
Rats--6-7 wk; mice--6-8 wk	Rats--7 wk; mice--6-8 wk	Rats--7 wk; mice--8 wk
Age When Killed		
Rats--8-9 wk; mice--8-10 wk	Rats--21 wk; mice--20-22 wk	Rats--111 wk; mice--112 wk
Necropsy Dates		
10/13/79	3/24/80-3/25/80	Rats--11/29/82-12/1/82; mice--12/6/82-12/8/82
Method of Animal Distribution		
According to a table of random numbers	Same as 14-d studies	Assigned to cages according to one table of random numbers and then to groups according to another table
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, Manhasset, NY)	Ancubes (Ancare, Manhasset, NY)	Same as 13-wk studies
Water		
Tap water in glass bottles; available ad libitum	Automatic watering system (Edstrom Industries, Waterford, WI) with half tap/half deionized water; available ad libitum	Same as 13-wk studies but with Osmonic water
Cages		
Stainless steel wire mesh (Shoreline, Kansas City, MO)	Polycarbonate (Lab Products, Inc., Rochelle Park, NJ)	Same as 13-wk studies
Cage Filters		
None	Polyester filters (Snow Filtration, Cincinnati, OH)	Same as 13-wk studies
Animals per Cage		
5	5	5
Other Chemicals on Study in the Same Room		
None	None	None
Animal Room Environment		
Temp--72.7° ± 1.95° F; hum--69.5% ± 7.07%; fluorescent light 12 h/d; 12 room air changes/h	Temp--68°-76° F; hum--38%-76%; fluorescent light 12 h/d; 12 room air changes/h	Temp--73.2° ± 1.84° F; hum--56.9% ± 13.9%; fluorescent light 12 h/d; 12 room air changes/h

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

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

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

Animal Maintenance

Rats and mice were housed five per cage in polycarbonate cages. Feed and water (Osmonic) were available ad libitum. Rack position was shifted once per week; cages were not rotated within racks. Details of animal maintenance are summarized in Table 6.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded at least once per month. Body weights by cage were recorded once per week for the first 12 weeks of the studies and at least 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 6.

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, 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 to be missing or dead from other than natural causes; 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: life table tests, incidental tumor analysis, and Fisher exact/Cochran-Armitage trend analyses. Tests of significance include pairwise comparisons of high dose and low dose groups with vehicle controls and tests for overall dose-response trends. For studies in which administration of the test compound has little effect on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death. Continuity-corrected tests are used in the analysis of tumor incidence, and reported P values are one-sided. The procedures described below also were used to evaluate selected nonneoplastic lesions.

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 (1959) 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 actually examined for tumors 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.)

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

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

III. RESULTS

RATS

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

III. RESULTS: RATS

FOURTEEN-DAY STUDIES

One female rat that received 1,200 mg/kg penicillin VK died before the end of the study (Table 7). Final mean body weights of all groups of dosed males were 5%-17% lower than that of the controls. Final mean body weights of dosed and control female rats were comparable. Diarrhea was observed in all dosed groups of animals; the incidence increased with increasing dose. Animals salivated excessively after they were dosed. No compound-related histopathologic effects were observed.

Because of minimal response (no dose-related histopathologic lesions or deaths) of rats at 2,400 mg/kg, the highest dose for the 13-week studies was set at 3,000 mg/kg.

THIRTEEN-WEEK STUDIES

No compound-related deaths occurred (Table 8). Final mean body weights of rats that received 3,000 mg/kg were 11% lower than those of the vehicle controls for males and 6% lower for females. Diarrhea was observed for males that received 750 mg/kg or more and for females that received 1,500 or 3,000 mg/kg. Minimal to mild mucous cell metaplasia of the glandular stomach was observed in 7/9 males and 8/8 females that received 1,500 mg/kg and in 4/6 males and 8/8 females that received 3,000 mg/kg. This change occurred primarily adjacent to the junction of the glandular stomach and forestomach and consisted of a replacement of parietal and chief cells by a mucous cell type.

Dose Selection Rationale: Because of body weight changes and clinical signs at the highest dose in the 13-week studies, doses selected for rats for the 2-year studies were 500 and 1,000 mg/kg penicillin VK, administered in corn oil by gavage, 5 days per week.

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

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
0	5/5	129 ± 3	201 ± 2	+72 ± 3	--
150	5/5	127 ± 3	191 ± 5	+64 ± 4	95
300	5/5	124 ± 3	188 ± 4	+64 ± 5	94
600	5/5	123 ± 2	188 ± 3	+65 ± 3	94
1,200	5/5	124 ± 2	184 ± 2	+60 ± 3	92
2,400	5/5	124 ± 2	166 ± 2	+42 ± 2	83
FEMALE					
0	5/5	110 ± 4	138 ± 4	+28 ± 1	--
150	5/5	114 ± 1	142 ± 3	+28 ± 2	103
300	5/5	117 ± 4	141 ± 3	+24 ± 0	102
600	5/5	117 ± 2	143 ± 3	+26 ± 2	104
1,200	(d) 4/5	118 ± 4	144 ± 2	+23 ± 1	104
2,400	5/5	112 ± 3	137 ± 4	+25 ± 2	99

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Day of death: 3

TABLE 8. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF PENICILLIN VK

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	113 ± 3	359 ± 7	+246 ± 6	--
180	10/10	117 ± 1	349 ± 5	+232 ± 4	97
370	10/10	112 ± 3	325 ± 10	+213 ± 9	91
750	10/10	115 ± 3	347 ± 5	+232 ± 7	97
1,500	10/10	109 ± 3	328 ± 6	+219 ± 6	91
3,000	10/10	114 ± 3	321 ± 4	+207 ± 5	89
FEMALE					
0	10/10	92 ± 1	197 ± 3	+105 ± 2	--
180	10/10	89 ± 2	194 ± 3	+105 ± 3	98
370	10/10	86 ± 2	197 ± 3	+111 ± 4	100
750	(d) 9/10	90 ± 1	192 ± 3	+102 ± 3	97
1,500	(d) 9/10	94 ± 1	195 ± 3	+101 ± 3	99
3,000	(e) 9/10	92 ± 1	185 ± 3	+93 ± 2	94

(a) Number surviving/number initially in group; all deaths judged to be gavage related.
(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
(d) Week of death: 3
(e) Week of death: 4

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed and vehicle control male and female rats were comparable (Table 9 and Figure 5). Diarrhea (male: vehicle control, 0/50; low dose, 15/50; high dose, 41/50; female: 1/50; 5/50; 18/50) and excessive urination (male: 0/50; 9/50; 16/50; female: 12/50; 28/50; 43/50) were observed in dosed animals.

TABLE 9. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF PENICILLIN VK

Weeks on Study	Vehicle Control		500 mg/kg			1,000 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	154	50	151	98	50	153	99	50
1	185	50	184	99	50	179	97	50
2	216	50	217	100	50	210	97	50
3	238	50	238	100	50	233	98	50
4	256	50	259	101	50	252	98	50
5	275	50	276	100	50	270	98	50
6	287	50	290	101	50	282	98	50
7	298	50	304	102	50	297	100	50
8	312	50	317	102	50	311	100	50
9	321	50	327	102	50	322	100	50
10	329	50	332	101	50	331	101	50
11	335	50	344	103	50	343	102	50
12	332	50	344	104	50	330	99	50
16	360	50	372	103	49	365	101	50
20	367	50	370	101	49	356	97	50
25	388	50	386	99	49	390	101	50
28	411	50	407	99	49	407	99	49
32	429	50	432	101	48	426	99	48
36	446	50	440	99	48	437	98	48
40	462	50	445	96	48	449	97	46
44	468	50	469	100	48	461	99	46
48	469	50	467	100	48	438	93	46
52	457	50	466	102	48	435	95	45
56	463	50	454	98	48	428	92	42
60	467	50	456	98	46	446	96	39
64	461	50	455	99	46	444	96	39
68	466	50	446	96	44	432	93	39
72	463	50	461	100	42	440	95	39
76	470	50	466	99	41	448	95	37
80	456	50	449	98	37	433	95	34
84	459	49	460	100	34	436	95	32
88	461	47	444	96	33	438	95	29
92	443	46	451	102	31	429	97	25
96	448	42	447	100	27	421	94	19
100	436	35	432	99	21	412	94	16
102	438	34	421	96	20	410	94	16
FEMALE								
0	121	50	121	100	50	119	98	50
1	138	50	136	99	50	134	97	50
2	149	50	147	99	50	145	97	50
3	156	50	155	99	50	153	98	50
4	168	50	168	100	50	168	100	50
5	174	50	176	101	49	175	101	48
6	186	50	183	98	49	182	98	48
7	190	50	189	99	49	187	98	47
8	198	50	192	99	49	192	99	47
9	195	50	196	101	49	192	98	47
10	201	50	201	100	49	201	100	47
11	200	50	205	103	49	200	100	47
12	203	50	206	101	49	201	99	47
16	213	50	215	101	49	212	100	47
20	213	50	218	102	49	220	103	47
25	217	50	225	104	49	223	103	47
28	228	50	237	104	49	229	100	47
32	248	50	253	102	49	253	102	47
36	255	50	287	113	49	277	109	47
40	261	50	263	101	49	265	102	46
44	267	50	277	104	49	275	103	46
48	273	50	283	104	49	269	99	44
52	278	50	290	104	49	285	103	44
56	275	50	284	103	49	278	101	42
60	286	50	300	105	48	290	101	41
64	297	50	308	104	48	303	102	41
68	309	50	317	103	46	317	103	41
72	311	50	323	104	45	316	102	41
76	314	50	330	105	45	327	104	40
80	322	47	333	103	43	326	101	37
84	331	47	333	101	40	328	99	33
88	332	47	341	103	37	333	100	31
92	328	47	336	102	34	331	101	29
96	338	43	342	101	32	335	99	22
100	335	31	337	101	30	332	99	18
102	336	29	340	101	27	335	100	16

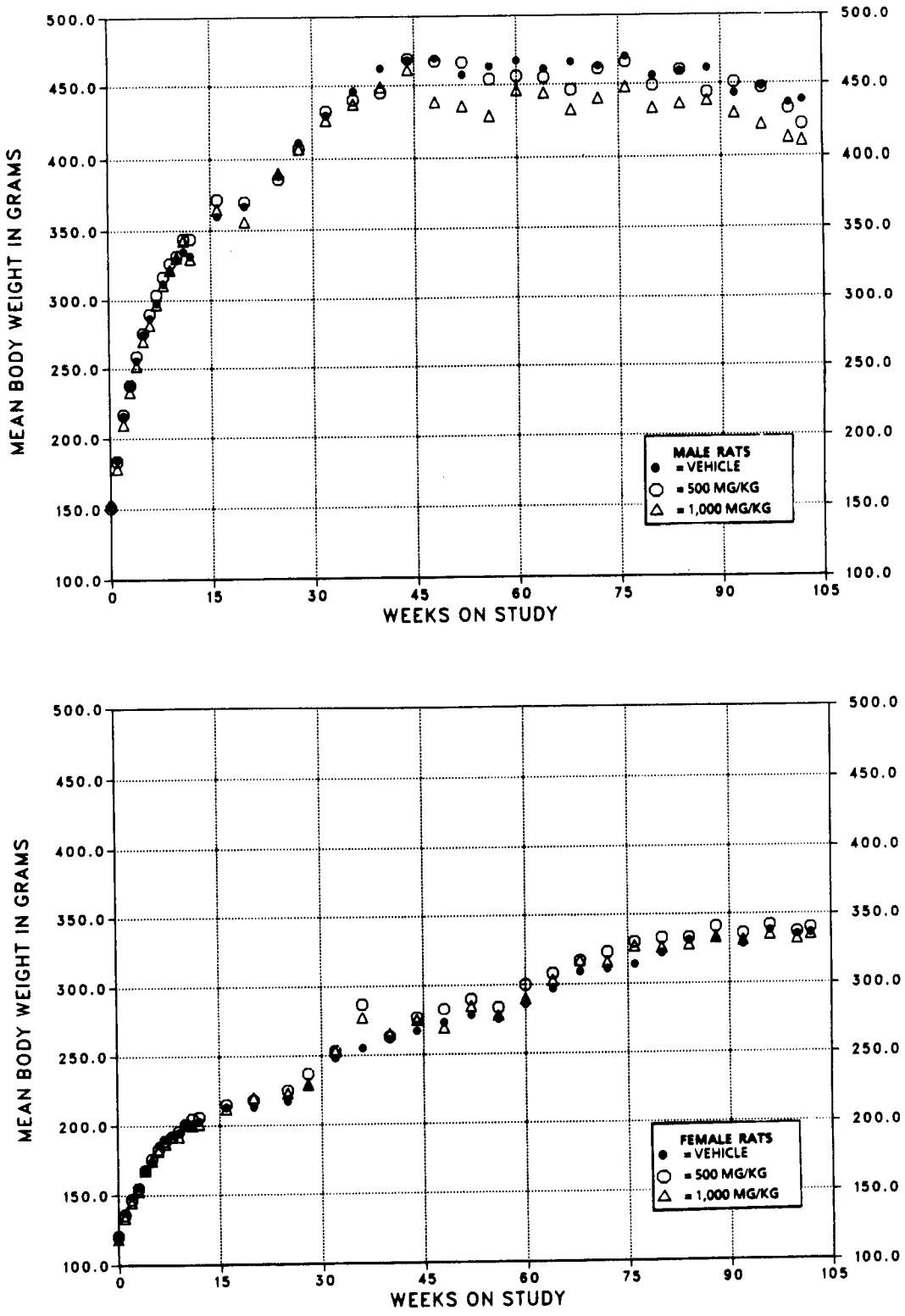


FIGURE 5. GROWTH CURVES FOR RATS ADMINISTERED PENICILLIN VK IN CORN OIL BY GAVAGE FOR TWO YEARS

III. RESULTS: RATS

Survival

Estimates of the probabilities of survival for male and female rats administered penicillin VK at the doses used in these studies and for vehicle controls are shown in Table 10 and in the Kaplan and Meier curves in Figure 6. The survival of both the low (after week 71) and high (after week 75) dose groups of male rats was significantly lower than that of the vehicle controls. The survival of the high dose group of female rats was significantly lower than that of the vehicle controls after week 82.

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 anterior pituitary gland, thyroid gland, mammary gland, clitoral gland, nasal mucosa, lung, liver, and forestomach.

Lesions in male rats are summarized in Appendix A. Histopathologic findings on neoplasms are summarized in Table A1. Table A2 gives the survival and tumor status for individual male rats. Table A3 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 Table A3 (footnotes). Historical incidences of tumors in corn oil vehicle control male rats are listed in Table A4. Findings on nonneoplastic lesions are summarized in Table A5.

Lesions in female rats are summarized in Appendix B. Histopathologic findings on neoplasms are summarized in Table B1. Table B2 gives the survival and tumor status for individual female rats. Table B3 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 Table B3 (footnotes). Historical incidences of tumors in corn oil vehicle control female rats are listed in Table B4. Findings on nonneoplastic lesions are summarized in Table B5.

TABLE 10. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF PENICILLIN VK

	Vehicle Control	500 mg/kg	1,000 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	16	30	26
Accidentally killed	0	1	8
Killed at termination	34	17	16
Died during termination period	0	2	0
Survival P values (c)	0.001	0.002	0.002
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	21	23	30
Accidentally killed	0	1	4
Killed at termination	28	26	16
Died during termination period	1	0	0
Survival P values (c)	0.005	0.461	0.004

(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.

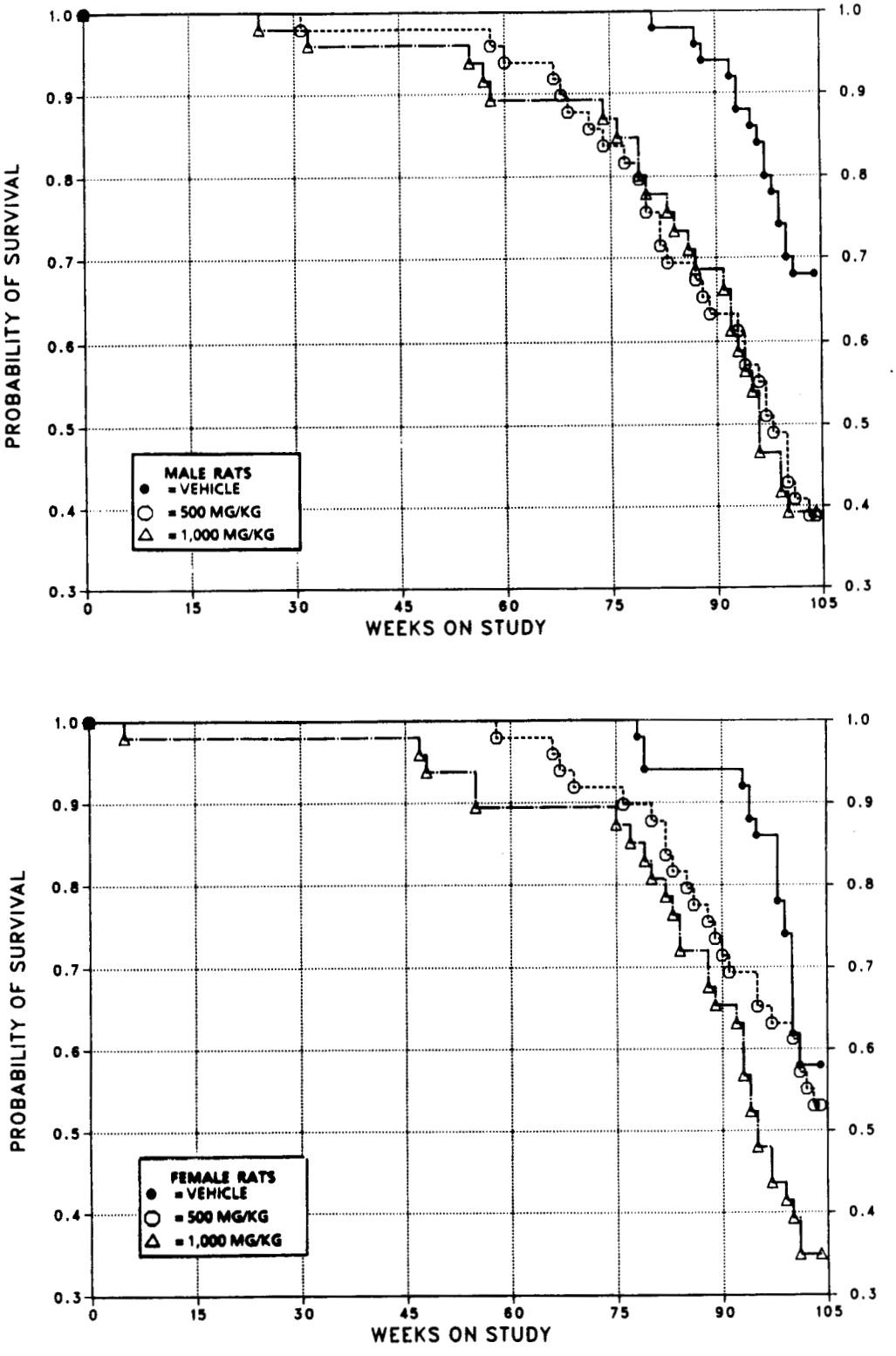


FIGURE 6. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED PENICILLIN VK IN CORN OIL BY GAVAGE FOR TWO YEARS

Anterior Pituitary Gland: Adenomas in male rats occurred with a marginal positive trend by the incidental tumor test; the incidence in the high dose group was slightly greater than that in the vehicle controls (Table 11). The incidence of hyperplasia was lower in high dose male rats than in vehicle controls. The incidences of adenomas or carcinomas (combined) in female rats were as follows: vehicle control, 24/48; low dose, 22/49; high dose, 20/48.

TABLE 11. ANALYSIS OF ANTERIOR PITUITARY GLAND LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF PENICILLIN VK (a)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Hyperplasia			
Overall Rates	14/48 (29%)	13/44 (30%)	7/48 (15%)
Adenoma			
Overall Rates	10/48 (21%)	11/44 (25%)	13/48 (27%)
Adjusted Rates	29.2%	42.2%	59.2%
Terminal Rates	9/33 (27%)	5/17 (29%)	8/16 (50%)
Week of First Observation	100	72	83
Life Table Tests	P=0.007	P=0.075	P=0.007
Incidental Tumor Tests	P=0.056	P=0.204	P=0.040
Carcinoma			
Overall Rates	0/48 (0%)	0/44 (0%)	1/48 (2%)
Adenoma or Carcinoma (b)			
Overall Rates	10/48 (21%)	11/44 (25%)	14/48 (29%)
Adjusted Rates	29.2%	42.2%	60.9%
Terminal Rates	9/33 (27%)	5/17 (29%)	8/16 (50%)
Week of First Observation	100	72	83
Life Table Tests	P=0.003	P=0.075	P=0.003
Incidental Tumor Tests	P=0.033	P=0.204	P=0.023

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix A, Table A3 (footnotes).
(b) Historical incidence at study laboratory: 12/46 (26%); historical incidence in NTP studies (mean ± SD): 476/1,654 (29% ± 11%)

Thyroid Gland: C-Cell adenomas and C-cell adenomas or carcinomas (combined) in female rats occurred with significant positive trends; the incidence of adenomas or carcinomas (combined) in the high dose group was slightly greater than that in the vehicle controls (Table 12). The higher incidences were considered to be related not to chemical administration but to differing sectioning techniques used for dosed and vehicle control groups. More than 60% of the female rats in the high dose group had longitudinal sections of the thyroid gland, in contrast to the vehicle control group, all of which had cross sections. Longitudinal sections include a greater proportion of the thyroid gland than do cross sections; hence, a greater proportion of tissue was examined in the dosed females than in the vehicle control females. The incidences of C-cell adenomas or carcinomas (combined) in male rats were as follows: vehicle control, 2/48; low dose, 3/48; high dose, 3/48.

TABLE 12. ANALYSIS OF THYROID GLAND C-CELL LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF PENICILLIN VK

	Vehicle Control	500 mg/kg	1,000 mg/kg
Hyperplasia			
Overall Rates	8/49 (16%)	13/47 (28%)	16/47 (34%)
Adenoma			
Overall Rates	6/49 (12%)	6/47 (13%)	10/47 (21%)
Adjusted Rates	16.4%	22.2%	44.4%
Terminal Rates	2/29 (7%)	4/24 (17%)	5/16 (31%)
Week of First Observation	98	97	84
Life Table Tests	P=0.015	P=0.481	P=0.020
Incidental Tumor Tests	P=0.049	P=0.288	P=0.091
Carcinoma			
Overall Rates	0/49 (0%)	1/47 (2%)	1/47 (2%)
Adenoma or Carcinoma (a)			
Overall Rates	6/49 (12%)	7/47 (15%)	11/47 (23%)
Adjusted Rates	16.4%	24.3%	49.5%
Terminal Rates	2/29 (7%)	4/24 (17%)	6/16 (38%)
Week of First Observation	98	90	84
Life Table Tests	P=0.007	P=0.356	P=0.009
Incidental Tumor Tests	P=0.033	P=0.255	P=0.048

(a) Historical incidence at study laboratory: 2/50 (4%); historical incidence in NTP studies (mean ± SD): 186/1,668 (11% ± 7%)

Mammary Gland: Fibroadenomas and adenomas or fibroadenomas (combined) in female rats occurred with marginally increased trends; the incidences in the low dose group were marginally increased, but this effect was not seen in the high dose group and is not considered to be chemically related (Table 13).

Clitoral Gland: Adenomas in female rats occurred with a significant positive trend (vehicle control, 0/50; low dose, 1/50; high dose, 3/50; $P<0.025$); the incidence of adenomas in the high dose group was slightly greater than that in the vehicle controls ($P=0.05$). The incidences of adenomas or carcinomas (combined) in dosed female rats were not significantly different from that in the vehicle controls (1/50; 2/50; 3/50).

Nasal Mucosa: Suppurative inflammation occurred at increased incidences ($P<0.01$) in high dose rats (male: vehicle control, 14/50; low dose, 17/50; high dose, 36/50; female: 7/50; 6/50; 21/50). These microscopic lesions were characterized by the presence of acute inflammatory exudate, hair or other foreign materials, and sometimes yellow globular material that was interpreted as corn oil.

Lung: Aspiration pneumonia was observed at increased incidences ($P<0.01$) in high dose rats (male: vehicle control, 2/49; low dose, 7/50; high dose, 13/47; female: 0/49; 0/50; 7/50). It was present in many rats that died before termination of the study, and it was considered to be the primary cause of death in these animals.

Liver: Congestion was observed at an increased incidence ($P<0.05$) in high dose male rats (male: vehicle control, 1/49; low dose, 2/50; high dose, 8/49; female: 0/50; 1/49; 1/50). Centrilobular degeneration was observed at increased incidences ($P<0.05$) in dosed female rats (male: 0/49; 2/50; 2/49; female: 0/50; 6/49; 4/50).

Forestomach: Hyperkeratosis and acanthosis were observed at increased incidences ($P<0.05$) in low dose male rats but not in high dose male rats (hyperkeratosis--male: vehicle control, 1/46; low dose, 7/49; high dose, 1/48; female: 0/49; 2/48; 3/47; acanthosis--male: 6/46; 15/49; 8/48; female: 8/49; 10/48; 8/47).

TABLE 13. ANALYSIS OF MAMMARY GLAND LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF PENICILLIN VK

	Vehicle Control	500 mg/kg	1,000 mg/kg
Hyperplasia			
Overall Rates	1/50 (2%)	0/50 (0%)	4/50 (8%)
Fibroadenoma (a)			
Overall Rates	15/50 (30%)	21/50 (42%)	16/50 (32%)
Adjusted Rates	44.0%	63.5%	67.2%
Terminal Rates	11/29 (38%)	14/26 (54%)	9/16 (56%)
Week of First Observation	98	91	84
Life Table Tests	P=0.016	P=0.069	P=0.024
Incidental Tumor Tests	P=0.043	P=0.016	P=0.081
Adenoma			
Overall Rates	2/50 (4%)	0/50 (0%)	1/50 (2%)
Adenoma or Fibroadenoma			
Overall Rates	17/50 (34%)	21/50 (42%)	17/50 (34%)
Adjusted Rates	48.4%	63.5%	68.4%
Terminal Rates	12/29 (41%)	14/26 (54%)	9/16 (56%)
Week of First Observation	98	91	84
Life Table Tests	P=0.022	P=0.135	P=0.030
Incidental Tumor Tests	P=0.057	P=0.038	P=0.101

(a) Historical incidence at study laboratory: 16/50 (32%); historical incidence in NTP studies (mean ± SD): 436/1,700 (26% ± 7%)

FOURTEEN-DAY STUDIES

All deaths were considered to be due to gavage error (foreign oily material was observed in lungs) (Table 14). Final mean body weights of males that received 600, 1,200, or 2,400 mg/kg were 5%-9% lower than that of the controls. Final mean body weights of dosed females were 5%-8% lower than that of the controls. Diarrhea was observed in all dosed groups. No compound-related histopathologic effects were observed.

Because of the minimal response (no dose-related histopathologic lesions or deaths) of mice at 2,400 mg/kg, the highest dose for the 13-week studies was set at 3,000 mg/kg.

TABLE 14. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOURTEEN-DAY GAVAGE STUDIES OF PENICILLIN VK

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
0	5/5	27.4 ± 0.5	29.6 ± 1.5	+2.2 ± 1.5	--
150	5/5	26.8 ± 0.5	28.8 ± 0.6	+2.0 ± 0.5	97.3
300	(d) 4/5	27.0 ± 0.9	29.3 ± 1.0	+1.8 ± 0.3	99.0
600	(e) 4/5	25.4 ± 0.7	27.0 ± 0.9	+1.3 ± 0.3	91.2
1,200	5/5	25.6 ± 0.7	27.0 ± 1.0	+1.4 ± 0.7	91.2
2,400	5/5	26.4 ± 0.4	28.2 ± 0.6	+1.8 ± 0.8	95.3
FEMALE					
0	5/5	20.4 ± 0.4	23.6 ± 0.5	+3.2 ± 0.4	--
150	(f) 2/5	20.4 ± 0.2	22.5 ± 0.5	+2.5 ± 0.5	95.3
300	5/5	20.6 ± 0.2	21.8 ± 0.8	+1.2 ± 0.6	92.4
600	(g) 3/5	21.4 ± 0.6	22.3 ± 1.2	+0.7 ± 0.3	94.5
1,200	(h) 3/5	21.2 ± 0.4	22.0 ± 0.6	+0.7 ± 0.7	93.2
2,400	(i) 2/5	20.6 ± 0.2	22.0 ± 1.0	+2.0 ± 1.0	93.2

(a) Number surviving/number initially in group; all deaths judged to be gavage related.
(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
(d) Day of death: 11
(e) Day of death: 4
(f) Day of death: 6,8,10
(g) Day of death: 6,9
(h) Day of death: 4,6
(i) Day of death: 1,10,10

THIRTEEN-WEEK STUDIES

All deaths were considered to be due to gavage error (Table 15). The final mean body weights of dosed groups were not markedly different from those of the vehicle controls.

Inflammation, mucous cell metaplasia of the glandular stomach, and papillary hyperplasia or hyperkeratosis of the forestomach were seen at increased incidences in dosed groups (Table 16). The degree of severity was dose dependent. Eosinophilic cytoplasmic change, characterized by the accumulation of eosinophilic material in the cytoplasm of glandular epithelial cells near the junction of the glandular stomach and forestomach, occurred in dosed mice.

Dose Selection Rationale: Because of the incidences and severity of stomach lesions, doses selected for mice for the 2-year studies were 500 and 1,000 mg/kg penicillin VK, administered in corn oil by gavage, 5 days per week.

TABLE 15. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF PENICILLIN VK

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	24.2 ± 0.5	33.6 ± 1.1	+9.4 ± 0.9	--
250	10/10	24.2 ± 1.2	38.5 ± 1.0	+14.3 ± 1.2	114.6
500	10/10	23.3 ± 1.2	36.2 ± 0.8	+12.9 ± 1.1	107.7
1,000	10/10	25.8 ± 0.4	35.6 ± 0.9	+9.8 ± 0.7	106.0
2,000	(d) 9/10	25.5 ± 1.2	37.6 ± 0.9	+12.3 ± 1.3	111.9
3,000	10/10	25.4 ± 0.3	34.1 ± 0.6	+8.7 ± 0.5	101.5
FEMALE					
0	10/10	20.5 ± 0.6	28.0 ± 1.0	+7.5 ± 1.1	--
250	10/10	15.1 ± 0.2	26.6 ± 0.4	+11.5 ± 0.3	95.0
500	10/10	18.4 ± 0.9	28.2 ± 0.7	+9.8 ± 1.1	100.7
1,000	10/10	19.6 ± 0.4	27.1 ± 0.7	+7.5 ± 0.5	96.8
2,000	10/10	20.1 ± 0.3	26.7 ± 0.4	+6.6 ± 0.3	95.4
3,000	(e) 7/10	18.6 ± 0.8	27.0 ± 0.6	+7.9 ± 1.0	96.4

(a) Number surviving/number initially in group; all deaths judged to be gavage related.
(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
(d) Week of death: 10
(e) Week of death: 7,9,11

TABLE 16. INCIDENCE AND SEVERITY OF STOMACH LESIONS IN MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF PENICILLIN VK

Dose (mg/kg)	Glandular Stomach			Forestomach	
	Eosinophilic Cytoplasmic Change at Junction	Mucous Cell Metaplasia	Inflammation	Papillary Hyperplasia	Hyperkeratosis
MALE (a)					
0	0/7	0/9	0/10	0/7	0/7
250	0/8	7/9 (1.6)	4/9 (2.0)	0/7	5/7 (1.6)
500	1/7	9/9 (2.1)	1/9 (2.0)	1/9 (1.0)	6/8 (1.7)
1,000	4/10	10/10 (2.2)	2/10 (2.0)	3/10 (1.0)	8/10 (2.0)
2,000	6/7	9/10 (2.4)	4/10 (1.7)	6/8 (2.2)	9/9 (2.7)
3,000	3/7	8/8 (2.6)	7/8 (1.6)	6/7 (2.7)	8/8 (2.9)
FEMALE (a)					
0	0/8	0/9	0/9	0/8	1/8 (1.0)
250	2/10	10/10 (2.1)	8/10 (1.7)	0/10	6/10 (1.8)
500	2/7	7/10 (2.6)	4/10 (1.5)	0/7	4/7 (1.2)
1,000	1/8	10/10 (2.2)	7/10 (2.3)	0/6	6/6 (1.8)
2,000	2/8	8/8 (2.5)	9/10 (2.2)	1/7 (1.0)	6/7 (1.8)
3,000	6/9	8/8 (3.2)	7/10 (2.6)	5/9 (1.8)	9/9 (2.3)

(a) Number of animals with lesion/number of animals with tissue sections satisfactory for evaluation. Number in parentheses = average degree of severity of lesion; degree of severity scored as: 1 (minimal), 2 (mild), 3 (moderate), 4 (severe).

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed and vehicle control male mice were comparable (Table 17 and Figure 7). Mean body weights of dosed female mice were 4%-16% lower than those of the vehicle controls from week 28 to the end of the study. Diarrhea was observed at increased incidences for dosed male mice (vehicle control, 0/50; low dose, 15/50; high dose, 31/50) but not for dosed female mice (3/50; 0/50; 0/50).

TABLE 17. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF PENICILLIN VK

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	500 mg/kg Av. Wt. (grams)	500 mg/kg Wt. (percent of veh. controls)	500 mg/kg No. of Survivors	1,000 mg/kg Av. Wt. (grams)	1,000 mg/kg Wt. (percent of veh. controls)	1,000 mg/kg No. of Survivors
MALE								
0	25.2	50	25.2	100	50	25.3	100	50
1	25.6	50	25.3	99	50	25.3	99	50
2	27.3	50	26.0	95	50	26.8	98	50
3	28.5	50	27.8	98	50	28.1	99	50
4	29.9	50	27.9	93	50	28.4	95	50
5	30.1	50	29.2	97	50	29.6	98	50
6	30.3	50	28.8	95	50	29.1	96	50
7	31.3	50	31.0	99	50	30.3	97	50
8	33.0	50	32.0	97	50	31.5	95	50
9	32.2	50	32.6	101	50	33.1	103	50
10	33.1	50	32.2	97	50	32.0	97	50
11	35.6	50	34.1	96	50	34.7	97	50
12	34.1	49	34.1	100	50	33.9	99	50
16	33.7	49	35.8	106	50	33.4	99	50
20	38.4	49	39.8	104	49	38.1	99	49
24	41.2	49	40.6	99	48	40.7	99	49
28	40.4	49	39.4	98	48	38.7	96	48
32	41.6	48	40.9	98	48	41.3	99	48
36	43.0	48	42.4	99	48	42.2	98	48
40	44.0	48	41.4	94	48	41.1	93	48
46	43.5	48	42.7	98	48	42.9	99	47
48	44.3	47	42.6	96	48	41.9	95	47
52	45.1	47	43.8	97	48	42.2	94	42
56	44.4	46	43.6	98	48	43.3	98	42
60	44.8	45	44.7	100	47	43.4	97	41
64	45.4	45	43.2	95	47	43.8	96	38
68	44.4	45	45.0	101	46	45.5	102	37
72	44.5	45	43.4	98	46	45.1	101	37
76	45.5	44	45.6	100	45	45.9	101	36
80	43.6	43	45.5	104	45	45.1	103	36
84	44.8	39	45.6	102	44	46.5	104	36
88	43.2	39	44.5	103	44	46.3	107	34
92	42.8	38	44.0	103	43	45.0	105	32
96	40.7	34	44.8	110	43	46.4	114	31
100	41.8	29	43.7	105	38	45.4	109	28
102	41.5	26	42.6	103	36	44.9	108	26
FEMALE								
0	19.2	50	19.4	101	50	19.6	102	50
1	19.9	50	20.0	101	50	20.2	102	50
2	20.6	50	21.5	104	50	21.5	104	50
3	21.9	50	22.6	103	50	22.9	105	50
4	22.4	50	22.7	101	50	22.7	101	49
5	22.6	50	23.8	105	50	23.5	104	48
6	23.1	50	22.8	99	50	23.0	100	48
7	22.9	50	23.6	103	50	23.7	103	48
8	24.1	50	24.4	101	50	24.1	100	48
9	24.1	50	24.6	102	50	24.8	103	48
10	24.1	50	24.0	100	50	24.6	102	48
11	25.6	50	25.1	98	50	25.5	100	48
12	24.5	50	25.7	105	50	25.6	104	48
16	23.9	48	24.3	102	50	24.2	101	48
20	27.8	48	27.1	97	50	26.7	96	46
24	28.9	48	29.3	101	50	29.2	101	46
28	31.8	48	28.1	88	50	28.9	91	46
32	32.3	48	30.3	94	50	31.1	96	46
36	34.3	48	30.3	88	50	32.0	93	46
40	35.6	48	29.8	84	50	30.9	87	46
46	35.7	47	32.0	90	50	32.7	92	45
48	37.1	47	32.2	87	50	32.6	88	45
52	37.0	47	32.8	89	50	33.7	91	45
56	37.2	47	33.0	89	48	34.0	91	45
60	37.9	47	33.3	88	48	33.9	89	45
64	38.2	47	34.3	90	48	35.1	92	44
68	39.0	47	34.4	88	48	35.4	91	43
72	39.0	47	34.5	88	48	36.0	92	43
76	41.4	46	37.0	89	47	38.0	92	43
80	41.2	45	37.2	90	46	39.1	95	42
84	42.0	43	37.7	90	45	39.9	95	40
88	42.1	43	38.1	90	44	39.4	94	38
92	42.2	43	40.1	95	40	40.0	95	37
96	43.2	40	39.0	90	39	40.8	94	36
100	42.5	38	38.3	90	33	39.0	92	33
102	43.3	36	38.6	89	32	38.9	90	33

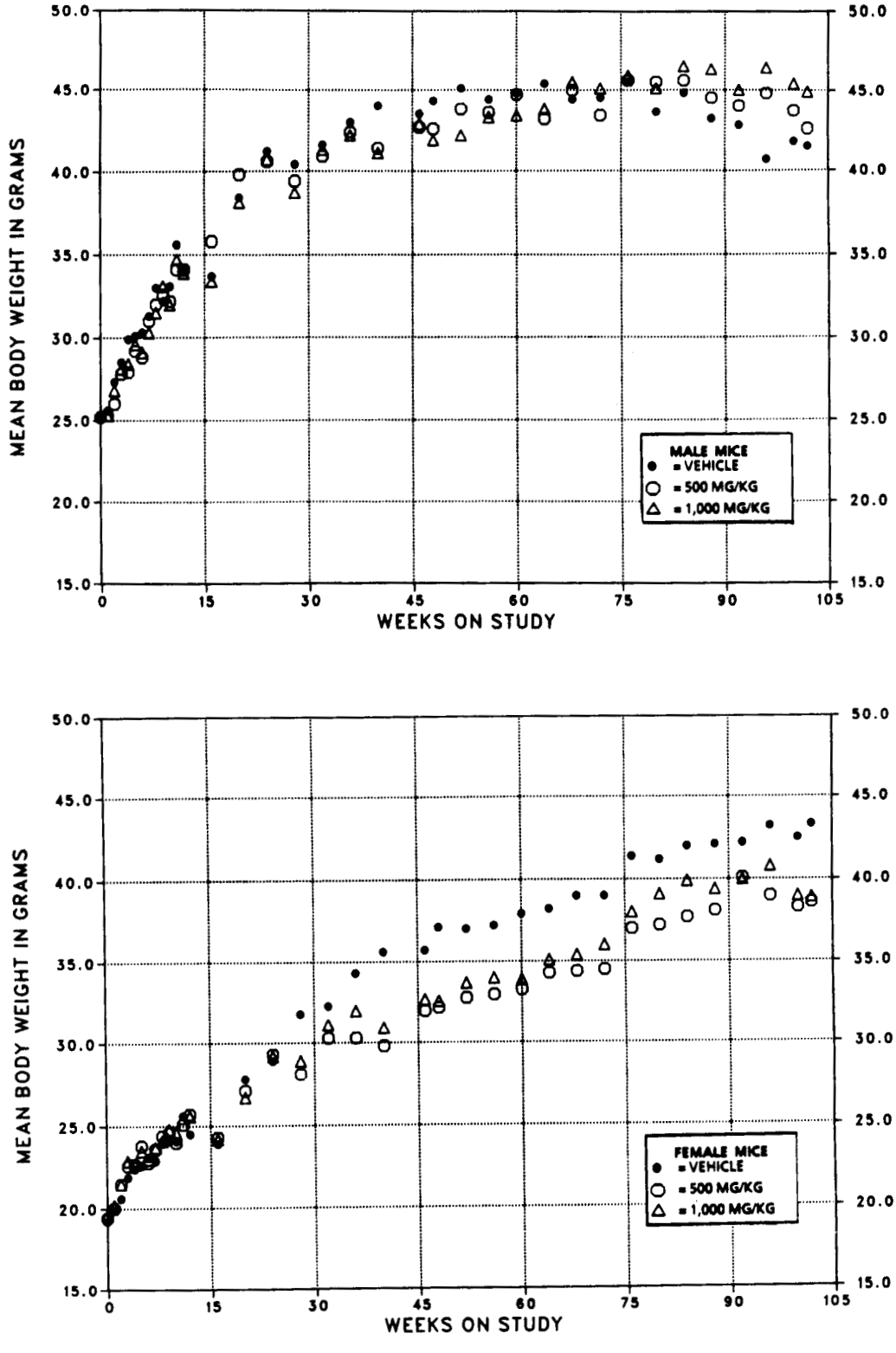


FIGURE 7. GROWTH CURVES FOR MICE ADMINISTERED PENICILLIN VK IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered penicillin VK at the doses used in these studies and for vehicle controls are shown in Table 18 and in the Kaplan and Meier curves in Figure 8. The survival of the low dose group of male mice was significantly greater than that of the vehicle controls after week 103. No other significant differences in survival were observed between any groups of either sex.

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 stomach, gallbladder, skin, hematopoietic system, and liver.

Lesions in male mice are summarized in Appendix C. Histopathologic findings on neoplasms are summarized in Table C1. Table C2 gives the survival and tumor status for individual male mice. Table C3 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 Table C3 (footnotes). Historical incidences of tumors in corn oil vehicle control male mice are listed in Table C4. Findings on nonneoplastic lesions are summarized in Table C5.

Lesions in female mice are summarized in Appendix D. Histopathologic findings on neoplasms are summarized in Table D1. Table D2 gives the survival and tumor status for individual female mice. Table D3 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 Table D3 (footnotes). Historical incidences of tumors in corn oil vehicle control female mice are listed in Table D4. Findings on nonneoplastic lesions are summarized in Table D5.

TABLE 18. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF PENICILLIN VK

	Vehicle Control	500 mg/kg	1,000 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	24	13	24
Accidentally killed	2	1	0
Killed at termination	24	36	26
Survival P values (c)	0.839	0.034	0.865
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	12	18	11
Accidentally killed	2	0	7
Killed at termination	36	31	32
Died during termination period	0	1	0
Survival P values (c)	1.000	0.328	0.977

(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.

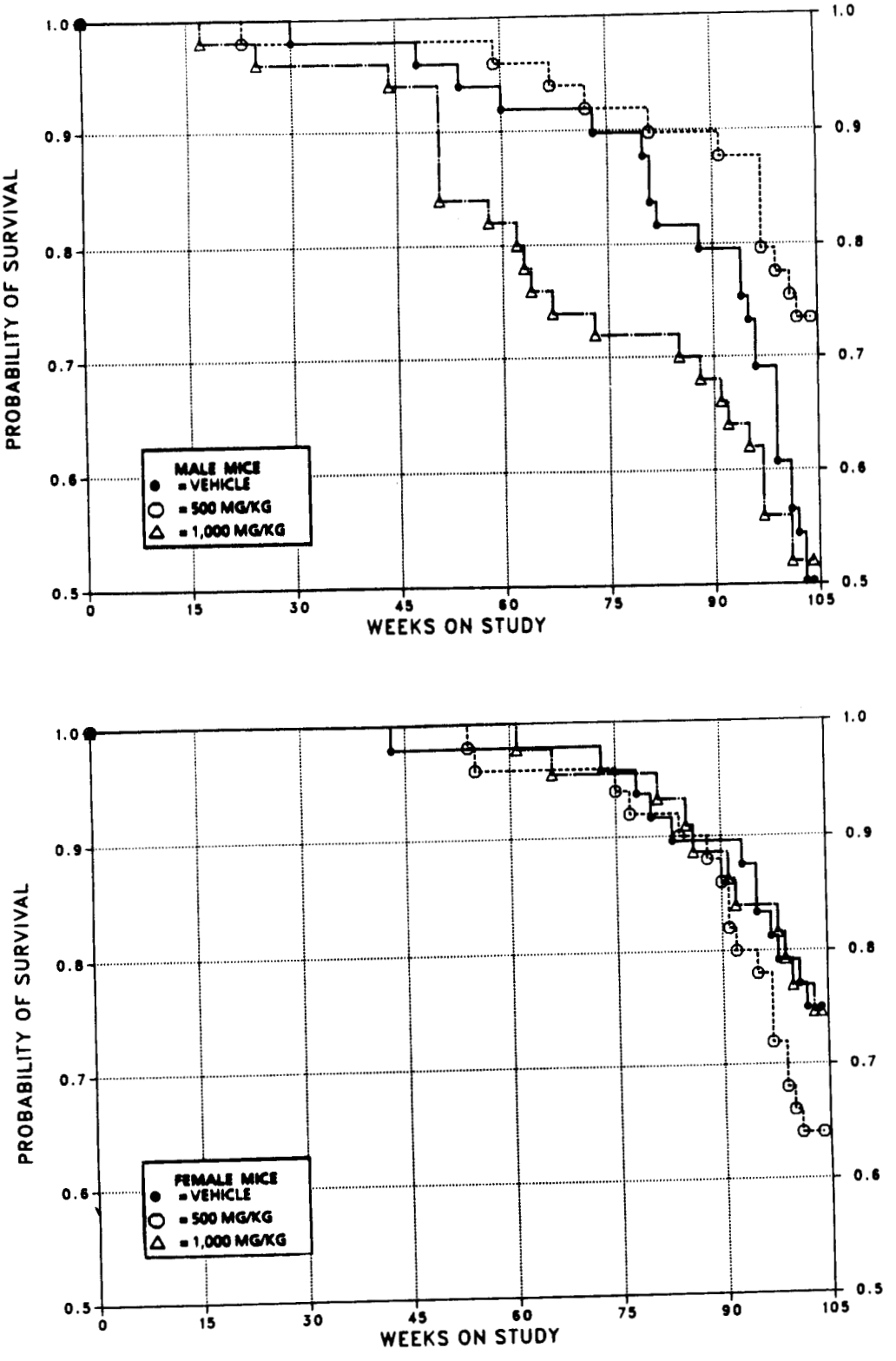


FIGURE 8. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED PENICILLIN VK IN CORN OIL BY GAVAGE FOR TWO YEARS

Stomach: Chronic focal inflammation, epithelial hyperplasia, cysts, dilatation (high dose only), fibrosis (high dose only), squamous metaplasia (high dose only), and eosinophilic cytoplasmic change occurred at increased incidences in the glandular stomach of dosed mice relative to those of vehicle controls (Table 19). These lesions were characterized by accumulations of mononuclear inflammatory cells with variable numbers of neutrophils in the lamina propria and submucosa, increased depth of the mucosal epithelium including the lamina epithelialis of the gastric pits, the mucous neck cells, and the parietal cells in the fundic glands (hyperplasia), greatly dilated glands lined by cuboidal cells that extended into the submucosa and occasionally through the muscularis (cysts), and accumulation of homogeneous eosinophilic material within the cytoplasm of epithelial cells lining the gastric glands. An adenoma occurred in the fundic region of the glandular stomach of one high dose female mouse, and an adenomatous polyp occurred in the pylorus of another. Benign epithelial tumors of the glandular stomach are rare in female B6C3F$_1$ mice. Only one adenoma and one adenomatous polyp were observed in the glandular stomach of 1,709 historical corn oil vehicle control female B6C3F$_1$ mice; one adenomatous polyp in the pylorus was observed in 1,709 historical corn oil vehicle control female B6C3F$_1$ mice.

TABLE 19. NUMBER OF MICE WITH LESIONS OF THE STOMACH IN THE TWO-YEAR GAVAGE STUDIES OF PENICILLIN VK

	Vehicle Control	500 mg/kg	1,000 mg/kg
MALE			
Number examined	46	47	46
Gastric fundal gland			
Eosinophilic cytoplasmic change	2	(a) 32	(a) 43
Dilatation	3	3	(a) 16
Glandular stomach			
Cyst	0	(b) 8	(a) 20
Chronic focal inflammation	1	(c) 11	(a) 21
Fibrosis	0	1	(a) 13
Epithelial hyperplasia	1	(a) 26	(a) 34
Squamous metaplasia	0	1	(b) 7
FEMALE			
Number examined	44	45	47
Gastric fundal gland			
Eosinophilic cytoplasmic change	3	(a) 34	(a) 41
Dilatation	1	5	(a) 13
Glandular stomach			
Cyst	0	(b) 5	(a) 15
Chronic focal inflammation	0	(c) 10	(a) 30
Fibrosis	0	2	(a) 11
Epithelial hyperplasia	0	(a) 19	(a) 38
Squamous metaplasia	0	1	(b) 5

(a) $P<0.001$ vs. vehicle controls
(b) $P<0.05$ vs. vehicle controls
(c) $P<0.01$ vs. vehicle controls

Gallbladder: Eosinophilic cytoplasmic change of the mucosal epithelium of the gallbladder was observed at increased incidences in dosed male mice (vehicle control, 1/50; low dose, 15/50; high dose, 15/50; $P<0.001$). This change was similar to that occurring in the epithelium of the glandular stomach and consisted of the accumulation of homogeneous eosinophilic material within the cytoplasm.

Skin: Epithelial hyperplasia was observed at an increased incidence ($P<0.05$) in high dose male mice (vehicle control, 2/50; low dose, 5/50; high dose, 11/50).

Hematopoietic System: Lymphoid hyperplasia was observed at increased incidences in the spleen, lymph nodes, mandibular lymph nodes, and mesenteric lymph nodes of low dose male mice (spleen: vehicle control, 8/48; low dose, 17/50; high dose, 12/48; lymph nodes: 3/48; 8/48; 3/44; mandibular lymph nodes: 3/48; 12/48; 4/44; mesenteric lymph nodes: 4/48; 15/48; 9/44).

Liver: Hepatocellular adenomas and adenomas or carcinomas (combined) in male mice occurred with significant negative trends; the incidences in the high dose group were significantly lower than those in the vehicle controls (Table 20).

TABLE 20. ANALYSIS OF HEPATOCELLULAR TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF PENICILLIN VK (a)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Adenoma			
Overall Rates	14/50 (28%)	15/49 (31%)	4/49 (8%)
Adjusted Rates	46.4%	38.0%	15.4%
Terminal Rates	9/24 (38%)	12/36 (33%)	4/26 (15%)
Week of First Observation	73	91	104
Life Table Tests	P=0.006N	P=0.258N	P=0.008N
Incidental Tumor Tests	P=0.015N	P=0.561N	P=0.012N
Carcinoma			
Overall Rates	6/50 (12%)	7/49 (14%)	4/49 (8%)
Adjusted Rates	15.6%	18.6%	11.0%
Terminal Rates	1/24 (4%)	6/36 (17%)	1/26 (4%)
Week of First Observation	80	97	62
Life Table Tests	P=0.343N	P=0.531N	P=0.441N
Incidental Tumor Tests	P=0.344N	P=0.340	P=0.373N
Adenoma or Carcinoma (b)			
Overall Rates	19/50 (38%)	18/49 (37%)	8/49 (16%)
Adjusted Rates	52.8%	44.6%	25.2%
Terminal Rates	9/24 (38%)	14/36 (39%)	5/26 (19%)
Week of First Observation	73	91	62
Life Table Tests	P=0.012N	P=0.138N	P=0.022N
Incidental Tumor Tests	P=0.019N	P=0.582N	P=0.014N

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix C, Table C3 (footnotes).
(b) Historical incidence at study laboratory: 9/50 (18%); historical incidence in NTP studies (mean ± SD): 569/1,736 (33% ± 9%)

IV. DISCUSSION AND CONCLUSIONS

IV. DISCUSSION AND CONCLUSIONS

Penicillin VK has been used in the United States for over 30 years, but the drug's toxicity and carcinogenicity in rodents had not been previously studied. Because of this, 14-day, 13-week, and 2-year studies were performed by administering penicillin VK to F344/N rats and B6C3F$_1$ mice by gavage. The oral route was chosen because the drug is used orally in the treatment of infectious diseases in humans.

In the 14-day studies, penicillin VK was administered at doses up to 2,400 mg/kg. No dose-related deaths or histopathologic lesions were observed in these studies. Final mean body weights of dosed male rats and male and female mice were lower than those of vehicle controls, and diarrhea was seen in all groups of dosed animals.

In the 13-week studies, penicillin VK was administered at doses up to 3,000 mg/kg. The gastrointestinal tract was the site primarily affected, with glandular stomach and/or forestomach lesions observed in dosed rats and mice. No dose-related deaths occurred; the extent and severity of gastrointestinal lesions and body weight data were the primary factors used to select doses for the 2-year studies.

In the 2-year studies, penicillin VK was administered 5 days per week at doses of 0, 500, or 1,000 mg/kg. Survival of low and high dose male rats and high dose female rats was reduced toward the end of the studies. Survival in all groups of rats was 50% or greater until week 92, and although the reduced survival in dosed rats reduced the sensitivity of the studies for detecting a carcinogenic response, survival was considered adequate for a meaningful evaluation. There was no decrease in survival in mice. Mean body weights of dosed female mice were lower than those of corresponding vehicle controls; mean body weights of other dose groups were comparable to those of corresponding vehicle controls. Diarrhea was seen for dosed male and female rats and for dosed male mice.

The incidence of adenomas of the pituitary gland was marginally increased in the high dose group of male rats, but hyperplasia of the pituitary gland was decreased. Hyperplasia and adenomas of the pituitary gland are part of a morphologic continuum, and the combined incidence of hyperplasia and adenomas in high dose male rats was not increased. For these reasons, this lesion is not considered to be related to administration of penicillin VK.

Penicillin VK administration was associated with a reduced incidence of hepatocellular adenomas in male mice. The mechanism for this cannot be determined from the results of these studies.

Increased incidences of suppurative inflammation of the nasal mucosa and of aspiration pneumonia occurred in male and female rats. The pathogenesis of the inflammation in the nose is uncertain. It is possible that penicillin VK altered the bacterial population in the nose of dosed rats, providing a suitable environment for opportunistic bacterial infections. Alternatively, poor gavage technique may have resulted in deposition or aspiration of material into the nasopharynx. The pneumonia in rats was associated with foreign material that had the appearance of lipid droplets believed to be corn oil. The aspiration pneumonia was probably the result of poor gavage technique and deposition of the penicillin VK/corn oil mixture into the lung.

The slightly increased incidences of hyperkeratosis and acanthosis in the forestomach seen in low dose but not high dose male rats may not be a direct effect of penicillin VK, since the incidences were not dose related. This type of lesion may result from irritation or trauma, and the mechanical irritation by the gavage tube may be a contributing factor.

Increased incidences of a variety of nonneoplastic lesions occurred in the stomach of male and female mice. The spectrum of lesions indicates that the long-term administration of penicillin VK was irritating to the glandular mucosa, producing inflammation, fibrosis, and degenerative and hyperplastic changes of the glandular epithelium. Two benign tumors of the stomach (an adenoma in the fundic region of the glandular stomach and an adenomatous polyp of the pylorus) occurred in high dose female mice. These tumors occur rarely in female B6C3F$_1$ mice. Only two glandular stomach tumors and one benign tumor of the pylorus have been

observed in over 1,700 corn oil vehicle control female B6C3F$_1$ mice. Because of their low incidence, these tumors were not considered to be clearly related to compound administration.

Results of 2-year toxicology and carcinogenesis studies on another penicillin, ampicillin trihydrate, have been reported (NTP, 1987). Ampicillin trihydrate was administered by oral gavage in corn oil, 5 days per week for 103 weeks, to F344/N rats at doses of 0, 750, or 1,500 mg/kg and to B6C3F$_1$ mice at doses of 0, 1,500, or 3,000 mg/kg. There was equivocal evidence of carcinogenicity for male rats, as indicated by marginally increased incidences of pheochromocytomas of the adrenal gland medulla and of mononuclear cell leukemia. There was no evidence of carcinogenicity for female rats or for male or female mice.

In both the 13-week and 2-year studies of penicillin VK in F344/N rats and B6C3F$_1$ mice, the gastrointestinal tract was a primary site for toxicity. In the ampicillin trihydrate 2-year studies, gastrointestinal toxicity also was seen in F344/N rats and B6C3F$_1$ mice (NTP, 1987). In rats administered ampicillin trihydrate, diarrhea and hyperkeratosis and acanthosis of the forestomach were seen for dosed animals. Mice administered ampicillin trihydrate had dose-related forestomach lesions (not glandular stomach lesions as seen in the penicillin VK study), including inflammation, hyperkeratosis, acanthosis, and ulcers. β-Lactam antibiotics have been shown to cause gastrointestinal toxicity in humans (Kitano et al., 1984; Braver, 1983; Norrby, 1986) and in rodents (Murakami, 1971; Berg, 1981). Oral penicillin administration altered the population of enteric bacteria in mice, decreased the total anaerobe population, and allowed an overgrowth of gram-negative enteric bacilli in the ceca (Berg, 1981).

Although penicillin is an antimicrobial agent, Salmonella can be used to assay its mutagenic activity because an end point other than cell death is monitored; the mutagenic activity of penicillin was measured at doses that did not produce excessive toxicity. The presence of the plasmid pKM101 in strains TA98 and TA100 confers resistance to penicillin but not total immunity. Therefore, the doses of penicillin VK tested in these two strains are almost 100-fold higher than the highest nontoxic dose tested in strains TA1535 and TA1537; in all cases, no evidence for mutagenicity was observed before toxic concentrations were reached. Penicillin VK, other penicillins, and penicillin analogs are consistently nonmutagenic when tested in bacteria.

Penicillin VK is genotoxic and clastogenic in cultured Chinese hamster ovary cells, inducing both sister chromatid exchanges and chromosomal aberrations. However, the doses at which positive responses were recorded in these assays were unusually high, particularly in the chromosomal aberration tests, suggesting that the ionic effects due to high potassium concentration in the medium or similar indirect activity might play an important role in the effects observed (Ashby and Ishidate, 1986). In contrast to the positive results in the mouse lymphoma L5178Y cell assay with penicillin VK in the presence of S9, no significant increase in mutations was observed when penicillin V was tested in this assay in either the presence or absence of exogenous metabolic activation (Appendix E, Table E2). This further indicates that ionic influences may be an important factor in the observed responses to salts in in vitro mutagenicity tests.

The sodium salt of benzylpenicillin has induced chromosomal aberrations in the meiotic cells of the grasshopper, *Poecilocerus pictus* (Subramanyam and Reddy, 1975). A single injection of 50 mg/kg penicillin G induced chromosomal aberrations in mouse bone marrow cells (Manna and Bardhan, 1973), but penicillin G at doses of 200 or 800 mg/kg per day for 5 days to CFLP male mice did not produce increases in dominant lethal mutations in the offspring (James and Smith, 1982). No sperm head abnormalities were observed in male CBA × BALB/c mice administered penicillin (type unspecified) by intraperitoneal injection at doses up to 1,600 mg/kg per day for 5 days (Topham, 1980).

The experimental and tabulated data for the NTP Technical Report on penicillin VK were examined for accuracy, consistency, and compliance with Good Laboratory Practice requirements. As summarized in Appendix H, the audit revealed no major problems with the conduct of the studies or with the collection and

documentation of the experimental data. No discrepancies were found that influenced the final interpretation of the results of these studies.

Conclusions: Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of penicillin VK for F344/N rats or for $B6C3F_1$ mice administered 500 or 1,000 mg/kg penicillin VK in corn oil by gavage, 5 days per week for 2 years. Nonneoplastic lesions were seen in the glandular stomach of dosed mice. Decreased survival of low and high dose male rats and of high dose female rats reduced the sensitivity of the studies for determining the presence or absence of a carcinogenic response in this species.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 8.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 11.

V. REFERENCES

V. REFERENCES

1. Alanis, A.; Weinstein, A.J. (1983) Adverse reactions associated with the use of oral penicillins and cephalosporins. Med. Clin. North Am. 67:113-129.

2. American Institute of Chemical Engineers (AICE) (1970) The History of Penicillin Production. Chemical Engineering Progress Symposium Series, No. 100, Vol. 66. New York: AICE.

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

4. Aronoff, S.C.; Klinger, J.D.; O'Brien, C.A.; Jaffe, A.C.; Blumer, J.L. (1984) A double-blinded comparative study of sultamicillin and potassium penicillin V in the treatment of childhood streptococcal pharyngitis. J. Antimicrob. Chemother. 14:261-265.

5. Ashby, J.; Ishidate, M., Jr. (1986) Clastogenicity in vitro of the Na, K, Ca and Mg salts of saccharin; and of magnesium chloride; consideration of significance. Mutat. Res. 163:63-73.

6. Auhagen, E.; Gloxhuber, C.; Hecht, G.; Knott, T.; Rauenbusch, E.; Schawartz, J.; Schmid, J.; Scholtan, W.; Walter, A.M. (1962) Propicillin-Baycillin®. Arzneim. Forsch. 12:751-768.

7. Behrens, O.K. (1948) Biosynthesis of penicillins. IV. New crystalline biosynthetic penicillins. J. Biol. Chem. 175:793-809.

8. 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.

9. Berg, R.D. (1981) Promotion of the translocation of enteric bacteria from the gastrointestinal tracts of mice by oral treatment with penicillin clindamycin or metronidazole. Infect. Immun. 33:854-861.

10. Boorman, G.A.; Montgomery, C.A., Jr.; Eustis, S.L.; Wolfe, M.J.; McConnell, E.E.; Hardisty, J.F. (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.

11. Brandl, E.; Giovannini, M.; Margreiter, H. (1953) Untersuchung uber das saurestabile, oral wirksame Phenoxymethyl Penicillin (Penicillin V). Wien. Med. Wochenschr. 103:602-607.

12. Braver, J.M. (1983) Drug reactions and the gastrointestinal tract. Postgrad. Radiol. 3:123-137.

13. Charles, D. (1954) Placental transmission of antibiotics. J. Obstet. Gynaecol. 61:750-757.

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

15. Code of Federal Regulations (CFR) (1977) Title 21, Food and Drugs, Parts 300-499, April 1. Washington, DC: U.S. Government Printing Office.

16. Cole, M.; Kenig, M.D.; Hewitt, V.A. (1973) Metabolism of penicillins to penicilloic acids and 6-aminopenicillanic acid in man and its significance in assessing penicillin absorption. Antimicrob. Agents Chemother. 3:463-468.

17. Colquhoun, J.; Scorer, E.C.; Sandler, G.; Wilson, G.M. (1957) Absorption of free acid, potassium, and benzathine phenoxymethylpenicillin after oral administration. Br. Med. J., pp. 1451-1452.

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

19. Drugs in Japan (Ethical Drugs) (1982) 6th ed. Edited by Japan Pharmaceutical Information Center. Tokyo: Yakugyo Jiho Co., Ltd.

20. Dunham, J.M. (1972) Potassium phenoxymethyl penicillin. Florey, K., Ed.: Analytical Profiles of Drug Substances, Vol. 1. New York: Academic Press, pp. 249-289.

21. Elek, E.; Ivan, E.; Arr, M. (1972) Passage of penicillins from mother to foetus in humans. Int. J. Clin. Pharmacol. Ther. Toxicol. 6:223-228.

22. Erffmeyer, J.E. (1981) Adverse reactions to penicillin. Ann. Allergy 47:294-300.

23. Food and Drug Administration (FDA) (1986) Drug Utilization in the U.S.-1985. Seventh Annual Review. U.S. Department of Health and Human Services, Public Health Service, National Center for Drugs and Biologics.

24. Friedman, G.D.; Ury, H.K. (1980) Initial screening for carcinogenicity of commonly used drugs. J. Natl. Cancer Inst. 65:723-733.

25. Galloway, S.M.; Bloom, A.D.; Resnick, M.; Margolin, B.H.; 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.

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

27. Gaston, M.H.; Verter, J.I.; Woods, G.; Pegelow, C.; Kelleher, J.; Presbury, G.; Zarkowsky, H.; Vichinsky, E.; Iyer, R.; Lobel, J.S.; Diamond, S.; Holbrook, C.T.; Gill, F.M.; Ritchey, K.; Falletta, J.M. (1986) Prophylaxis with oral penicillin in children with sickle cell anemia: A randomized trial. N. Engl. J. Med. 314:1593-1599.

28. Goldenthal, E.I. (1971) A compilation of LD50 values in newborn and adult animals. Toxicol. Appl. Pharmacol. 18:185-207.

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

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

31. Haseman, J.K.; Huff, J.; Rao, G.N.; Arnold, J.; Boorman, G.A.; McConnell, E.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.

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

33. Herzberg, O.; Moult, J. (1987) Bacterial resistance to β-lactam antibiotics: Crystal structure of β-lactamase from *Staphylococcus aureus* PC1 at 2.5 Å resolution. Science 236:694-701.

34. James, D.A.; Smith, D.M. (1982) Analysis of results from a collaborative study of the dominant lethal assay. Mutat. Res. 97:303-314.

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

36. Juncher, H.; Raaschou, F. (1957) The solubility of oral preparations of penicillin V. Antibiot. Med. Clin. Ther. 4:497-507.

37. Kada, T.; Tutikawa, K.; Sadaie, Y. (1972) In vitro and host-mediated "rec-assay" procedures for screening chemical mutagens; and phloxine, a mutagenic red dye detected. Mutat. Res. 16:165-174.

38. Kaipainen, W.J.; Harkonen, P. (1956) Serum concentrations after oral administration of phenoxymethylpenicillin acid and phenoxymethylpenicillin potassium. Scand. J. Clin. Lab. Invest. 8:18-20.

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

V. REFERENCES

40. Kelly, J.A.; Moews, P.C.; Knox, J.R.; Frere, J.-M.; Ghuysen, J.-M. (1982) Penicillin target enzyme and the antibiotic binding site. Science 218:479-480.

41. Kitano, A.; Matsumoto, T.; Hiki, M.; Hashimura, H.; Yoshiyasu, K.; Ookawa, K.; Kuwazima, S.; Kobayashi, K. (1984) Clinical study of drug-induced hemorrhagic colitis. J. Jpn. Soc. Colo-Proctol. 37:673-677.

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

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

44. Mandell, G.L.; Sande, M.A. (1985) Antimicrobial agents--penicillins, cephalosporins, and other beta-lactam antibiotics. Gilman, A.G.; Goodman, L.S.; Rall, T.W.; Murad, F., Eds.: *Goodman and Gilman's* The Pharmacological Basis of Therapeutics, 7th ed. New York: Macmillan Publishing Co., pp. 1115-1149.

45. Manna, G.K.; Bardhan, S. (1973) Penicillin induced bone marrow chromosome aberrations in mice. Indian J. Zool. 1:1-12.

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

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

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

49. McCracken, G.H., Jr.; Ginsburg, C.M.; Clahsen, J.C.; Thomas, M.L. (1978) Pharmacologic evaluation of orally administered antibiotics in infants and children: Effect of feeding on bioavailability. Pediatrics 62:738-743.

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. Murakami, H. (1971) Morphological effects of penicillin administration on the gastrointestinal tract of rats. Exp. Anim. (Tokyo) 20:139-144.

52. Myhr, B.; Bowers, L.; Caspary, W.J. (1985) Assays for the induction of gene mutations at the thymidine kinase locus in L5178Y mouse lymphoma cells in culture. Prog. Mutat. Res. 5:555-568.

53. 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.

54. National Institutes of Health (NIH) (1978) Open Formula Rat and Mouse Ration (NIH-07). Specification NIH-11-1335. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

55. National Toxicology Program (NTP) (1987) Toxicology and Carcinogenesis Studies of Ampicillin Trihydrate in F344/N Rats and B6C3F$_1$ Mice. NTP Technical Report No. 318. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. 190 p.

56. Neu, H.C. (1977) The penicillins. II. Overview of pharmacology, toxicology, and clinical use. N.Y. State J. Med. May, pp. 962-967.

57. Norrby, S.R. (1986) Problems in evaluation of adverse reactions to beta-lactam antibiotics. Rev. Infect. Dis. 8(Suppl. 3):S358-S370.

58. Ostanina, L.N.; Dudnik, Y.V.; Kozmyan, L.I. (1977) Beromycin, an anthracycline antibiotic: Formation of complexes with DNA and suppression of nucleic acid biosynthesis. Antibiotiki (Moscow) 22:498-502.

59. Parida, B.B. (1972) Spermatocyte chromosome aberrations induced by antibiotics in grasshoppers. I. Penicillin. Sci. Cult. 38:523-525.

60. Peck, F.B., Jr.; Griffith, R.S. (1957-1958) Comparative clinical laboratory studies of potassium penicillin V with acid penicillin V. Antibiot. Ann. Clinical Laboratory Studies, pp. 1004-1011.

61. Physicians' Desk Reference (PDR) (1986), 40th ed. Oradell, NJ: Medical Economics Co. Inc.

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

63. Remington's Pharmaceutical Sciences (1985) Penicillin V potassium. Gennaro, A.R., Ed. Easton, PA: Mack Publishing Co.

64. Rolinson, G.N.; Sutherland, R. (1965) The binding of antibiotics to serum proteins. Br. J. Pharmacol. 25:638-650.

65. Rosenkranz, H.S. (1981) Mutagenicity of selected chemicals in Escherichia coli DNA repair deficient assays. Environ. Sci. Res. 24:5-18.

66. Sadtler Pharmaceutical Spectra, No. R540. Philadelphia: Sadtler Research Laboratories.

67. Schwartz, R.H.; Wientzen, R.L., Jr.; Pedreira, F.; Feroli, E.J.; Mella, G.W.; Guandolo, V.L. (1981) Penicillin V for group A streptococcal pharyngotonsillitis. A randomized trial of seven vs ten days' therapy. J. Am. Med. Assoc. 246:1790-1795.

68. Selwyn, S. (1980) The Beta-Lactam Antibiotics: Penicillins and Cephalosporins in Perspective. London: Hodder and Stoughton, p. 34.

69. Slater, E.E.; Anderson, M.D.; Rosenkranz, H.S. (1971) Rapid detection of mutagens and carcinogens. Cancer Res. 31:970-973.

70. Subramanyam, S.; Reddy, G.P.V. (1975) Effects of penicillin and streptomycin on *Poecilocerus pictus*--A cytological study. Proc. Indian Acad. Sci. 81B:118-126.

71. Suter, W.; Jaeger, I. (1982) Comparative evaluation of different pairs of DNA repair-deficient and DNA repair-proficient bacterial tester strains for rapid detection of chemical mutagens and carcinogens. Mutat. Res. 97:1-18.

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

73. Topham, J.C. (1980) The detection of carcinogen-induced sperm head abnormalities in mice. Mutat. Res. 69:149-155.

74. Tsuji, A.; Yoshikawa, T.; Nishide, K.; Minami, H.; Kimura, M.; Nakashima, E.; Terasaki, T.; Miyamoto, E.; Nightingale, C.H.; Yamana, T. (1983) Physiologically based pharmacokinetic model for β-lactam antibiotics I: Tissue distribution and elimination in rats. J. Pharm. Sci. 72:1239-1252.

75. *The United States* Pharmacopeia (USP) (1985) 16th ed., 21st rev. Rockville, MD: United States Pharmacopeial Convention, Inc., pp. 799-802.

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

77. Wendel, G.D., Jr.; Stark, B.J.; Jamison, R.B.; Molina, R.D.; Sullivan, T.J. (1985) Penicillin allergy and desensitization in serious infections during pregnancy. N. Engl. J. Med. 312:1229-1232.

78. Wilson, J.T.; Brown, R.D.; Cherek, D.R.; Dailey, J.W.; Hilman, B.; Jobe, P.C.; Manno, B.R.; Manno, J.E.; Redetzki, H.M.; Stewart, J.J. (1980) Drug excretion in human breast milk: Principles, pharmacokinetics and projected consequences. Clin. Pharmacokinet. 5:1-66.

79. Wilson, W.L.; Avdovich, H.W.; Hughes, D.W. (1974) Applications of NMR spectroscopy to antibiotics. Part 1. Specific identification of penicillins and cephalosporins. J. Assoc. Off. Anal. Chem. 57:1300-1313.

APPENDIX A

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

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

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Papilloma, NOS	3 (6%)		
Keratoacanthoma	†2 (4%)	1 (2%)	4 (8%)
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS		1 (2%)	
Fibroma	3 (6%)	5 (10%)	
Fibrosarcoma	2 (4%)	1 (2%)	
Myxosarcoma		1 (2%)	
Lipoma	1 (2%)		
Liposarcoma		1 (2%)	
Neurilemoma	4 (8%)	1 (2%)	2 (4%)
Neurilemoma, malignant		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(49)	(50)	(47)
Alveolar/bronchiolar carcinoma	1 (2%)		
Pheochromocytoma, metastatic	1 (2%)	1 (2%)	
Osteosarcoma, metastatic	1 (2%)		
Chordoma, metastatic	1 (2%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS			1 (2%)
Malignant lymphoma, undifferentiated type	1 (2%)		
Leukemia, mononuclear cell	12 (24%)	8 (16%)	5 (10%)
#Bone marrow	(46)	(50)	(50)
Osteosarcoma, invasive	1 (2%)		
#Splenic red pulp	(49)	(49)	(48)
Leukemia, mononuclear cell	2 (4%)	1 (2%)	
CIRCULATORY SYSTEM			
#Heart	(49)	(50)	(49)
Neurilemoma	1 (2%)		1 (2%)
DIGESTIVE SYSTEM			
#Salivary gland	(46)	(46)	(49)
Fibrosarcoma, invasive		1 (2%)	
Neurilemoma		1 (2%)	
#Liver	(49)	(50)	(49)
Hepatocellular carcinoma		1 (2%)	
Sarcoma, NOS, unclear primary or metastatic		1 (2%)	
#Pancreas	(49)	(48)	(48)
Adenoma, NOS	2 (4%)		
#Stomach	(46)	(49)	(48)
Leiomyosarcoma	1 (2%)		
#Small intestine	(45)	(49)	(48)
Leiomyosarcoma	1 (2%)		
#Cecum	(48)	(49)	(48)
Leiomyoma		1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(44)	(48)
Carcinoma, NOS			1 (2%)
Adenoma, NOS	10 (21%)	11 (25%)	13 (27%)
#Adrenal medulla	(48)	(50)	(49)
Pheochromocytoma	13 (27%)	14 (28%)	13 (27%)
Pheochromocytoma, malignant	2 (4%)	1 (2%)	
#Thyroid	(48)	(48)	(48)
Follicular cell adenoma			2 (4%)
C-cell adenoma	2 (4%)	3 (6%)	3 (6%)
#Pancreatic islets	(49)	(48)	(48)
Islet cell adenoma	2 (4%)	5 (10%)	4 (8%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS		1 (2%)	
Fibroadenoma		1 (2%)	
*Preputial gland	(50)	(50)	(50)
Carcinoma, NOS		2 (4%)	
Adenoma, NOS	1 (2%)		
#Testis	(50)	(49)	(50)
Interstitial cell tumor	48 (96%)	42 (86%)	34 (68%)
NERVOUS SYSTEM			
#Brain	(49)	(49)	(49)
Granular cell tumor, benign		1 (2%)	
Astrocytoma		1 (2%)	
#Brain stem	(49)	(49)	(49)
Oligodendroglioma			1 (2%)
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Adenoma, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Bone/lower extremity	(50)	(50)	(50)
Osteosarcoma	1 (2%)		
BODY CAVITIES			
*Anterior mediastinum	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, invasive	1 (2%)		
*Peritoneum	(50)	(50)	(50)
Mesothelioma, NOS		1 (2%)	1 (2%)
*Mesentery	(50)	(50)	(50)
Sarcoma, NOS, unclear primary or metastatic		1 (2%)	
*Tunica vaginalis	(50)	(50)	(50)
Mesothelioma, NOS	2 (4%)	2 (4%)	2 (4%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Neurilemoma, metastatic		1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	7	15	19
Moribund sacrifice	9	17	7
Terminal sacrifice	34	17	16
Dosing accident		1	3
Accidentally killed, nda			5
TUMOR SUMMARY			
Total animals with primary tumors**	50	46	39
Total primary tumors	118	112	87
Total animals with benign tumors	49	45	39
Total benign tumors	93	87	76
Total animals with malignant tumors	21	19	7
Total malignant tumors	23	20	8
Total animals with secondary tumors##	4	4	
Total secondary tumors	5	4	
Total animals with tumors uncertain--benign or malignant	2	2	2
Total uncertain tumors	2	3	3
Total animals with tumors uncertain--primary or metastatic		1	
Total uncertain tumors		2	

* Number of animals receiving complete necropsy examinations; 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
† Multiple occurrence of morphology in the same tissue; tissue is counted once only.

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

ANIMAL NUMBER	048	035	045	022	034	039	014	008	028	043	040	004	013	027	038	029	001	002	003	005	006	007	009	010	011
WEEKS ON STUDY	081	087	088	092	093	093	095	096	097	097	098	099	099	100	100	101	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+
Papilloma, NOS																X			X						
Keratoacanthoma				X											@X										
Subcutaneous tissue	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+
Fibroma				X																X					
Fibrosarcoma							X																	X	
Lipoma											X														
Neurilemoma											X							X			X				X
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Pheochromocytoma, metastatic																									
Osteosarcoma, metastatic																					X				
Chordoma, metastatic															X										
Trachea	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	−	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, invasive																					X				
Spleen	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																									
Lymph nodes	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	−	−	+	+	−	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma															X										
DIGESTIVE SYSTEM																									
Salivary gland	−	+	−	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																X									
Esophagus	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	−	+	−	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma					X																				
Small intestine	−	+	−	+	−	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Large intestine	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	
Adenoma, NOS															X				X	X		X			X
Adrenal	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma													X				X					X	X		
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma			X																						
Parathyroid	−	+	+	+	+	−	+	+	+	+	+	+	−	+	−	+	+	−	+	+	+	−	+	−	+
Pancreatic islets	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	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	X		X	X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma																					X				
BODY CAVITIES																									
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar carcinoma, invasive																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																X							X		
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, undifferentiated type												X													
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
@: Multiple occurrence of morphology
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	012	015	016	017	018	019	020	021	023	024	025	026	030	031	032	033	036	037	041	042	044	046	047	049	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																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Papilloma, NOS				X																						3
Keratoacanthoma																										2
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma												X														3
Fibrosarcoma																										2
Lipoma																										1
Neurilemoma																										4
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma													X													1
Pheochromocytoma, metastatic																			X							1
Osteosarcoma, metastatic																										1
Chordoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	46
Osteosarcoma, invasive																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia, mononuclear cell														X											X	2
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	−	+	+	−	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	38
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neurilemoma																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS																X										2
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Leiomyosarcoma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Leiomyosarcoma																								X		1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	44
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS	X		X								X	X		X												10
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma			X	X	X		X					X		X			X			X	X				13
Pheochromocytoma, malignant																X			X							2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell adenoma			X																							2
Parathyroid	+	+	+	−	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	−	−	+	+	+	+	38
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma																	X							X		2
REPRODUCTIVE SYSTEM																										
Mammary gland	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	X	X	X	X	X	X	48
Prostate	+	+	−	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	45
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS						X																				1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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																										1
BODY CAVITIES																										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Alveolar/bronchiolar carcinoma, invasiv													X													1
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS																										2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, undifferent type																										1
Leukemia, mononuclear cell															X							X		X		12

* Animals necropsied

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

ANIMAL NUMBER	048	012	009	035	039	006	026	011	003	002	024	033	043	034	044	042	036	029	028	013	004	025	049	005	017
WEEKS ON STUDY	013	031	058	060	067	068	069	072	074	077	079	080	080	082	082	083	087	088	089	093	094	094	096	097	097
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS					X																				
Fibroma												X													
Fibrosarcoma									X																
Myxosarcoma										X															
Liposarcoma																									
Neurilemoma																									X
Neurilemoma, malignant														X											
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma, metastatic																									
Chordoma, metastatic																	X								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																									
Lymph nodes	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	–	+	+	–	–	+	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+
Fibrosarcoma, invasive									X																
Neurilemoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Sarcoma, NOS, unclear primary or metastatic																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Leiomyoma																					X				
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	–	+	+	+	+
Adenoma, NOS								X				X			X									X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																						X	X		
Pheochromocytoma, malignant																									
Thyroid	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
C-cell adenoma																								X	
Parathyroid	–	+	–	+	+	–	–	–	–	–	+	–	+	–	–	–	+	+	–	+	–	+	–	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																			X						
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	+	N	N	N	N	+	N	+	N	N	N	N	N	+	N	N	N	+	N	+	+	N
Adenocarcinoma, NOS																									
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor			X			X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																					X				
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, benign																									
Astrocytoma						X																			
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	+	N	+	N	N	N	N	N	N	N	N	N	N	+	N	N	N	+	+	N
Adenoma, 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									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																X									
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
Sarcoma, NOS, unclear primary or 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
Neurilemoma, metastatic														X											
Leukemia, mononuclear cell								X					X					X					X		

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	0038	0001	0200	0223	0446	0007	0008	0110	0114	0115	0116	0118	0119	0201	0202	0207	0230	0231	0232	0237	0240	0241	0245	0247	0250	TOTAL:
WEEKS ON STUDY	098	100	100	100	101	103	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
Keratoacanthoma																		X								1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibroma		X	X																			X	X			5
Fibrosarcoma																										1
Myxosarcoma																										1
Liposarcoma		X																								1
Neurilemoma																										1
Neurilemoma, malignant																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma, metastatic																							X			1
Chordoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia, mononuclear cell									X																	1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	−	−	+	+	+	+	+	+	−	−	−	−	−	+	+	−	−	−	−	−	−	−	−	+	28
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	46
Fibrosarcoma, invasive																										1
Neurilemoma						X																				1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																						X				1
Sarcoma, NOS, unclear primary or meta													X													1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	44
Adenoma, NOS	X		X				X	X	X	X							X									11
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma		X				X	X	X	X	X				X		X	X		X		X				X	14
Pheochromocytoma, malignant																							X			1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell adenoma												X								X						3
Parathyroid	+	+	+	+	+	−	−	+	+	+	−	+	−	−	+	+	+	+	−	−	+	+	+	+	+	29
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma						X		X	X										X							5
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	N	+	+	N	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																								X		1
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	X	X	42
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	−	44
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS								X																		2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granular cell tumor, benign														X												1
Astrocytoma																										1
SPECIAL SENSE ORGANS																										
Zymbal gland	+	N	N	+	N	+	+	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	*50
Adenoma, 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
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS																							X			2
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
Sarcoma, NOS, unclear primary or meta													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
Neurilemoma, metastatic																										1
Leukemia, mononuclear cell					X			X						X		X										8

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF PENICILLIN VK: HIGH DOSE

ANIMAL NUMBER	0009	0024	0042	0034	0006	0002	0110	0339	0441	0116	0338	0223	0550	0111	0336	0337	0449	0004	0332	0228	0331	0225	0443	0144	0440
WEEKS ON STUDY	0255	0332	0399	0400	0552	0544	0555	0555	0566	0577	0588	0744	0766	0799	0799	0800	0833	0844	0866	0877	0877	0900	0911	0922	0922
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+
Neurilemoma																			X						
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	−	+	+	+	+	+	+	+	+	−	−	−	−	−	+	−	+	+	+	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma																									
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Small intestine	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Large intestine	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS																	X				X		X		
Adrenal	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																							X	X	
Thyroid	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																		X							
C-cell adenoma																									X
Parathyroid	+	+	+	−	−	+	+	−	+	+	+	−	−	−	+	−	−	+	+	+	+	+	+	−	+
Pancreatic islets	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																		X					X	X	
REPRODUCTIVE SYSTEM																									
Mammary gland	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
Prostate	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma																									
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									X
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS																X									
Leukemia, mononuclear cell												X													

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	013	046	033	021	026	043	001	008	048	003	005	007	012	015	017	018	019	020	022	027	029	030	035	045	047	TOTAL:
WEEKS ON STUDY	093	094	095	098	098	096	099	099	100	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Keratoacanthoma						X	X	X								X										4
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Neurilemoma									X																	2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	47
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	−	+	+	+	−	−	−	+	+	−	+	−	+	+	−	+	+	+	+	+	+	+	+	−	32
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neurilemoma	X																									1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS			X																							1
Adenoma, NOS		X							X		X			X		X		X			X		X	X	X	13
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma		X	X					X	X				X			X	X			X	X	X			X	13
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma															X											2
C-cell adenoma	X																								X	3
Parathyroid	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	39
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma																X										4
REPRODUCTIVE SYSTEM																										
Mammary gland	+	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	X	X	X	X	34
Prostate	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Oligodendroglioma																					X					1
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, NOS																					X					1
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS																					X					2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS																										1
Leukemia, mononuclear cell												X			X			X			X					5

* Animals necropsied

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

	Vehicle Control	500 mg/kg	1,000 mg/kg
Skin: Papilloma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	8.6%	0.0%	0.0%
Terminal Rates (c)	2/34 (6%)	0/19 (0%)	0/16 (0%)
Week of First Observation	101		
Life Table Tests (d)	P=0.109N	P=0.237N	P=0.286N
Incidental Tumor Tests (d)	P=0.087N	P=0.196N	P=0.244N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.121N	P=0.121N
Skin: Keratoacanthoma			
Overall Rates (a)	2/50 (4%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (b)	4.8%	5.3%	19.9%
Terminal Rates (c)	0/34 (0%)	1/19 (5%)	1/16 (6%)
Week of First Observation	92	104	96
Life Table Tests (d)	P=0.067	P=0.662N	P=0.095
Incidental Tumor Tests (d)	P=0.154	P=0.476N	P=0.260
Cochran-Armitage Trend Test (d)	P=0.238		
Fisher Exact Test (d)		P=0.500N	P=0.339
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	3/50 (6%)	5/50 (10%)	0/50 (0%)
Adjusted Rates (b)	7.9%	20.1%	0.0%
Terminal Rates (c)	2/34 (6%)	2/19 (11%)	0/16 (0%)
Week of First Observation	92	80	
Life Table Tests (d)	P=0.390N	P=0.142	P=0.267N
Incidental Tumor Tests (d)	P=0.190N	P=0.302	P=0.128N
Cochran-Armitage Trend Test (d)	P=0.133N		
Fisher Exact Test (d)		P=0.357	P=0.121N
Subcutaneous Tissue: Sarcoma, Fibrosarcoma, or Myxosarcoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	5.1%	6.8%	0.0%
Terminal Rates (c)	1/34 (3%)	0/19 (0%)	0/16 (0%)
Week of First Observation	95	67	
Life Table Tests (d)	P=0.340N	P=0.370	P=0.403N
Incidental Tumor Tests (d)	P=0.028N	P=0.302N	P=0.357N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test (d)		P=0.500	P=0.247N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	5/50 (10%)	6/50 (12%)	0/50 (0%)
Adjusted Rates (b)	12.8%	22.0%	0.0%
Terminal Rates (c)	3/34 (9%)	2/19 (11%)	0/16 (0%)
Week of First Observation	92	74	
Life Table Tests (d)	P=0.217N	P=0.217	P=0.131N
Incidental Tumor Tests (d)	P=0.050N	P=0.548	P=0.056N
Cochran-Armitage Trend Test (d)	P=0.042N		
Fisher Exact Test (d)		P=0.500	P=0.028N
Subcutaneous Tissue: Fibroma, Sarcoma, Fibrosarcoma, or Myxosarcoma			
Overall Rates (a)	5/50 (10%)	8/50 (16%)	0/50 (0%)
Adjusted Rates (b)	12.8%	25.5%	0.0%
Terminal Rates (c)	3/34 (9%)	2/19 (11%)	0/16 (0%)
Week of First Observation	92	67	
Life Table Tests (d)	P=0.257N	P=0.091	P=0.131N
Incidental Tumor Tests (d)	P=0.024N	P=0.548	P=0.056N
Cochran-Armitage Trend Test (d)	P=0.055N		
Fisher Exact Test (d)		P=0.277	P=0.028N

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

	Vehicle Control	500 mg/kg	1,000 mg/kg
Subcutaneous Tissue: Neurilemoma			
Overall Rates (a)	4/50 (8%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	11.1%	3.7%	8.8%
Terminal Rates (c)	3/34 (9%)	0/19 (0%)	0/16 (0%)
Week of First Observation	98	97	86
Life Table Tests (d)	P=0.537N	P=0.371N	P=0.667
Incidental Tumor Tests (d)	P=0.355N	P=0.295N	P=0.476N
Cochran-Armitage Trend Test (d)	P=0.238N		
Fisher Exact Test (d)		P=0.181N	P=0.339N
Subcutaneous Tissue: Neurilemoma or Malignant Neurilemoma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	11.1%	6.3%	8.8%
Terminal Rates (c)	3/34 (9%)	0/19 (0%)	0/16 (0%)
Week of First Observation	98	82	86
Life Table Tests (d)	P=0.557N	P=0.574N	P=0.667
Incidental Tumor Tests (d)	P=0.309N	P=0.409N	P=0.476N
Cochran-Armitage Trend Test (d)	P=0.252N		
Fisher Exact Test (d)		P=0.339N	P=0.339N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	14/50 (28%)	9/50 (18%)	5/50 (10%)
Adjusted Rates (b)	32.8%	33.1%	26.9%
Terminal Rates (c)	7/34 (21%)	4/19 (21%)	4/16 (25%)
Week of First Observation	81	72	74
Life Table Tests (d)	P=0.303N	P=0.555	P=0.332N
Incidental Tumor Tests (d)	P=0.046N	P=0.195N	P=0.069N
Cochran-Armitage Trend Test (d)	P=0.015N		
Fisher Exact Test (d)		P=0.171N	P=0.020N
Anterior Pituitary Gland: Adenoma			
Overall Rates (a)	10/48 (21%)	11/44 (25%)	13/48 (27%)
Adjusted Rates (b)	29.2%	42.2%	59.2%
Terminal Rates (c)	9/33 (27%)	5/17 (29%)	8/16 (50%)
Week of First Observation	100	72	83
Life Table Tests (d)	P=0.007	P=0.075	P=0.007
Incidental Tumor Tests (d)	P=0.056	P=0.204	P=0.040
Cochran-Armitage Trend Test (d)	P=0.276		
Fisher Exact Test (d)		P=0.410	P=0.317
Anterior Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	10/48 (21%)	11/44 (25%)	14/48 (29%)
Adjusted Rates (b)	29.2%	42.2%	60.9%
Terminal Rates (c)	9/33 (27%)	5/17 (29%)	8/16 (50%)
Week of First Observation	100	72	83
Life Table Tests (d)	P=0.003	P=0.075	P=0.003
Incidental Tumor Tests (d)	P=0.033	P=0.204	P=0.023
Cochran-Armitage Trend Test (d)	P=0.205		
Fisher Exact Test (d)		P=0.410	P=0.240
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	13/48 (27%)	14/50 (28%)	13/49 (27%)
Adjusted Rates (b)	37.0%	59.8%	57.2%
Terminal Rates (c)	12/34 (35%)	10/19 (53%)	7/16 (44%)
Week of First Observation	99	94	90
Life Table Tests (d)	P=0.013	P=0.037	P=0.025
Incidental Tumor Tests (d)	P=0.044	P=0.067	P=0.096
Cochran-Armitage Trend Test (d)	P=0.521N		
Fisher Exact Test (d)		P=0.550	P=0.566N

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

	Vehicle Control	500 mg/kg	1,000 mg/kg
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	15/48 (31%)	15/50 (30%)	13/49 (27%)
Adjusted Rates (b)	42.7%	64.3%	57.2%
Terminal Rates (c)	14/34 (41%)	11/19 (58%)	7/16 (44%)
Week of First Observation	99	94	90
Life Table Tests (d)	P=0.027	P=0.041	P=0.052
Incidental Tumor Tests (d)	P=0.082	P=0.074	P=0.167
Cochran-Armitage Trend Test (d)	P=0.345N		
Fisher Exact Test (d)		P=0.534N	P=0.386N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	2/48 (4%)	3/48 (6%)	3/48 (6%)
Adjusted Rates (b)	5.0%	13.8%	13.3%
Terminal Rates (c)	1/34 (3%)	2/19 (11%)	1/16 (6%)
Week of First Observation	88	97	92
Life Table Tests (d)	P=0.148	P=0.279	P=0.236
Incidental Tumor Tests (d)	P=0.328	P=0.422	P=0.545
Cochran-Armitage Trend Test (d)	P=0.412		
Fisher Exact Test (d)		P=0.500	P=0.500
Pancreatic Islets: Islet Cell Adenoma			
Overall Rates (a)	2/49 (4%)	5/48 (10%)	4/48 (8%)
Adjusted Rates (b)	5.9%	22.5%	15.6%
Terminal Rates (c)	2/34 (6%)	3/19 (16%)	1/16 (6%)
Week of First Observation	104	89	84
Life Table Tests (d)	P=0.066	P=0.059	P=0.113
Incidental Tumor Tests (d)	P=0.244	P=0.106	P=0.392
Cochran-Armitage Trend Test (d)	P=0.273		
Fisher Exact Test (d)		P=0.209	P=0.329
Testis: Interstitial Cell Tumor			
Overall Rates (a)	48/50 (96%)	42/49 (86%)	34/50 (68%)
Adjusted Rates (b)	100.0%	97.6%	97.0%
Terminal Rates (c)	34/34 (100%)	17/18 (94%)	15/16 (94%)
Week of First Observation	81	58	55
Life Table Tests (d)	P=0.014	P=0.005	P=0.017
Incidental Tumor Tests (d)	P=0.071N	P=0.685	P=0.231N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.075N	P<0.001N
All Sites: Benign Tumors			
Overall Rates (a)	49/50 (98%)	45/50 (90%)	39/50 (78%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	34/34 (100%)	19/19 (100%)	16/16 (100%)
Week of First Observation	81	58	55
Life Table Tests (d)	P=0.001	P=0.003	P=0.001
Incidental Tumor Tests (d)	P=0.428N	P=0.500	P=0.688
Cochran-Armitage Trend Test (d)	P=0.001N		
Fisher Exact Test (d)		P=0.103N	P=0.002N
All Sites: Malignant Tumors			
Overall Rates (a)	21/50 (42%)	19/50 (38%)	7/50 (14%)
Adjusted Rates (b)	46.6%	56.0%	32.1%
Terminal Rates (c)	11/34 (32%)	7/19 (37%)	4/16 (25%)
Week of First Observation	81	67	74
Life Table Tests (d)	P=0.260N	P=0.152	P=0.204N
Incidental Tumor Tests (d)	P=0.004N	P=0.265N	P=0.015N
Cochran-Armitage Trend Test (d)	P=0.002N		
Fisher Exact Test (d)		P=0.419N	P=0.002N

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

	Vehicle Control	500 mg/kg	1,000 mg/kg
All Sites: All Tumors			
Overall Rates (a)	50/50 (100%)	46/50 (92%)	39/50 (78%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	34/34 (100%)	19/19 (100%)	16/16 (100%)
Week of First Observation	81	58	55
Life Table Tests (d)	P=0.002	P=0.003	P=0.002
Incidental Tumor Tests (d)	P=0.091N	(e)	P=0.718N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.059N	P<0.001N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because all low dose animals dying after the first death in the vehicle controls had tumors.

TABLE A4. HISTORICAL INCIDENCE OF ANTERIOR PITUITARY GLAND TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Springborn Institute for Bioresearch, Inc.			
Ampicillin trihydrate	11/46 (23.9%)	1/46 (2.1%)	12/46 (26.1%)
Overall Historical Incidence			
TOTAL	(b) 444/1,654 (26.8%)	(c) 33/1,654 (2.0%)	(b,c) 476/1,654 (28.8%)
SD (d)	10.52%	2.66%	10.71%
Range (e)			
High	26/48	4/47	26/48
Low	5/50	0/50	6/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Includes 34 chromophobe adenomas and 1 acidophil adenoma
(c) Includes two adenocarcinomas, NOS, and four chromophobe carcinomas
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

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

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Epidermal inclusion cyst		1 (2%)	
Inflammation, chronic focal			1 (2%)
Acanthosis		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Hemorrhage		1 (2%)	
Inflammation, suppurative		1 (2%)	
Inflammation, acute suppurative		1 (2%)	
Inflammation, chronic		1 (2%)	
Inflammation, chronic suppurative		1 (2%)	
Inflammation, granulomatous		1 (2%)	
Granuloma, NOS	1 (2%)		
Granulation tissue		1 (2%)	
Necrosis, fat	1 (2%)	1 (2%)	
RESPIRATORY SYSTEM			
*Nasal mucosa	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	38 (76%)	37 (74%)	38 (76%)
Inflammation, suppurative	14 (28%)	17 (34%)	36 (72%)
Metaplasia, squamous			2 (4%)
#Trachea	(48)	(49)	(49)
Inflammation, suppurative			1 (2%)
Inflammation, acute			1 (2%)
Inflammation, acute diffuse			1 (2%)
Inflammation, acute suppurative			1 (2%)
#Lung/bronchus	(49)	(50)	(47)
Inflammation, acute suppurative		1 (2%)	
Inflammation, chronic focal			1 (2%)
Metaplasia, squamous			1 (2%)
#Lung	(49)	(50)	(47)
Foreign body, NOS	1 (2%)		
Congestion, acute	3 (6%)	7 (14%)	12 (26%)
Hemorrhage	1 (2%)	1 (2%)	
Lymphocytic inflammatory infiltrate	6 (12%)		2 (4%)
Inflammation, interstitial	1 (2%)	4 (8%)	3 (6%)
Pneumonia, aspiration	2 (4%)	7 (14%)	13 (28%)
Inflammation, chronic focal	4 (8%)	1 (2%)	1 (2%)
Inflammation, granulomatous focal		1 (2%)	
Necrosis, focal	1 (2%)	1 (2%)	
Infarct, NOS	1 (2%)		
#Lung/alveoli	(49)	(50)	(47)
Edema, NOS			3 (6%)
Histiocytosis	7 (14%)		
HEMATOPOIETIC SYSTEM			
*Blood erythrocytes	(50)	(50)	(50)
Reticulocytosis	4 (8%)	2 (4%)	2 (4%)
Erythroblastosis		5 (10%)	
Normoblastosis	6 (12%)	2 (4%)	1 (2%)
#Bone marrow	(46)	(50)	(50)
Necrosis, focal	1 (2%)		
Myelofibrosis	1 (2%)		
Hyperplasia, erythroid	14 (30%)	4 (8%)	11 (22%)
Hyperplasia, granulocytic	11 (24%)	7 (14%)	11 (22%)

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Spleen	(49)	(49)	(48)
Infarct, NOS	1 (2%)		
Depletion, lymphoid	3 (6%)	1 (2%)	3 (6%)
#Splenic red pulp	(49)	(49)	(48)
Congestion, NOS	3 (6%)		
Congestion, acute	1 (2%)		2 (4%)
Hemosiderosis	2 (4%)		
Atrophy, NOS		1 (2%)	
Hematopoiesis	5 (10%)	8 (16%)	3 (6%)
#Mandibular lymph node	(48)	(49)	(48)
Cyst, NOS		2 (4%)	1 (2%)
Hemorrhage	1 (2%)		2 (4%)
Hyperplasia, focal	1 (2%)		
Plasmacytosis	3 (6%)	1 (2%)	2 (4%)
Hyperplasia, lymphoid	10 (21%)	7 (14%)	11 (23%)
#Bronchial lymph node	(48)	(49)	(48)
Hemorrhage	1 (2%)		
#Mediastinal lymph node	(48)	(49)	(48)
Hemorrhage	2 (4%)	4 (8%)	5 (10%)
Necrosis, NOS		1 (2%)	
Hemosiderosis		1 (2%)	1 (2%)
Depletion, lymphoid			1 (2%)
Histiocytosis	2 (4%)	1 (2%)	
Plasmacytosis	1 (2%)		
Hyperplasia, lymphoid		3 (6%)	
#Pancreatic lymph node	(48)	(49)	(48)
Hematopoiesis	1 (2%)		
#Mesenteric lymph node	(48)	(49)	(48)
Hemorrhage	1 (2%)	1 (2%)	2 (4%)
Hemosiderosis	1 (2%)		
Depletion, lymphoid	1 (2%)		
Hyperplasia, lymphoid	4 (8%)		
#Lung/bronchus	(49)	(50)	(47)
Hyperplasia, lymphoid			1 (2%)
#Liver	(49)	(50)	(49)
Hematopoiesis	2 (4%)		1 (2%)
#Peyer's patch	(45)	(49)	(48)
Hyperplasia, lymphoid	5 (11%)	1 (2%)	
#Adrenal cortex	(48)	(50)	(49)
Hematopoiesis	7 (15%)	4 (8%)	3 (6%)
#Thymus	(39)	(28)	(32)
Hemorrhage		2 (7%)	4 (13%)
CIRCULATORY SYSTEM			
#Heart/atrium	(49)	(50)	(49)
Thrombosis, NOS		1 (2%)	
#Myocardium	(49)	(50)	(49)
Inflammation, granulomatous focal		1 (2%)	2 (4%)
Degeneration, NOS	31 (63%)	23 (46%)	29 (59%)
#Endocardium of left atrium	(49)	(50)	(49)
Fibrosis			1 (2%)
#Pancreas	(49)	(48)	(48)
Periarteritis	1 (2%)		
#Adrenal medulla	(48)	(50)	(49)
Thrombosis, NOS		1 (2%)	
#Thyroid	(48)	(48)	(48)
Periarteritis		1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM			
*Oral mucosa	(50)	(50)	(50)
Hyperkeratosis		1 (2%)	
*Palate	(50)	(50)	(50)
Epidermal inclusion cyst			1 (2%)
#Salivary gland	(46)	(46)	(49)
Cyst, NOS			1 (2%)
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, chronic focal	1 (2%)	1 (2%)	
Fibrosis		1 (2%)	
Fibrosis, focal	1 (2%)		
Degeneration, NOS	1 (2%)		
Nuclear size alteration	1 (2%)		
Atrophy, focal	5 (11%)	2 (4%)	
Regeneration, NOS		1 (2%)	
#Liver	(49)	(50)	(49)
Mineralization	1 (2%)		
Congestion, NOS	1 (2%)	2 (4%)	8 (16%)
Inflammation, suppurative		1 (2%)	
Inflammation, chronic focal		3 (6%)	
Inflammation, granulomatous focal			2 (4%)
Necrosis, NOS	7 (14%)	3 (6%)	4 (8%)
Cytoplasmic vacuolization	2 (4%)	1 (2%)	1 (2%)
Basophilic cyto change	18 (37%)	12 (24%)	16 (33%)
Focal cellular change	4 (8%)	8 (16%)	2 (4%)
Eosinophilic cyto change	1 (2%)	1 (2%)	
Clear cell change	2 (4%)		2 (4%)
Angiectasis	2 (4%)		
Regeneration, NOS	1 (2%)		
#Liver/centrilobular	(49)	(50)	(49)
Degeneration, NOS		2 (4%)	2 (4%)
Cytoplasmic vacuolization	1 (2%)		
Angiectasis	1 (2%)		
#Liver/periportal	(49)	(50)	(49)
Lymphocytic inflammatory infiltrate	2 (4%)		1 (2%)
#Liver/hepatocytes	(49)	(50)	(49)
Cytoplasmic vacuolization	6 (12%)		
#Bile duct	(49)	(50)	(49)
Hyperplasia, NOS		4 (8%)	1 (2%)
Hyperplasia, focal	32 (65%)	15 (30%)	15 (31%)
#Pancreas	(49)	(48)	(48)
Cyst, NOS			1 (2%)
Lymphocytic inflammatory infiltrate			1 (2%)
Fibrosis, focal			1 (2%)
Hemosiderosis		1 (2%)	
Atrophy, NOS		4 (8%)	
Atrophy, focal	16 (33%)	15 (31%)	2 (4%)
Hyperplasia, focal			1 (2%)
#Stomach	(46)	(49)	(48)
Granulation tissue		1 (2%)	
#Gastric mucosa	(46)	(49)	(48)
Hemorrhage			1 (2%)
Ulcer, NOS		1 (2%)	
Fibrosis	30 (65%)	33 (67%)	31 (65%)
Fibrosis, focal	5 (11%)		2 (4%)
Fibrosis, diffuse	1 (2%)		1 (2%)
Necrosis, focal	1 (2%)		1 (2%)
#Glandular stomach	(46)	(49)	(48)
Dilatation, NOS	1 (2%)		
#Forestomach	(46)	(49)	(48)
Ulcer, NOS		2 (4%)	
Inflammation, suppurative		3 (6%)	1 (2%)

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

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM			
#Forestomach (Continued)	(46)	(49)	(48)
Inflammation, chronic		1 (2%)	
Inflammation, chronic suppurative		1 (2%)	
Hyperkeratosis	1 (2%)	7 (14%)	1 (2%)
Acanthosis	6 (13%)	15 (31%)	8 (17%)
#Small intestine	(45)	(49)	(48)
Congestion, NOS			1 (2%)
#Small intestine/serosa	(45)	(49)	(48)
Inflammation, suppurative			1 (2%)
#Colon	(48)	(49)	(48)
Distention		1 (2%)	
Congestion, NOS			1 (2%)
Parasitism	5 (10%)	3 (6%)	2 (4%)
#Cecum	(48)	(49)	(48)
Hemorrhage			1 (2%)
*Rectum	(50)	(50)	(50)
Distention	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(50)	(49)
Hydronephrosis			1 (2%)
Multiple cysts	1 (2%)		
Congestion, acute		1 (2%)	3 (6%)
Inflammation, suppurative		1 (2%)	1 (2%)
Nephrosis, NOS	45 (90%)	38 (76%)	32 (65%)
#Kidney/tubule	(50)	(50)	(49)
Dilatation, NOS		1 (2%)	
Pigmentation, NOS	1 (2%)	2 (4%)	1 (2%)
#Urinary bladder	(44)	(48)	(47)
Distention	2 (5%)		
Hemorrhage		1 (2%)	2 (4%)
#Urinary bladder/submucosa	(44)	(48)	(47)
Hemorrhage	1 (2%)		
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(44)	(48)
Cyst, NOS	2 (4%)	1 (2%)	2 (4%)
Congestion, NOS			1 (2%)
Hemorrhage	2 (4%)		
Hyperplasia, focal	12 (25%)	13 (30%)	7 (15%)
Hyperplasia, diffuse	2 (4%)		
#Adrenal cortex	(48)	(50)	(49)
Hamartoma			1 (2%)
Cytoplasmic vacuolization	5 (10%)		1 (2%)
Hypertrophy, focal	1 (2%)		
Hyperplasia, focal	8 (17%)	4 (8%)	4 (8%)
#Adrenal medulla	(48)	(50)	(49)
Hyperplasia, focal	11 (23%)	8 (16%)	5 (10%)
#Thyroid	(48)	(48)	(48)
Follicular cyst, NOS		1 (2%)	
Lymphocytic inflammatory infiltrate	2 (4%)		
Inflammation, chronic		1 (2%)	
Fibrosis, focal		1 (2%)	
Hyperplasia, C-cell	9 (19%)	6 (13%)	9 (19%)
Hyperplasia, follicular cell			1 (2%)
#Pancreatic islets	(49)	(48)	(48)
Hyperplasia, NOS			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM			
*Mammary duct	(50)	(50)	(50)
Distention	3 (6%)		2 (4%)
*Preputial gland	(50)	(50)	(50)
Retention of content	3 (6%)		2 (4%)
Inflammation, suppurative	1 (2%)	1 (2%)	3 (6%)
Inflammation, chronic	6 (12%)	2 (4%)	5 (10%)
Inflammation, chronic focal	20 (40%)	16 (32%)	15 (30%)
Inflammation, chronic diffuse	1 (2%)		
Hyperkeratosis			1 (2%)
#Prostate	(45)	(44)	(47)
Lymphocytic inflammatory infiltrate	1 (2%)		1 (2%)
Inflammation, suppurative		2 (5%)	1 (2%)
Inflammation, acute suppurative	1 (2%)		
Abscess, NOS		1 (2%)	
Inflammation, chronic	3 (7%)		
Inflammation, chronic focal	12 (27%)	15 (34%)	19 (40%)
Hyperplasia, focal	2 (4%)		1 (2%)
*Seminal vesicle	(50)	(50)	(50)
Distention	1 (2%)		1 (2%)
Atrophy, NOS		1 (2%)	1 (2%)
Atrophy, diffuse	3 (6%)		
#Testis	(50)	(49)	(50)
Inflammation, granulomatous focal	1 (2%)		
Atrophy, NOS	7 (14%)	4 (8%)	7 (14%)
Atrophy, focal	6 (12%)		4 (8%)
Atrophy, diffuse	14 (28%)		3 (6%)
Hyperplasia, interstitial cell	2 (4%)	2 (4%)	5 (10%)
#Spermatid	(50)	(49)	(50)
Dysplasia, NOS	4 (8%)	4 (8%)	
*Epididymis	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)
Degeneration, NOS	1 (2%)		1 (2%)
Cytoplasmic vacuolization	10 (20%)	5 (10%)	2 (4%)
NERVOUS SYSTEM			
#Brain	(49)	(49)	(49)
Congestion, NOS	1 (2%)		
Congestion, acute			1 (2%)
#Brain stem	(49)	(49)	(49)
Hemorrhage	1 (2%)	1 (2%)	1 (2%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Hemorrhage		1 (2%)	
Inflammation, chronic		1 (2%)	
Phthisis bulbi	1 (2%)		
*Harderian gland	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, chronic focal	1 (2%)		
*Ear canal	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	9 (18%)	9 (18%)	9 (18%)
MUSCULOSKELETAL SYSTEM			
None			

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

	Vehicle Control	Low Dose	High Dose
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Hemorrhage		1 (2%)	
*Anterior mediastinum	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
*Mesentery	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	
Necrosis, fat	4 (8%)	7 (14%)	1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Inflammation, chronic focal			1 (2%)
Hyperplasia, focal	1 (2%)		
Tail			
Healed fracture			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 B

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

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

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell carcinoma			1 (2%)
Basal cell carcinoma	1 (2%)		
Keratoacanthoma	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	2 (4%)		1 (2%)
Fibrosarcoma	1 (2%)		
Lipoma	1 (2%)		
Neurilemoma		3 (6%)	1 (2%)
Neurilemoma, metastatic		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(49)	(50)	(50)
Adenocarcinoma, NOS, metastatic	1 (2%)		
Alveolar/bronchiolar adenoma	1 (2%)		1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	12 (24%)	14 (28%)	9 (18%)
#Splenic red pulp	(49)	(49)	(48)
Leukemia, mononuclear cell	1 (2%)		
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Papilloma, NOS			1 (2%)
#Liver	(50)	(49)	(50)
Bile duct adenoma	1 (2%)		
Neoplastic nodule		1 (2%)	
#Duodenum	(49)	(48)	(47)
Endometrial stromal sarcoma, metastatic			1 (2%)
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Pituitary intermedia	(48)	(49)	(48)
Adenoma, NOS			1 (2%)
#Anterior pituitary	(48)	(49)	(48)
Carcinoma, NOS	1 (2%)	3 (6%)	
Adenoma, NOS	23 (48%)	19 (39%)	20 (42%)
#Adrenal	(49)	(49)	(49)
Cortical adenoma	2 (4%)		
#Adrenal medulla	(49)	(49)	(49)
Pheochromocytoma	3 (6%)	5 (10%)	5 (10%)
Pheochromocytoma, malignant		2 (4%)	

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(49)	(47)	(47)
Follicular cell adenoma			2 (4%)
Follicular cell carcinoma	1 (2%)		
C-cell adenoma	6 (12%)	6 (13%)	10 (21%)
C-cell carcinoma		1 (2%)	1 (2%)
#Pancreatic islets	(48)	(46)	(49)
Islet cell adenoma		1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS	2 (4%)		1 (2%)
Adenocarcinoma, NOS	5 (10%)	2 (4%)	3 (6%)
Fibroadenoma	15 (30%)	21 (42%)	16 (32%)
*Clitoral gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)	1 (2%)	1 (2%)
Adenoma, NOS		1 (2%)	3 (6%)
*Vagina	(50)	(50)	(50)
Endometrial stromal sarcoma	2 (4%)		
#Uterus	(48)	(47)	(49)
Endometrial stromal polyp	7 (15%)	3 (6%)	10 (20%)
Endometrial stromal sarcoma			2 (4%)
#Uterus/endometrium	(48)	(47)	(49)
Papillary adenoma			1 (2%)
#Ovary	(48)	(48)	(49)
Thecoma	1 (2%)		
Granulosa cell tumor			1 (2%)
NERVOUS SYSTEM			
#Brain	(49)	(50)	(50)
Choroid plexus papilloma			1 (2%)
Astrocytoma	1 (2%)		
#Brain/thalamus	(49)	(50)	(50)
Carcinoma, NOS, invasive		1 (2%)	
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
*Mandible	(50)	(50)	(50)
Ameloblastoma		1 (2%)	
*Scapula	(50)	(50)	(50)
Osteosarcoma	1 (2%)		
BODY CAVITIES			
*Peritoneal cavity	(50)	(50)	(50)
Neurilemoma, malignant		1 (2%)	
ALL OTHER SYSTEMS			
None			

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

	Vehicle Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	7	9	15
Moribund sacrifice	15	14	15
Terminal sacrifice	28	26	16
Dosing accident			3
Accidentally killed, nda		1	1
TUMOR SUMMARY			
Total animals with primary tumors**	44	45	38
Total primary tumors	92	85	94
Total animals with benign tumors	39	37	36
Total benign tumors	65	60	75
Total animals with malignant tumors	22	21	17
Total malignant tumors	27	24	18
Total animals with secondary tumors##	1	2	1
Total secondary tumors	1	2	1
Total animals with tumors uncertain--benign or malignant		1	1
Total uncertain tumors		1	1

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

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

ANIMAL NUMBER	0032	0034	0039	0014	0025	0042	0002	0006	0022	0024	0029	0027	0045	0010	0013	0016	0021	0031	0046	0001	0035	0003	0004	0005	0007
WEEKS ON STUDY	078	079	079	093	094	094	095	098	098	098	098	099	099	100	100	100	100	100	100	101	101	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma					X																				
Fibrosarcoma																									
Lipoma					X																				
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic										X															
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																									
Lymph nodes	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Thymus	+	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	–	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct adenoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma																	X		X						
Thyroid	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																		X							
C-cell adenoma										X						X	X	X						X	
Parathyroid	–	–	–	–	–	+	+	+	–	–	–	+	+	–	–	+	+	–	–	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS								X																	
Adenocarcinoma, NOS					X					X														X	
Fibroadenoma									X		X			X					X				X	X	
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																	X								
Vagina	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Endometrial stromal sarcoma			X																		X				
Uterus	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																					X				X
Ovary	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thecoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma																									
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				

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

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	008	009	011	012	015	017	018	019	020	023	026	028	030	033	036	037	038	040	041	043	044	047	048	049	050	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Basal cell carcinoma																								X		1
Keratoacanthoma						X																				1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma						X																				2
Fibrosarcoma																								X		1
Lipoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS, metastatic																										1
Alveolar/bronchiolar adenoma																			X							1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia, mononuclear cell																								X		1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymus	+	−	+	+	+	−	+	−	−	+	−	+	+	+	+	+	+	+	−	+	+	+	+	−	+	40
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct adenoma																					X					1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	42
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS																										1
Adenoma, NOS		X		X			X	X			X	X				X	X	X	X	X	X	X		X	X	23
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma						X									X											2
Pheochromocytoma										X																3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell carcinoma																										1
C-cell adenoma																							X			6
Parathyroid	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	−	+	+	+	+	+	34
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS									X																	2
Adenocarcinoma, NOS					X					X																5
Fibroadenoma	X			X				X								X	X	X			X	X			X	15
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
Vagina	N	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
Endometrial stromal sarcoma																										2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	48
Endometrial stromal polyp			X					X		X						X							X			7
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	48
Thecoma		X																								1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Astrocytoma	X																									1
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	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	12

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF PENICILLIN VK: LOW DOSE

ANIMAL NUMBER	0018	0028	0116	0550	0466	0333	0224	0112	0422	0441	0227	0119	0331	0111	0006	0449	0001	0003	0325	0455	0008	0447	0229	0113	0002
WEEKS ON STUDY	0004	0058	0686	0677	0699	0767	0800	0822	0882	0833	0858	0866	0888	0899	0900	0911	0995	0995	0997	1000	1001	1011	1022	1033	1044
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma									X														X		
Neurilemoma, metastatic												X													
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	−	+	+	+	+	−	+	+	−	−	−	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Liver	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																					X				
Bile duct	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	−	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	−	+	+	−	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																						X		X	
Adenoma, NOS					X	X	X		X				X						X		X		X		X
Adrenal	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																		X					X		
Pheochromocytoma, malignant				X																				X	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																			X				X		
C-cell carcinoma															X										
Parathyroid	+	+	−	+	−	−	+	−	−	+	−	+	−	+	−	−	+	+	+	+	−	+	−	+	−
Pancreatic islets	−	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	N	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
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
Carcinoma, NOS																									
Adenoma, NOS																									
Uterus	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp					X																				
Ovary	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																									
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
Ameloblastoma														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
Neurilemoma, 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
Leukemia, mononuclear cell						X		X			X			X	X	X	X	X	X	X					

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

ANIMAL NUMBER	0004	0005	0007	0009	0010	0014	0015	0017	0020	0021	0022	0023	0025	0028	0030	0034	0035	0036	0037	0038	0039	0040	0043	0044	0048	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
Neurilemoma																			X							3
Neurilemoma, metastatic																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	−	−	−	+	+	−	+	+	−		38
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreas	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Esophagus	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS						X																				3
Adenoma, NOS					X			X	X					X				X	X		X		X	X	X	19
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma						X									X							X				5
Pheochromocytoma, malignant																										2
Thyroid	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	47
C-cell adenoma						X	X					X		X												6
C-cell carcinoma																										1
Parathyroid	+	−	−	+	+	+	−	+	−	−	+	−	−	−	−	+	+	+	+	+	+	+	−	+	+	28
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Islet cell adenoma		X																								1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS	X																	X								2
Fibroadenoma			X		X		X		X	X	X	X				X	X	X	X				X	X	X	21
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS							X																			1
Adenoma, NOS								X																		1
Uterus	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Endometrial stromal polyp			X			X																				3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive						X																				1
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Ameloblastoma																										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
Neurilemoma, malignant																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell							X					X	X					X								14

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF PENICILLIN VK: HIGH DOSE

ANIMAL NUMBER	0017	0046	0033	0113	0444	0336	0003	0339	0228	0440	0005	0119	0224	0223	0335	0227	0332	0007	0447	0337	0004	0114	0115	0445	0112
WEEKS ON STUDY	0005	0005	0006	0337	0447	0448	0555	0555	0559	0775	0777	0779	0880	0882	0883	0884	0884	0888	0888	0889	0992	0993	0993	0993	0994
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+
Fibroma																						X			
Neurilemoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																						X			
Trachea	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	−	+	−	−	+	+	+	+	−	+	+	+	+	+	+
Thymus	+	+	+	+	−	+	+	+	+	−	+	−	+	+	+	+	−	−	+	−	+	+	+	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papilloma, NOS																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	−	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	−	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal sarcoma, metastatic																									
Large intestine	+	+	+	+	+	−	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	−	+	−	+	+	+	+	−	+	+	+	−	+	+	+	+	−	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Adenoma, NOS														X	X					X			X	X	
Adrenal	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																						X			
Thyroid	−	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																		X							
C-cell adenoma																	X			X					
C-cell carcinoma																									
Parathyroid	−	−	−	+	−	+	+	−	+	+	−	+	+	−	−	+	+	−	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	+	N	+	+	N	N	N	N	+	N	N	+	+	+	N	+	+	+	+	+	+	+
Adenoma, NOS																									
Adenocarcinoma, NOS																									
Fibroadenoma																	X				X		X	X	
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Adenoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Papillary adenoma																									
Endometrial stromal polyp										X	X							X			X				
Endometrial stromal sarcoma																				X					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor																							X		
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Choroid plexus papilloma																									
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
Carcinoma, NOS														X											
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell																		X					X	X	

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

ANIMAL NUMBER	020	001	030	026	029	009	022	034	048	002	006	008	010	011	016	018	021	025	031	038	041	042	043	049	050	TOTAL:
WEEKS ON STUDY	094	095	095	097	097	099	100	101	101	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 carcinoma										X																1
Subcutaneous tissue	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										1
Neurilemoma			X																							1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Trachea	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Thymus	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papilloma, NOS	X																									1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Endometrial stromal sarcoma, metastat					X																					1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS	X		X			X	X		X	X			X	X	X	X		X	X	X	X		X		X	21
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma						X					X											X	X			5
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular cell adenoma														X												2
C-cell adenoma	X						X		X					X			X		X			X	X			10
C-cell carcinoma										X																1
Parathyroid	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	37
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma																					X					1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS	X																									1
Adenocarcinoma, NOS									X			X			X											3
Fibroadenoma				X	X			X		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
Carcinoma, NOS																							X			1
Adenoma, NOS		X																					X		X	3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papillary adenoma												X														1
Endometrial stromal polyp											X	X							X		X		X		X	10
Endometrial stromal sarcoma						X																				2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa cell tumor																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Choroid plexus papilloma										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	*50
Carcinoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell	X			X	X			X											X					X		9

* Animals necropsied

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

	Vehicle Control	500 mg/kg	1,000 mg/kg
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted Rates (b)	8.9%	0.0%	3.4%
Terminal Rates (c)	2/29 (7%)	0/26 (0%)	0/16 (0%)
Week of First Observation	94		93
Life Table Tests (d)	P=0.310N	P=0.155N	P=0.519N
Incidental Tumor Tests (d)	P=0.297N	P=0.184N	P=0.479N
Cochran-Armitage Trend Test (d)	P=0.176N		
Fisher Exact Test (d)		P=0.121N	P=0.309N
Subcutaneous Tissue: Neurilemoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	0.0%	9.4%	4.2%
Terminal Rates (c)	0/29 (0%)	1/26 (4%)	0/16 (0%)
Week of First Observation		82	95
Life Table Tests (d)	P=0.235	P=0.111	P=0.379
Incidental Tumor Tests (d)	P=0.359	P=0.127	P=0.435
Cochran-Armitage Trend Test (d)	P=0.378		
Fisher Exact Test (d)		P=0.121	P=0.500
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	13/50 (26%)	14/50 (28%)	9/50 (18%)
Adjusted Rates (b)	35.0%	36.1%	35.1%
Terminal Rates (c)	7/29 (24%)	4/26 (15%)	2/16 (13%)
Week of First Observation	93	76	88
Life Table Tests (d)	P=0.348	P=0.321	P=0.391
Incidental Tumor Tests (d)	P=0.345N	P=0.457	P=0.590N
Cochran-Armitage Trend Test (d)	P=0.206N		
Fisher Exact Test (d)		P=0.500	P=0.235N
Anterior Pituitary Gland: Adenoma			
Overall Rates (a)	23/48 (48%)	19/49 (39%)	20/48 (42%)
Adjusted Rates (b)	64.7%	55.0%	78.1%
Terminal Rates (c)	17/29 (59%)	11/25 (44%)	11/16 (69%)
Week of First Observation	94	69	83
Life Table Tests (d)	P=0.071	P=0.512N	P=0.048
Incidental Tumor Tests (d)	P=0.290	P=0.373N	P=0.190
Cochran-Armitage Trend Test (d)	P=0.303N		
Fisher Exact Test (d)		P=0.241N	P=0.341N
Anterior Pituitary Gland: Carcinoma			
Overall Rates (a)	1/48 (2%)	3/49 (6%)	0/48 (0%)
Adjusted Rates (b)	2.3%	10.6%	0.0%
Terminal Rates (c)	0/29 (0%)	1/25 (4%)	0/16 (0%)
Week of First Observation	98	101	
Life Table Tests (d)	P=0.571N	P=0.259	P=0.653N
Incidental Tumor Tests (d)	P=0.522N	P=0.121	P=0.569N
Cochran-Armitage Trend Test (d)	P=0.378N		
Fisher Exact Test (d)		P=0.316	P=0.500N
Anterior Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	24/48 (50%)	22/49 (45%)	20/48 (42%)
Adjusted Rates (b)	65.6%	61.2%	78.1%
Terminal Rates (c)	17/29 (59%)	12/25 (48%)	11/16 (69%)
Week of First Observation	94	69	83
Life Table Tests (d)	P=0.084	P=0.468	P=0.066
Incidental Tumor Tests (d)	P=0.323	P=0.528	P=0.248
Cochran-Armitage Trend Test (d)	P=0.237N		
Fisher Exact Test (d)		P=0.382N	P=0.270N

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

	Vehicle Control	500 mg/kg	1,000 mg/kg
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	3/49 (6%)	5/49 (10%)	5/49 (10%)
Adjusted Rates (b)	8.7%	17.2%	25.5%
Terminal Rates (c)	1/29 (3%)	3/26 (12%)	3/16 (19%)
Week of First Observation	100	95	93
Life Table Tests (d)	P=0.076	P=0.289	P=0.103
Incidental Tumor Tests (d)	P=0.112	P=0.154	P=0.154
Cochran-Armitage Trend Test (d)	P=0.297		
Fisher Exact Test (d)		P=0.357	P=0.357
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	3/49 (6%)	7/49 (14%)	5/49 (10%)
Adjusted Rates (b)	8.7%	22.0%	25.5%
Terminal Rates (c)	1/29 (3%)	3/26 (12%)	3/16 (19%)
Week of First Observation	100	67	93
Life Table Tests (d)	P=0.079	P=0.123	P=0.103
Incidental Tumor Tests (d)	P=0.144	P=0.061	P=0.154
Cochran-Armitage Trend Test (d)	P=0.308		
Fisher Exact Test (d)		P=0.159	P=0.357
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	6/49 (12%)	6/47 (13%)	10/47 (21%)
Adjusted Rates (b)	16.4%	22.2%	44.4%
Terminal Rates (c)	2/29 (7%)	4/24 (17%)	5/16 (31%)
Week of First Observation	98	97	84
Life Table Tests (d)	P=0.015	P=0.481	P=0.020
Incidental Tumor Tests (d)	P=0.049	P=0.288	P=0.091
Cochran-Armitage Trend Test (d)	P=0.141		
Fisher Exact Test (d)		P=0.590	P=0.181
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	6/49 (12%)	7/47 (15%)	11/47 (23%)
Adjusted Rates (b)	16.4%	24.3%	49.5%
Terminal Rates (c)	2/29 (7%)	4/24 (17%)	6/16 (38%)
Week of First Observation	98	90	84
Life Table Tests (d)	P=0.007	P=0.356	P=0.009
Incidental Tumor Tests (d)	P=0.033	P=0.255	P=0.048
Cochran-Armitage Trend Test (d)	P=0.093		
Fisher Exact Test (d)		P=0.467	P=0.122
Mammary Gland: Fibroadenoma			
Overall Rates (a)	15/50 (30%)	21/50 (42%)	16/50 (32%)
Adjusted Rates (b)	44.0%	63.5%	67.2%
Terminal Rates (c)	11/29 (38%)	14/26 (54%)	9/16 (56%)
Week of First Observation	98	91	84
Life Table Tests (d)	P=0.016	P=0.069	P=0.024
Incidental Tumor Tests (d)	P=0.043	P=0.016	P=0.081
Cochran-Armitage Trend Test (d)	P=0.458		
Fisher Exact Test (d)		P=0.149	P=0.500
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (a)	17/50 (34%)	21/50 (42%)	17/50 (34%)
Adjusted Rates (b)	48.4%	63.5%	68.4%
Terminal Rates (c)	12/29 (41%)	14/26 (54%)	9/16 (56%)
Week of First Observation	98	91	84
Life Table Tests (d)	P=0.022	P=0.135	P=0.030
Incidental Tumor Tests (d)	P=0.057	P=0.038	P=0.101
Cochran-Armitage Trend Test (d)	P=0.541		
Fisher Exact Test (d)		P=0.268	P=0.583

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

	Vehicle Control	500 mg/kg	1,000 mg/kg
Mammary Gland: Adenocarcinoma			
Overall Rates (a)	5/50 (10%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	14.3%	7.7%	17.4%
Terminal Rates (c)	3/29 (10%)	2/26 (8%)	2/16 (13%)
Week of First Observation	94	104	101
Life Table Tests (d)	P=0.563N	P=0.290N	P=0.597
Incidental Tumor Tests (d)	P=0.527N	P=0.351N	P=0.638N
Cochran-Armitage Trend Test (d)	P=0.274N		
Fisher Exact Test (d)		P=0.218N	P=0.357N
Mammary Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	7/50 (14%)	2/50 (4%)	4/50 (8%)
Adjusted Rates (b)	19.6%	7.7%	20.5%
Terminal Rates (c)	4/29 (14%)	2/26 (8%)	2/16 (13%)
Week of First Observation	94	104	94
Life Table Tests (d)	P=0.499N	P=0.134N	P=0.593
Incidental Tumor Tests (d)	P=0.444N	P=0.183N	P=0.571N
Cochran-Armitage Trend Test (d)	P=0.187N		
Fisher Exact Test (d)		P=0.080N	P=0.262N
Clitoral Gland: Adenoma			
Overall Rates (a)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	0.0%	3.8%	16.1%
Terminal Rates (c)	0/29 (0%)	1/26 (4%)	2/16 (13%)
Week of First Observation		104	95
Life Table Tests (d)	P=0.018	P=0.478	P=0.040
Incidental Tumor Tests (d)	P=0.023	P=0.478	P=0.050
Cochran-Armitage Trend Test (d)	P=0.060		
Fisher Exact Test (d)		P=0.500	P=0.121
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	2.7%	7.7%	16.1%
Terminal Rates (c)	0/29 (0%)	2/26 (8%)	2/16 (13%)
Week of First Observation	100	104	95
Life Table Tests (d)	P=0.080	P=0.454	P=0.124
Incidental Tumor Tests (d)	P=0.101	P=0.384	P=0.161
Cochran-Armitage Trend Test (d)	P=0.222		
Fisher Exact Test (d)		P=0.500	P=0.309
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	7/48 (15%)	3/47 (6%)	10/49 (20%)
Adjusted Rates (b)	24.0%	10.0%	44.3%
Terminal Rates (c)	6/28 (21%)	2/25 (8%)	6/16 (38%)
Week of First Observation	101	69	75
Life Table Tests (d)	P=0.045	P=0.202N	P=0.045
Incidental Tumor Tests (d)	P=0.154	P=0.168N	P=0.201
Cochran-Armitage Trend Test (d)	P=0.244		
Fisher Exact Test (d)		P=0.167N	P=0.314
All Sites: Benign Tumors			
Overall Rates (a)	39/50 (78%)	37/50 (74%)	36/50 (72%)
Adjusted Rates (b)	90.6%	92.3%	100.0%
Terminal Rates (c)	25/29 (86%)	23/26 (88%)	16/16 (100%)
Week of First Observation	94	69	75
Life Table Tests (d)	P=0.002	P=0.352	P=0.002
Incidental Tumor Tests (d)	P=0.019	P=0.195	P=0.019
Cochran-Armitage Trend Test (d)	P=0.283N		
Fisher Exact Test (d)		P=0.408N	P=0.323N

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

	Vehicle Control	500 mg/kg	1,000 mg/kg
All Sites: Malignant Tumors			
Overall Rates (a)	22/50 (44%)	21/50 (42%)	17/50 (34%)
Adjusted Rates (b)	51.7%	51.0%	61.0%
Terminal Rates (c)	10/29 (34%)	7/26 (27%)	6/16 (38%)
Week of First Observation	79	67	82
Life Table Tests (d)	P=0.194	P=0.402	P=0.187
Incidental Tumor Tests (d)	P=0.372N	P=0.548	P=0.590
Cochran-Armitage Trend Test (d)	P=0.179N		
Fisher Exact Test (d)		P=0.500N	P=0.206N
All Sites: All Tumors			
Overall Rates (a)	44/50 (88%)	45/50 (90%)	38/50 (76%)
Adjusted Rates (b)	93.6%	97.8%	100.0%
Terminal Rates (c)	26/29 (90%)	25/26 (96%)	16/16 (100%)
Week of First Observation	79	67	75
Life Table Tests (d)	P=0.007	P=0.162	P=0.006
Incidental Tumor Tests (d)	P=0.140	P=0.074	P=0.090
Cochran-Armitage Trend Test (d)	P=0.063N		
Fisher Exact Test (d)		P=0.500	P=0.097N

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

TABLE B4a. HISTORICAL INCIDENCE OF THYROID GLAND C-CELL TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Springborn Institute for Bioresearch, Inc.			
Ampicillin trihydrate	1/50 (2%)	2/50 (4%)	2/50 (4%)
Overall Historical Incidence			
TOTAL	131/1,668 (7.9%)	59/1,668 (3.5%)	186/1,668 (11.2%)
SD (b)	6.53%	3.09%	6.88%
Range (c)			
High	15/50	5/49	15/50
Low	0/50	0/50	0/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE B4b. HISTORICAL INCIDENCE OF MAMMARY GLAND FIBROADENOMAS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls
Historical Incidence at Springborn Institute for Bioresearch, Inc.	
Ampicillin trihydrate	16/50 (32%)
Overall Historical Incidence	
TOTAL	436/1,700 (25.6%)
SD (b)	7.49%
Range (c)	
High	20/50
Low	6/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

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

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Hamartoma	1 (2%)		
Epidermal inclusion cyst	2 (4%)		
*Subcutaneous tissue	(50)	(50)	(50)
Inflammation, NOS			1 (2%)
Inflammation, suppurative			2 (4%)
Necrosis, fat		1 (2%)	
RESPIRATORY SYSTEM			
*Nasal mucosa	(50)	(50)	(50)
Foreign body, NOS		1 (2%)	
Lymphocytic inflammatory infiltrate	32 (64%)	36 (72%)	35 (70%)
Inflammation, suppurative	7 (14%)	6 (12%)	21 (42%)
Inflammation, chronic focal		1 (2%)	
*Larynx	(50)	(50)	(50)
Inflammation, chronic focal			1 (2%)
#Trachea	(48)	(50)	(46)
Inflammation, suppurative		1 (2%)	1 (2%)
Inflammation, chronic		1 (2%)	
#Lung/bronchus	(49)	(50)	(50)
Fibrosis			1 (2%)
#Lung	(49)	(50)	(50)
Congestion, acute	3 (6%)	6 (12%)	13 (26%)
Edema, NOS	1 (2%)		1 (2%)
Hemorrhage			1 (2%)
Lymphocytic inflammatory infiltrate	3 (6%)	3 (6%)	
Inflammation, interstitial	5 (10%)	4 (8%)	2 (4%)
Pneumonia, aspiration			7 (14%)
Inflammation, suppurative	1 (2%)	1 (2%)	3 (6%)
Inflammation, chronic focal	2 (4%)		1 (2%)
Inflammation, granulomatous	2 (4%)		1 (2%)
Histiocytosis	1 (2%)		1 (2%)
HEMATOPOIETIC SYSTEM			
*Blood erythrocytes	(50)	(50)	(50)
Reticulocytosis	7 (14%)	1 (2%)	4 (8%)
Normoblastosis	6 (12%)	5 (10%)	5 (10%)
#Bone marrow	(49)	(50)	(50)
Myelofibrosis			1 (2%)
Hyperplasia, erythroid	8 (16%)	2 (4%)	5 (10%)
Hyperplasia, granulocytic	9 (18%)	4 (8%)	7 (14%)
#Spleen	(49)	(49)	(48)
Depletion, lymphoid	2 (4%)	1 (2%)	
Plasmacytosis			1 (2%)
Hyperplasia, lymphoid	1 (2%)		
#Splenic follicles	(49)	(49)	(48)
Atrophy, diffuse			1 (2%)
#Splenic red pulp	(49)	(49)	(48)
Congestion, NOS	1 (2%)	1 (2%)	1 (2%)
Hemosiderosis	4 (8%)		
Atrophy, diffuse	2 (4%)		
Hematopoiesis	7 (14%)	7 (14%)	9 (19%)

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Mandibular lymph node	(47)	(50)	(45)
Hemorrhage	1 (2%)		1 (2%)
Inflammation, acute suppurative			1 (2%)
Plasmacytosis	5 (11%)		1 (2%)
Hyperplasia, lymphoid	7 (15%)	11 (22%)	10 (22%)
#Cervical lymph node	(47)	(50)	(45)
Hyperplasia, lymphoid		1 (2%)	
#Mediastinal lymph node	(47)	(50)	(45)
Hemorrhage	5 (11%)	2 (4%)	1 (2%)
Inflammation, granulomatous focal	1 (2%)		
Hemosiderosis	3 (6%)		
Histiocytosis	1 (2%)		
Hyperplasia, lymphoid	2 (4%)	1 (2%)	1 (2%)
#Mesenteric lymph node	(47)	(50)	(45)
Edema, NOS			1 (2%)
Hemorrhage	1 (2%)	1 (2%)	1 (2%)
Hemosiderosis	1 (2%)		1 (2%)
Histiocytosis			1 (2%)
Hyperplasia, lymphoid	2 (4%)		1 (2%)
#Renal lymph node	(47)	(50)	(45)
Hyperplasia, lymphoid		1 (2%)	
#Lung/bronchus	(49)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)		
#Liver	(50)	(49)	(50)
Hematopoiesis	5 (10%)		4 (8%)
#Peyer's patch	(49)	(48)	(47)
Hyperplasia, lymphoid	2 (4%)		
#Adrenal cortex	(49)	(49)	(49)
Hematopoiesis	2 (4%)		2 (4%)
#Adrenal medulla	(49)	(49)	(49)
Hematopoiesis		1 (2%)	
#Thymus	(40)	(38)	(41)
Congestion, acute	1 (3%)		
Hemorrhage	1 (3%)		
Hyperplasia, lymphoid	1 (3%)		
CIRCULATORY SYSTEM			
#Myocardium	(50)	(50)	(50)
Inflammation, chronic focal			1 (2%)
Inflammation, granulomatous focal			1 (2%)
Degeneration, NOS	22 (44%)	17 (34%)	16 (32%)
Hemosiderosis	1 (2%)		
*Hepatic vein	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)		
DIGESTIVE SYSTEM			
#Salivary gland	(47)	(46)	(48)
Inflammation, chronic focal	1 (2%)		
Atrophy, focal	1 (2%)		
Regeneration, NOS	2 (4%)		
#Liver	(50)	(49)	(50)
Hemorrhage	1 (2%)		
Inflammation, chronic focal	7 (14%)	23 (47%)	16 (32%)
Inflammation, granulomatous focal	1 (2%)		1 (2%)
Necrosis, focal			1 (2%)
Cytoplasmic vacuolization	2 (4%)		3 (6%)
Basophilic cyto change	34 (68%)	25 (51%)	23 (46%)
Focal cellular change	4 (8%)	4 (8%)	6 (12%)
Atrophy, focal	2 (4%)		

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

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM			
#Liver (Continued)	(50)	(49)	(50)
Hyperplasia, focal	1 (2%)	1 (2%)	
Angiectasis	1 (2%)		2 (4%)
#Liver/centrilobular	(50)	(49)	(50)
Congestion, acute		1 (2%)	1 (2%)
Degeneration, NOS		6 (12%)	4 (8%)
Necrosis, NOS	1 (2%)	1 (2%)	
Angiectasis	1 (2%)		1 (2%)
#Liver/periportal	(50)	(49)	(50)
Lymphocytic inflammatory infiltrate		1 (2%)	
#Bile duct	(50)	(49)	(50)
Hyperplasia, NOS	20 (40%)	7 (14%)	6 (12%)
#Pancreas	(48)	(46)	(49)
Inflammation, chronic focal		1 (2%)	
Atrophy, NOS	12 (25%)	14 (30%)	13 (27%)
Atrophy, diffuse			1 (2%)
#Pancreatic duct	(48)	(46)	(49)
Hyperplasia, NOS			1 (2%)
#Esophagus	(49)	(48)	(49)
Ulcer, NOS			1 (2%)
#Gastric mucosa	(49)	(48)	(47)
Fibrosis	36 (73%)	33 (69%)	31 (66%)
#Forestomach	(49)	(48)	(47)
Ulcer, NOS	2 (4%)		
Lymphocytic inflammatory infiltrate		1 (2%)	
Hyperkeratosis		2 (4%)	3 (6%)
Acanthosis	8 (16%)	10 (21%)	8 (17%)
#Intestinal villus	(49)	(48)	(47)
Atrophy, NOS	1 (2%)		
#Jejunum	(49)	(48)	(47)
Dilatation, NOS	1 (2%)		
#Ileum	(49)	(48)	(47)
Distention	1 (2%)		
#Colon	(49)	(47)	(47)
Parasitism	8 (16%)	5 (11%)	4 (9%)
#Cecum	(49)	(47)	(47)
Hypertrophy, focal		1 (2%)	
*Rectum	(50)	(50)	(50)
Distention			1 (2%)
URINARY SYSTEM			
#Kidney	(49)	(49)	(50)
Cyst, NOS	2 (4%)	1 (2%)	1 (2%)
Congestion, acute	2 (4%)	1 (2%)	
Inflammation, interstitial		1 (2%)	
Pyelonephritis, acute	1 (2%)		
Nephrosis, NOS	42 (86%)	33 (67%)	22 (44%)
Infarct, healed		1 (2%)	
#Renal papilla	(49)	(49)	(50)
Necrosis, NOS	1 (2%)		
#Kidney/tubule	(49)	(49)	(50)
Pigmentation, NOS	1 (2%)	2 (4%)	1 (2%)
Hemosiderosis	1 (2%)		
Hypoplasia, NOS			1 (2%)
Atrophy, diffuse		1 (2%)	
#Urinary bladder	(42)	(45)	(45)
Distention	1 (2%)		
Hemorrhage	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(49)	(48)
Cyst, NOS	9 (19%)	9 (18%)	7 (15%)
Congestion, NOS			1 (2%)
Hemorrhage	1 (2%)	3 (6%)	2 (4%)
Hemosiderosis			1 (2%)
Hyperplasia, NOS	14 (29%)	10 (20%)	13 (27%)
Hyperplasia, focal		1 (2%)	
Angiectasis		1 (2%)	
#Adrenal cortex	(49)	(49)	(49)
Cyst, NOS	1 (2%)		1 (2%)
Congestion, NOS	2 (4%)	1 (2%)	2 (4%)
Necrosis, focal	1 (2%)		
Cytoplasmic vacuolization	4 (8%)	1 (2%)	
Hyperplasia, NOS		2 (4%)	
Hyperplasia, focal	19 (39%)	6 (12%)	5 (10%)
#Adrenal medulla	(49)	(49)	(49)
Hematoma, NOS		1 (2%)	
Hyperplasia, focal	12 (24%)	16 (33%)	8 (16%)
#Thyroid	(49)	(47)	(47)
Ultimobranchial cyst	1 (2%)		
Hyperplasia, C-cell	8 (16%)	13 (28%)	16 (34%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Galactocele	1 (2%)		
Inflammation, suppurative	1 (2%)		2 (4%)
Inflammation, chronic focal	1 (2%)		
Atrophy, NOS			1 (2%)
Hyperplasia, NOS	1 (2%)		4 (8%)
*Mammary duct	(50)	(50)	(50)
Distention	11 (22%)	16 (32%)	7 (14%)
Polypoid hyperplasia	1 (2%)		
*Clitoral gland	(50)	(50)	(50)
Retention of content	1 (2%)	2 (4%)	1 (2%)
Inflammation, suppurative	2 (4%)	1 (2%)	1 (2%)
Inflammation, chronic focal	3 (6%)	3 (6%)	1 (2%)
Hyperplasia, focal	1 (2%)		
*Vagina	(50)	(50)	(50)
Inflammation, acute suppurative	1 (2%)		
#Uterus	(48)	(47)	(49)
Hydrometra	2 (4%)	6 (13%)	1 (2%)
Hemorrhage		1 (2%)	
Hematometra			1 (2%)
#Uterus/endometrium	(48)	(47)	(49)
Cyst, NOS	1 (2%)		
Inflammation, suppurative			1 (2%)
Hyperplasia, cystic	9 (19%)	7 (15%)	6 (12%)
Metaplasia, squamous			1 (2%)
#Ovary	(48)	(48)	(49)
Cyst, NOS	3 (6%)	7 (15%)	4 (8%)
Polyp, NOS	1 (2%)		
NERVOUS SYSTEM			
#Brain	(49)	(50)	(50)
Hydrocephalus, internal	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Phthisis bulbi		3 (6%)	1 (2%)
*Eye/retina	(50)	(50)	(50)
Degeneration, NOS	1 (2%)		
*Harderian gland	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	3 (6%)	1 (2%)	1 (2%)
Atrophy, NOS	1 (2%)		
*Ear canal	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	7 (14%)	12 (24%)	6 (12%)
Inflammation, suppurative		1 (2%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Osteosclerosis		1 (2%)	1 (2%)
*Mandible	(50)	(50)	(50)
Abscess, chronic	1 (2%)		
*Carpometacarpal joint	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
*Tarsal joint	(50)	(50)	(50)
Ankylosis		1 (2%)	
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Necrosis, fat	1 (2%)		
*Pleura	(50)	(50)	(50)
Inflammation, chronic focal	1 (2%)		
*Mesentery	(50)	(50)	(50)
Necrosis, fat	12 (24%)	15 (30%)	5 (10%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF PENICILLIN VK

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

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Nevus, NOS	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		
Sarcoma, NOS	6 (12%)	3 (6%)	5 (10%)
Fibroma	3 (6%)	5 (10%)	1 (2%)
Fibrosarcoma	1 (2%)	2 (4%)	3 (6%)
Lipoma		1 (2%)	
Neurofibrosarcoma	2 (4%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(49)
Hepatocellular carcinoma, metastatic	4 (8%)	1 (2%)	1 (2%)
Alveolar/bronchiolar adenoma	10 (20%)	9 (18%)	4 (8%)
Alveolar/bronchiolar carcinoma		1 (2%)	2 (4%)
Histiocytic sarcoma, metastatic	1 (2%)		
Sarcoma, NOS, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS	1 (2%)	1 (2%)	1 (2%)
Mast cell sarcoma	1 (2%)		
#Spleen	(48)	(50)	(48)
Malignant lymphoma, NOS	1 (2%)		
#Thymus	(31)	(31)	(26)
Malignant lymphoma, NOS	1 (3%)		
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hemangiosarcoma, unclear primary or meta		1 (2%)	
#Spleen	(48)	(50)	(48)
Hemangiosarcoma			1 (2%)
*Femur	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
#Liver	(50)	(49)	(49)
Hemangiosarcoma	1 (2%)	1 (2%)	3 (6%)
DIGESTIVE SYSTEM			
#Liver	(50)	(49)	(49)
Hepatocellular adenoma	14 (28%)	15 (31%)	4 (8%)
Hepatocellular carcinoma	6 (12%)	7 (14%)	4 (8%)
Mixed hepato/cholangio carcinoma		1 (2%)	
#Forestomach	(46)	(47)	(46)
Squamous cell papilloma	2 (4%)		1 (2%)
Squamous cell carcinoma	1 (2%)		
#Pylorus	(46)	(47)	(46)
Adenomatous polyp, NOS	1 (2%)		
#Duodenum	(42)	(45)	(42)
Adenocarcinoma, NOS		1 (2%)	1 (2%)

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

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney	(50)	(49)	(50)
Tubular cell adenocarcinoma	1 (2%)		
#Urinary bladder	(46)	(43)	(47)
Transitional cell carcinoma			1 (2%)
ENDOCRINE SYSTEM			
#Adrenal/capsule	(49)	(48)	(50)
Adenoma, NOS	1 (2%)	1 (2%)	1 (2%)
#Adrenal medulla	(49)	(48)	(50)
Pheochromocytoma	4 (8%)		
#Thyroid	(50)	(47)	(48)
Follicular cell adenoma		1 (2%)	1 (2%)
#Pancreatic islets	(48)	(47)	(46)
Islet cell adenoma			1 (2%)
REPRODUCTIVE SYSTEM			
#Testis	(47)	(50)	(50)
Interstitial cell tumor		1 (2%)	
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	5 (10%)	3 (6%)	3 (6%)
MUSCULOSKELETAL SYSTEM			
*Skeletal muscle	(50)	(50)	(50)
Sarcoma, NOS, invasive	1 (2%)		
*Abdominal muscle	(50)	(50)	(50)
Neurofibrosarcoma, metastatic	1 (2%)		
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Tubular cell adenocarcinoma, metastatic	1 (2%)		
Sarcoma, NOS, metastatic	1 (2%)		1 (2%)
Sarcoma, NOS, unclear primary or metastatic		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	15	9	20
Moribund sacrifice	9	4	4
Terminal sacrifice	24	36	26
Dosing accident	2	1	

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

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	36	35	29
Total primary tumors	65	55	37
Total animals with benign tumors	26	29	15
Total benign tumors	41	36	16
Total animals with malignant tumors	21	15	20
Total malignant tumors	24	17	21
Total animals with secondary tumors##	9	2	2
Total secondary tumors	9	2	2
Total animals with tumors uncertain--primary or metastatic		2	
Total uncertain tumors		2	

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

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

ANIMAL NUMBER	0015	0032	0020	0034	0037	0040	0012	0117	0043	0022	0033	0008	0055	0038	0027	0029	0042	0016	0026	0031	0046	0041	0049	0001	0002
WEEKS ON STUDY	012	030	048	054	060	073	080	081	081	082	083	088	094	094	095	096	096	099	099	099	099	101	101	102	103
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nevus, NOS																								X	
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																	X								
Sarcoma, NOS				X				X					X	X						X					
Fibroma																X						X			
Fibrosarcoma																							X		
Neurofibrosarcoma																				X					
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic							X	X	X												X				
Alveolar/bronchiolar adenoma									X				X				X		X			X		X	
Histiocytic sarcoma, metastatic																	X								
Trachea	−	−	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	−	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS																									
Lymph nodes	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Thymus	−	+	+	−	+	+	−	+	+	+	−	+	+	−	−	−	−	+	+	−	−	+	+	−	−
Malignant lymphoma, NOS																							X		
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma						X				X							X							X	
Hepatocellular carcinoma							X	X	X			X									X				
Hemangiosarcoma					X																				
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	+	+	N	+	N	+	N	+	N	+	N	+	+	+	N	+	+	N	+
Pancreas	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	−	+	+	+	+	+	+	−	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																							X		
Squamous cell carcinoma																									
Adenomatous polyp																									
Small intestine	+	−	−	−	+	+	+	+	−	+	−	−	−	+	−	+	+	+	+	+	+	+	+	+	+
Large intestine	+	−	−	+	+	+	+	+	−	+	−	+	+	+	−	+	+	+	+	+	+	+	+	−	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma																								X	
Urinary bladder	+	+	−	+	−	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	+	+	+	+	+	−	+	−	+	+
Adrenal	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																						X			
Pheochromocytoma																		X				X			
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	−	−	−	−	+	+	+	−	−	+	+	+	+	−	−	+	+	+	−	−	+	−	−	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																X		X				X		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
Hemangiosarcoma																									
Muscle	+	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, invasive													X												
Neurofibrosarcoma, metastatic																				X					
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Tubular cell adenocarcinoma, metastatic																								X	
Sarcoma, NOS, metastatic				X																					
Malignant lymphoma, NOS												X													
Mast cell sarcoma																									

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

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	003	004	006	007	009	010	011	013	014	018	019	021	023	024	025	028	030	035	036	039	044	045	047	048	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	103	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
Nevus, NOS																										1
Subcutaneous tissue	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Histiocytic sarcoma																										1
Sarcoma, NOS					X																					6
Fibroma																					X					3
Fibrosarcoma																										1
Neurofibrosarcoma																									X	2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										4
Alveolar/bronchiolar adenoma							X	X					X												X	10
Histiocytic sarcoma, metastatic																										1
Trachea	−	+	+	+	−	+	+	+	+	+	−	−	+	−	+	−	+	+	−	−	−	+	−	+	+	34
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Malignant lymphoma, NOS																		X								1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	−	+	−	−	−	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	31
Malignant lymphoma, NOS																										1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X	X	X		X	X									X	X				X			X		X	14
Hepatocellular carcinoma																				X						6
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	N	N	N	+	+	+	+	N	+	+	N	+	+	+	+	N	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Squamous cell papilloma			X																							2
Squamous cell carcinoma				X																						1
Adenomatous polyp																								X		1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenocarcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	−	−	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	40
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS																										1
Pheochromocytoma								X													X					4
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid	−	−	−	+	−	−	+	+	+	+	−	+	+	−	+	−	+	+	−	+	+	−	−	+	−	26
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Prostate	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	46
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS		X																								5
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
Hemangiosarcoma																					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
Sarcoma, NOS, invasive																										1
Neurofibrosarcoma, metastatic																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Tubular cell adenocarcinoma, metasta																										1
Sarcoma, NOS, metastatic																										1
Malignant lymphoma, NOS																										1
Mast cell sarcoma			X																							1

* Animals necropsied

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

ANIMAL NUMBER	047	023	026	029	020	041	036	003	033	042	045	017	005	012	001	002	004	006	007	008	009	010	011	013	014
WEEKS ON STUDY	017	023	059	067	072	081	091	097	097	097	097	099	101	102	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS								X														X			X
Fibroma																		X							
Fibrosarcoma													X												
Lipoma															X										
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																									
Alveolar/bronchiolar adenoma						X							X				X				X				
Alveolar/bronchiolar carcinoma																									
Sarcoma, NOS, metastatic								X																	
Trachea	+	−	+	+	−	+	−	+	+	−	−	+	+	+	−	+	+	+	+	−	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	−	−	−	−	−	−	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Liver	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma							X			X			X		X									X	X
Hepatocellular carcinoma											X				X								X	X	X
Mixed hepato/cholangio carcinoma						X																			
Hemangiosarcoma																				X					
Bile duct	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	+	N	N	+	N	N	N	N	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+
Pancreas	+	+	+	+	−	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
Stomach	+	−	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	−	−	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor																									
Prostate	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS							X																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																			
Hemangiosarcoma, unclear primary or metastatic																									
Malignant lymphoma, NOS																									

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	015	016	018	019	021	022	024	025	027	028	030	031	032	034	035	037	038	039	040	043	044	046	048	049	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	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										3
Fibroma	X		X						X					X												5
Fibrosarcoma												X														2
Lipoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																				X						1
Alveolar/bronchiolar adenoma							X		X			X										X			X	9
Alveolar/bronchiolar carcinoma																									X	1
Sarcoma, NOS, metastatic																										1
Trachea	−	+	+	+	−	+	−	+	−	+	+	+	+	+	−	+	−	−	+	+	−	+	+	+	+	35
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	−	+	+	+	+	−	−	+	+	−	+	+	−	+	+	+	+	−	−	+	+	−	+	+	31
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma	X			X		X		X					X	X			X		X					X		15
Hepatocellular carcinoma													X							X						7
Mixed hepato/cholangio carcinoma																										1
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenocarcinoma, NOS							X																			1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	42
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	43
ENDOCRINE SYSTEM																										
Pituitary	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adrenal	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	48
Adenoma, NOS																							X			1
Thyroid	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular cell adenoma																X										1
Parathyroid	−	+	+	−	+	−	−	+	−	+	+	+	+	+	−	+	−	−	−	+	−	+	+	+	+	27
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor										X																1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS					X																					3
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 metastat																										1
Hemangiosarcoma, unclear prim or meta															X											1
Malignant lymphoma, NOS												X														1

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF PENICILLIN VK: HIGH DOSE

ANIMAL NUMBER	0007	0003	0445	0116	0441	0442	0443	0444	0222	0440	0225	0339	0005	0229	0334	0220	0448	0449	0335	0446	0447	0550	0110	0332	0001
WEEKS ON STUDY	017	025	044	051	051	051	051	051	058	062	063	064	067	073	085	088	091	092	095	097	097	097	101	101	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N
Sarcoma, NOS															X		X	X	X						
Fibroma																			X						
Fibrosarcoma				X																					
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic													X												
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	–	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph nodes	+	+	–	+	+	+	+	–	+	–	+	+	+	+	+	+	–	–	–	+	+	+	+	+	+
Thymus	+	–	–	–	–	–	–	–	–	+	–	+	–	–	–	–	–	–	+	+	–	+	+	+	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma										X		X	X												
Hemangiosarcoma														X											X
Bile duct	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	N	N	+	N	N	N	N	N	N	+	N	+	N	N	N	+	N	+	N	+	+	+
Pancreas	+	+	–	+	+	–	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Stomach	+	+	–	+	–	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	+	–	+	–	+	+	+	–	–	+	+	+	+	+	–	–	–	+	–	+	+	+	+	+
Adenocarcinoma, NOS																					X				
Large intestine	+	+	–	+	+	+	+	+	–	–	+	+	+	+	+	+	–	–	+	–	+	–	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	–	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	–	–	+	+	+	+	+	+	+	–
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Thyroid	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	–	+	–	+	+	–	+	+	+	+	–	+	+	+	–	+	–	+	–	+	+	+	+	+	+
Pancreatic islets	+	+	–	+	+	–	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS															X								X	X	
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS, metastatic															X										
Malignant lymphoma, NOS																									

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	002	004	006	008	009	011	012	013	014	015	017	018	019	021	023	024	026	027	028	030	031	033	036	037	038	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																						X				5
Fibroma																										1
Fibrosarcoma																			X						X	3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma			X								X											X		X		4
Alveolar/bronchiolar carcinoma										X									X							2
Trachea	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	42
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																X										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Thymus	−	+	+	+	+	+	+	+	−	−	+	−	+	+	−	+	+	+	+	−	+	+	+	−	+	26
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma	X	X													X	X										4
Hepatocellular carcinoma																				X						4
Hemangiosarcoma																								X		3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Squamous cell papilloma																							X			1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Adenocarcinoma, NOS																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	42
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Transitional cell carcinoma													X													1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	−	+	+	+	−	+	+	+	−	+	+	+	−	+	+	+	+	+	+	41
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS									X																	1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma																									X	1
Parathyroid	+	+	+	−	−	+	+	+	+	+	+	+	+	−	+	−	+	−	−	+	−	+	+	+	−	35
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
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	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																										3
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS, metastatic																										1
Malignant lymphoma, NOS														X												1

* Animals necropsied

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

	Vehicle Control	500 mg/kg	1,000 mg/kg
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	3/50 (6%)	5/50 (10%)	1/50 (2%)
Adjusted Rates (b)	10.1%	13.9%	3.1%
Terminal Rates (c)	1/24 (4%)	5/36 (14%)	0/26 (0%)
Week of First Observation	96	104	95
Life Table Tests (d)	P=0.245N	P=0.564	P=0.326N
Incidental Tumor Tests (d)	P=0.370N	P=0.430	P=0.535N
Cochran-Armitage Trend Test (d)	P=0.264N		
Fisher Exact Test (d)		P=0.357	P=0.309N
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	3.4%	5.3%	9.7%
Terminal Rates (c)	0/24 (0%)	1/36 (3%)	2/26 (8%)
Week of First Observation	101	101	51
Life Table Tests (d)	P=0.221	P=0.609	P=0.319
Incidental Tumor Tests (d)	P=0.196	P=0.387	P=0.324
Cochran-Armitage Trend Test (d)	P=0.222		
Fisher Exact Test (d)		P=0.500	P=0.309
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	4/50 (8%)	7/50 (14%)	4/50 (8%)
Adjusted Rates (b)	13.3%	18.9%	12.5%
Terminal Rates (c)	1/24 (4%)	6/36 (17%)	2/26 (8%)
Week of First Observation	96	101	51
Life Table Tests (d)	P=0.554N	P=0.488	P=0.635
Incidental Tumor Tests (d)	P=0.446	P=0.260	P=0.496
Cochran-Armitage Trend Test (d)	P=0.566		
Fisher Exact Test (d)		P=0.262	P=0.643
Subcutaneous Tissue: Sarcoma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	9/50 (18%)	5/50 (10%)	8/50 (16%)
Adjusted Rates (b)	24.7%	12.8%	23.3%
Terminal Rates (c)	2/24 (8%)	3/36 (8%)	3/26 (12%)
Week of First Observation	54	97	51
Life Table Tests (d)	P=0.477N	P=0.098N	P=0.551N
Incidental Tumor Tests (d)	P=0.417	P=0.360N	P=0.476
Cochran-Armitage Trend Test (d)	P=0.444N		
Fisher Exact Test (d)		P=0.194N	P=0.500N
Subcutaneous Tissue: Fibroma, Sarcoma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	12/50 (24%)	10/50 (20%)	8/50 (16%)
Adjusted Rates (b)	32.7%	26.0%	23.3%
Terminal Rates (c)	3/24 (13%)	8/36 (22%)	3/26 (12%)
Week of First Observation	54	97	51
Life Table Tests (d)	P=0.210N	P=0.173N	P=0.289N
Incidental Tumor Tests (d)	P=0.415N	P=0.531N	P=0.497N
Cochran-Armitage Trend Test (d)	P=0.191N		
Fisher Exact Test (d)		P=0.405N	P=0.227N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	10/50 (20%)	9/50 (18%)	4/49 (8%)
Adjusted Rates (b)	30.6%	23.3%	15.4%
Terminal Rates (c)	4/24 (17%)	7/36 (19%)	4/26 (15%)
Week of First Observation	81	81	104
Life Table Tests (d)	P=0.055N	P=0.237N	P=0.083N
Incidental Tumor Tests (d)	P=0.139N	P=0.584N	P=0.175N
Cochran-Armitage Trend Test (d)	P=0.068N		
Fisher Exact Test (d)		P=0.500N	P=0.080N

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

	Vehicle Control	500 mg/kg	1,000 mg/kg
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	10/50 (20%)	9/50 (18%)	6/49 (12%)
Adjusted Rates (b)	30.6%	23.3%	23.1%
Terminal Rates (c)	4/24 (17%)	7/36 (19%)	6/26 (23%)
Week of First Observation	81	81	104
Life Table Tests (d)	P=0.157N	P=0.237N	P=0.209N
Incidental Tumor Tests (d)	P=0.308N	P=0.584N	P=0.367N
Cochran-Armitage Trend Test (d)	P=0.185N		
Fisher Exact Test (d)		P=0.500N	P=0.220N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	9.8%	2.8%	3.8%
Terminal Rates (c)	1/24 (4%)	1/36 (3%)	1/26 (4%)
Week of First Observation	88	104	104
Life Table Tests (d)	P=0.186N	P=0.209N	P=0.306N
Incidental Tumor Tests (d)	P=0.267N	P=0.381N	P=0.402N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test (d)		P=0.309N	P=0.309N
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	2/50 (4%)	(e) 2/50 (4%)	4/50 (8%)
Adjusted Rates (b)	6.3%	5.6%	13.9%
Terminal Rates (c)	1/24 (4%)	2/36 (6%)	3/26 (12%)
Week of First Observation	60	104	73
Life Table Tests (d)	P=0.247	P=0.579N	P=0.339
Incidental Tumor Tests (d)	P=0.343	P=0.581N	P=0.470
Cochran-Armitage Trend Test (d)	P=0.252		
Fisher Exact Test (d)		P=0.691	P=0.339
Liver: Hepatocellular Adenoma			
Overall Rates (a)	14/50 (28%)	15/49 (31%)	4/49 (8%)
Adjusted Rates (b)	46.4%	38.0%	15.4%
Terminal Rates (c)	9/24 (38%)	12/36 (33%)	4/26 (15%)
Week of First Observation	73	91	104
Life Table Tests (d)	P=0.006N	P=0.258N	P=0.008N
Incidental Tumor Tests (d)	P=0.015N	P=0.561N	P=0.012N
Cochran-Armitage Trend Test (d)	P=0.013N		
Fisher Exact Test (d)		P=0.474	P=0.010N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	6/50 (12%)	7/49 (14%)	4/49 (8%)
Adjusted Rates (b)	15.6%	18.6%	11.0%
Terminal Rates (c)	1/24 (4%)	6/36 (17%)	1/26 (4%)
Week of First Observation	80	97	62
Life Table Tests (d)	P=0.343N	P=0.531N	P=0.441N
Incidental Tumor Tests (d)	P=0.344N	P=0.340	P=0.373N
Cochran-Armitage Trend Test (d)	P=0.331N		
Fisher Exact Test (d)		P=0.484	P=0.384N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	19/50 (38%)	18/49 (37%)	8/49 (16%)
Adjusted Rates (b)	52.8%	44.6%	25.2%
Terminal Rates (c)	9/24 (38%)	14/36 (39%)	5/26 (19%)
Week of First Observation	73	91	62
Life Table Tests (d)	P=0.012N	P=0.138N	P=0.022N
Incidental Tumor Tests (d)	P=0.019N	P=0.582N	P=0.014N
Cochran-Armitage Trend Test (d)	P=0.013N		
Fisher Exact Test (d)		P=0.531N	P=0.013N

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

	Vehicle Control	500 mg/kg	1,000 mg/kg
Forestomach: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	3/46 (7%)	0/47 (0%)	1/46 (2%)
Adjusted Rates (b)	11.5%	0.0%	3.8%
Terminal Rates (c)	2/24 (8%)	0/36 (0%)	1/26 (4%)
Week of First Observation	101		104
Life Table Tests (d)	P=0.152N	P=0.067N	P=0.288N
Incidental Tumor Tests (d)	P=0.202N	P=0.110N	P=0.349N
Cochran-Armitage Trend Test (d)	P=0.175N		
Fisher Exact Test (d)		P=0.117N	P=0.308N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	4/49 (8%)	0/48 (0%)	0/50 (0%)
Adjusted Rates (b)	14.2%	0.0%	0.0%
Terminal Rates (c)	2/24 (8%)	0/34 (0%)	0/26 (0%)
Week of First Observation	99		
Life Table Tests (d)	P=0.012N	P=0.035N	P=0.067N
Incidental Tumor Tests (d)	P=0.029N	P=0.079N	P=0.113N
Cochran-Armitage Trend Test (d)	P=0.015N		
Fisher Exact Test (d)		P=0.061N	P=0.056N
Harderian Gland: Adenoma			
Overall Rates (a)	5/50 (10%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	16.1%	7.7%	9.7%
Terminal Rates (c)	1/24 (4%)	2/36 (6%)	0/26 (0%)
Week of First Observation	96	91	85
Life Table Tests (d)	P=0.294N	P=0.220N	P=0.390N
Incidental Tumor Tests (d)	P=0.572	P=0.536N	P=0.573
Cochran-Armitage Trend Test (d)	P=0.283N		
Fisher Exact Test (d)		P=0.357N	P=0.357N
All Sites: Benign Tumors			
Overall Rates (a)	26/50 (52%)	29/50 (58%)	15/50 (30%)
Adjusted Rates (b)	71.1%	72.2%	49.5%
Terminal Rates (c)	14/24 (58%)	25/36 (69%)	11/26 (42%)
Week of First Observation	73	81	85
Life Table Tests (d)	P=0.013N	P=0.165N	P=0.028N
Incidental Tumor Tests (d)	P=0.061N	P=0.512	P=0.093N
Cochran-Armitage Trend Test (d)	P=0.018N		
Fisher Exact Test (d)		P=0.344	P=0.021N
All Sites: Malignant Tumors			
Overall Rates (a)	21/50 (42%)	15/50 (30%)	20/50 (40%)
Adjusted Rates (b)	52.1%	37.0%	53.5%
Terminal Rates (c)	7/24 (29%)	11/36 (31%)	10/26 (38%)
Week of First Observation	54	81	51
Life Table Tests (d)	P=0.493N	P=0.035N	P=0.556N
Incidental Tumor Tests (d)	P=0.401	P=0.295N	P=0.477
Cochran-Armitage Trend Test (d)	P=0.459N		
Fisher Exact Test (d)		P=0.149N	P=0.500N
All Sites: All Tumors			
Overall Rates (a)	36/50 (72%)	35/50 (70%)	29/50 (58%)
Adjusted Rates (b)	81.3%	83.2%	75.7%
Terminal Rates (c)	16/24 (67%)	29/36 (81%)	17/26 (65%)
Week of First Observation	54	81	51
Life Table Tests (d)	P=0.126N	P=0.033N	P=0.202N
Incidental Tumor Tests (d)	P=0.279N	P=0.484N	P=0.311N
Cochran-Armitage Trend Test (d)	P=0.084N		
Fisher Exact Test (d)		P=0.500N	P=0.104N

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

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

TABLE C4. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Springborn Institute for Bioresearch, Inc.			
Ampicillin trihydrate	3/50 (6%)	6/50 (12%)	9/50 (18%)
Overall Historical Incidence			
TOTAL	254/1,736 (14.6%)	347/1,736 (20.0%)	569/1,736 (32.8%)
SD (b)	6.55%	7.39%	8.52%
Range (c)			
High	14/50	19/50	25/50
Low	0/50	3/49	7/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

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

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Ulcer, acute	2 (4%)		
Inflammation, acute focal	1 (2%)	2 (4%)	
Inflammation, acute/chronic			1 (2%)
Inflammation, chronic focal	1 (2%)		
Erosion	1 (2%)		1 (2%)
Parasitism	8 (16%)	6 (12%)	9 (18%)
Alopecia	5 (10%)	1 (2%)	
Hyperplasia, epithelial	2 (4%)	5 (10%)	11 (22%)
Hyperkeratosis	5 (10%)		2 (4%)
Parakeratosis			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Inflammation, acute focal		1 (2%)	
Abscess, NOS	1 (2%)	1 (2%)	
Inflammation, acute/chronic	1 (2%)		1 (2%)
Inflammation, chronic focal	1 (2%)		
Fibrosis, focal	1 (2%)		
Fibrosis, diffuse	1 (2%)		
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Inflammation, acute focal	13 (26%)	5 (10%)	4 (8%)
Inflammation, acute/chronic	1 (2%)		
Fibrosis, focal	1 (2%)		
Fibrosis, multifocal	1 (2%)		
Foreign material, NOS	15 (30%)	2 (4%)	3 (6%)
Metaplasia, NOS		1 (2%)	
#Trachea	(34)	(35)	(42)
Hyperplasia, epithelial	1 (3%)		
#Lung	(50)	(50)	(49)
Foreign body, NOS	1 (2%)		
Congestion, acute passive	2 (4%)	5 (10%)	7 (14%)
Edema, NOS		1 (2%)	
Hemorrhage	1 (2%)	1 (2%)	
Lymphocytic inflammatory infiltrate		4 (8%)	1 (2%)
Inflammation, interstitial	1 (2%)	1 (2%)	
Inflammation, acute focal	1 (2%)		1 (2%)
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic focal			1 (2%)
Hyperplasia, alveolar epithelium	2 (4%)		
Histiocytosis	1 (2%)	2 (4%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hyperplasia, lymphoid	2 (4%)	1 (2%)	1 (2%)
#Bone marrow	(50)	(50)	(49)
Congestion, acute passive	1 (2%)		
Hyperplasia, hematopoietic	29 (58%)	30 (60%)	26 (53%)
#Spleen	(48)	(50)	(48)
Atrophy, diffuse	1 (2%)		
Leukemoid reaction		3 (6%)	2 (4%)
Hyperplasia, lymphoid	8 (17%)	17 (34%)	12 (25%)
Hematopoiesis	15 (31%)	5 (10%)	10 (21%)

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Lymph node	(48)	(48)	(44)
Inflammation, chronic focal			1 (2%)
Pigmentation, NOS			1 (2%)
Hemosiderosis	2 (4%)		
Histiocytosis	1 (2%)		
Hyperplasia, lymphoid	3 (6%)	8 (17%)	3 (7%)
#Mandibular lymph node	(48)	(48)	(44)
Histiocytosis	1 (2%)		1 (2%)
Plasmacytosis			1 (2%)
Hyperplasia, lymphoid	3 (6%)	12 (25%)	4 (9%)
#Pancreatic lymph node	(48)	(48)	(44)
Hyperplasia, lymphoid		1 (2%)	
#Mesenteric lymph node	(48)	(48)	(44)
Hemorrhage	2 (4%)	2 (4%)	1 (2%)
Inflammation, chronic focal	1 (2%)		
Histiocytosis	3 (6%)		
Leukemoid reaction		1 (2%)	
Plasmacytosis	1 (2%)		
Hyperplasia, reticulum cell	1 (2%)		
Hyperplasia, lymphoid	4 (8%)	15 (31%)	9 (20%)
Hematopoiesis	1 (2%)	5 (10%)	4 (9%)
Erythropoiesis	1 (2%)		
#Thymic lymph node	(48)	(48)	(44)
Hemorrhage		1 (2%)	
Hyperplasia, lymphoid		1 (2%)	
#Lung	(50)	(50)	(49)
Hyperplasia, lymphoid		1 (2%)	1 (2%)
#Liver	(50)	(49)	(49)
Hematopoiesis	1 (2%)		1 (2%)
#Forestomach	(46)	(47)	(46)
Mastocytosis	1 (2%)		
#Peyer's patch	(42)	(45)	(42)
Hyperplasia, lymphoid		4 (9%)	
#Kidney	(50)	(49)	(50)
Hyperplasia, lymphoid		1 (2%)	1 (2%)
#Thymus	(31)	(31)	(26)
Inflammation, granulomatous focal			1 (4%)
Hyperplasia, epithelial	2 (6%)		
Hyperplasia, lymphoid	1 (3%)		2 (8%)
CIRCULATORY SYSTEM			
#Heart	(50)	(50)	(50)
Degeneration, NOS	1 (2%)		
#Myocardium	(50)	(50)	(50)
Inflammation, acute focal	2 (4%)		
Inflammation, chronic focal		2 (4%)	
Degeneration, NOS	1 (2%)	1 (2%)	
#Tricuspid valve	(50)	(50)	(50)
Pigmentation, NOS		1 (2%)	
*Superior pancreaticoduodenal artery	(50)	(50)	(50)
Inflammation, chronic focal	1 (2%)		
DIGESTIVE SYSTEM			
*Tooth	(50)	(50)	(50)
Deformity, NOS		1 (2%)	
Dysplasia, NOS	25 (50%)	43 (86%)	33 (66%)
*Pulp of tooth	(50)	(50)	(50)
Inflammation, acute focal	1 (2%		
#Salivary gland	(49)	(49)	(49)
Lymphocytic inflammatory infiltrate		1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Liver	(50)	(49)	(49)
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic focal	1 (2%)		
Necrosis, focal	1 (2%)		2 (4%)
Necrosis, coagulative		1 (2%)	1 (2%)
Necrosis, fat	1 (2%)		
Amyloidosis		1 (2%)	
Focal cellular change			5 (10%)
Eosinophilic cyto change		1 (2%)	
Cell size alteration	3 (6%)	1 (2%)	
#Liver/hepatocytes	(50)	(49)	(49)
Cytoplasmic vacuolization	1 (2%)	1 (2%)	1 (2%)
*Gallbladder	(50)	(50)	(50)
Eosinophilic cyto change	1 (2%)	15 (30%)	15 (30%)
#Bile duct	(50)	(49)	(49)
Cyst, NOS	1 (2%)		
#Pancreas	(48)	(47)	(46)
Dilatation/ducts	1 (2%)		
Inflammation, chronic focal		1 (2%)	2 (4%)
#Pancreatic acinus	(48)	(47)	(46)
Atrophy, focal	2 (4%)	5 (11%)	1 (2%)
Atrophy, diffuse		1 (2%)	
Hyperplasia, focal	2 (4%)		
#Esophagus	(49)	(46)	(48)
Dilatation, NOS	1 (2%)		
Hyperkeratosis	1 (2%)		
#Gastric fundal gland	(46)	(47)	(46)
Dilatation, NOS	3 (7%)	3 (6%)	16 (35%)
Eosinophilic cyto change	2 (4%)	32 (68%)	43 (93%)
#Glandular stomach	(46)	(47)	(46)
Cyst, NOS		8 (17%)	20 (43%)
Ulcer, NOS		1 (2%)	1 (2%)
Inflammation, acute focal			1 (2%)
Inflammation, chronic focal	1 (2%)	11 (23%)	21 (46%)
Fibrosis		1 (2%)	13 (28%)
Hyperplasia, NOS			1 (2%)
Hyperplasia, epithelial	1 (2%)	26 (55%)	34 (74%)
Squamous metaplasia		1 (2%)	7 (15%)
#Forestomach	(46)	(47)	(46)
Ulcer, NOS	3 (7%)		
Inflammation, acute focal		2 (4%)	
Inflammation, chronic focal	6 (13%)	1 (2%)	1 (2%)
Hyperplasia, epithelial	6 (13%)		2 (4%)
Hyperkeratosis	1 (2%)		1 (2%)
#Small intestine/serosa	(42)	(45)	(42)
Inflammation, chronic focal		1 (2%)	
#Colon	(44)	(42)	(42)
Hyperplasia, focal	1 (2%)		
#Colonic mucosa	(44)	(42)	(42)
Hyperplasia, diffuse		1 (2%)	
#Colonic submucosa	(44)	(42)	(42)
Cyst, NOS		1 (2%)	
#Colonic muscularis	(44)	(42)	(42)
Cyst, NOS			1 (2%)
#Cecum	(44)	(42)	(42)
Cyst, NOS			1 (2%)
*Rectum	(50)	(50)	(50)
Hyperplasia, diffuse		1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney	(50)	(49)	(50)
Cyst, NOS	1 (2%)		1 (2%)
Congestion, acute passive		1 (2%)	
Hemorrhage		1 (2%)	
Pyelonephritis, NOS	2 (4%)		
Inflammation, acute focal	1 (2%)		
Pyelonephritis, chronic	1 (2%)		
Inflammation, chronic focal	2 (4%)		
Nephropathy	6 (12%)	1 (2%)	1 (2%)
Infarct, healed		1 (2%)	
Hyperplasia, tubular cell		2 (4%)	
Metaplasia, osseous		1 (2%)	
#Perirenal tissue	(50)	(49)	(50)
Inflammation, chronic focal		1 (2%)	
#Kidney/glomerulus	(50)	(49)	(50)
Amyloidosis		1 (2%)	
#Kidney/tubule	(50)	(49)	(50)
Mineralization	1 (2%)		
Dilatation, NOS	1 (2%)		
Cytoplasmic vacuolization	1 (2%)		
Atrophy, focal	2 (4%)	1 (2%)	
#Urinary bladder	(46)	(43)	(47)
Cast, NOS	1 (2%)	1 (2%)	2 (4%)
Ulcer, acute	1 (2%)		
Inflammation, acute focal	1 (2%)		
Hyperplasia, epithelial	1 (2%)		
*Urethra	(50)	(50)	(50)
Cast, NOS	7 (14%)	4 (8%)	4 (8%)
Hyperplasia, epithelial			2 (4%)
*Prostatic urethra	(50)	(50)	(50)
Retention of content		1 (2%)	
Cast, NOS	3 (6%)	5 (10%)	3 (6%)
Hemorrhage		1 (2%)	
Hyperplasia, epithelial		1 (2%)	
ENDOCRINE SYSTEM			
#Anterior pituitary	(40)	(44)	(41)
Cyst, NOS	2 (5%)	1 (2%)	1 (2%)
Hyperplasia, focal		2 (5%)	
#Adrenal	(49)	(48)	(50)
Cyst, NOS		1 (2%)	
#Adrenal/capsule	(49)	(48)	(50)
Hyperplasia, focal	3 (6%)	3 (6%)	2 (4%)
#Adrenal cortex	(49)	(48)	(50)
Hemorrhage	1 (2%)		
Focal cellular change	1 (2%)		
Cytoplasmic matrix alteration	1 (2%)		
Hypertrophy, focal	5 (10%)	2 (4%)	1 (2%)
Hyperplasia, focal	1 (2%)		
#Adrenal medulla	(49)	(48)	(50)
Cyst, NOS			1 (2%)
Hyperplasia, focal	3 (6%)	1 (2%)	1 (2%)
#Thyroid	(50)	(47)	(48)
Follicular cyst, NOS	1 (2%)		
Inflammation, acute focal	1 (2%)		
Hyperplasia, focal		1 (2%)	
Hyperplasia, follicular cell	1 (2%)	2 (4%)	
#Pancreatic islets	(48)	(47)	(46)
Hyperplasia, focal	4 (8%)	4 (9%)	3 (7%)

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

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM			
*Epididymal lumen	(50)	(50)	(50)
Dilatation, NOS	1 (2%)		
*Prepuce	(50)	(50)	(50)
Polyp, NOS	4 (8%)		1 (2%)
*Preputial gland	(50)	(50)	(50)
Dilatation, NOS		2 (4%)	
Abscess, NOS	2 (4%)		
Inflammation, acute/chronic	5 (10%)	2 (4%)	2 (4%)
Inflammation, chronic	1 (2%)		
Inflammation, chronic focal	6 (12%)	15 (30%)	12 (24%)
Inflammation, chronic diffuse	1 (2%)		
Hyperplasia, NOS	5 (10%)	12 (24%)	10 (20%)
Hyperkeratosis	3 (6%)	1 (2%)	7 (14%)
#Prostate	(46)	(49)	(50)
Cast, NOS	1 (2%)		2 (4%)
Lymphocytic inflammatory infiltrate		1 (2%)	
Inflammation, acute focal	2 (4%)	1 (2%)	
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic focal	2 (4%)		
*Seminal vesicle	(50)	(50)	(50)
Mineralization	1 (2%)		
Retention of content	9 (18%)	7 (14%)	6 (12%)
Cast, NOS	1 (2%)		
Inflammation, chronic focal	1 (2%)		
#Periprostatic tissue	(46)	(49)	(50)
Lymphocytic inflammatory infiltrate		1 (2%)	
#Testis	(47)	(50)	(50)
Inflammation, acute focal		1 (2%)	
Hyperplasia, interstitial cell	2 (4%)	3 (6%)	
#Testis/tubule	(47)	(50)	(50)
Atrophy, focal	1 (2%)		
*Epididymis	(50)	(50)	(50)
Inflammation, chronic focal		1 (2%)	1 (2%)
Granuloma, spermatic	1 (2%)		
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate		1 (2%)	
Inflammation, chronic focal	1 (2%)		
#Brain/thalamus	(50)	(50)	(50)
Mineralization	9 (18%)	12 (24%)	7 (14%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Atrophy, diffuse	3 (6%)		
*Eye/crystalline lens	(50)	(50)	(50)
Cataract		1 (2%)	
*Eye/lacrimal gland	(50)	(50)	(50)
Inflammation, chronic focal		1 (2%)	1 (2%)
*Nasolacrimal duct	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Inflammation, acute	4 (8%)	1 (2%)	
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic	1 (2%)		
*Harderian gland	(50)	(50)	(50)
Hyperplasia, NOS			1 (2%)
Hyperplasia, focal			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
MUSCULOSKELETAL SYSTEM			
*Knee joint	(50)	(50)	(50)
Ankylosis	26 (52%)	21 (42%)	20 (40%)
*Tarsal joint	(50)	(50)	(50)
Ankylosis	11 (22%)	14 (28%)	9 (18%)
*Metatarsophalangeal	(50)	(50)	(50)
Ankylosis		1 (2%)	
*Skeletal muscle	(50)	(50)	(50)
Inflammation, chronic focal			1 (2%)
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Hemorrhage			1 (2%)
*Abdominal cavity	(50)	(50)	(50)
Hermaphroditism			1 (2%)
Lymphocytic inflammatory infiltrate		1 (2%)	
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic focal			1 (2%)
*Mesentery	(50)	(50)	(50)
Inflammation, acute focal		1 (2%)	
Inflammation, chronic focal		1 (2%)	
Necrosis, fat	1 (2%)	4 (8%)	1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate		1 (2%)	
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX D

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

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

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Papilloma, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(50)	(49)	(50)
Alveolar/bronchiolar adenoma	3 (6%)	1 (2%)	3 (6%)
Alveolar/bronchiolar carcinoma	1 (2%)		2 (4%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS	15 (30%)	12 (24%)	14 (28%)
Malignant lymphoma, histiocytic type	1 (2%)	2 (4%)	
*Subcutaneous tissue	(50)	(50)	(50)
Malignant lymphoma, NOS			1 (2%)
#Spleen	(50)	(48)	(50)
Malignant lymphoma, NOS			1 (2%)
#Jejunum	(44)	(40)	(41)
Malignant lymphoma, NOS	1 (2%)		
#Ileum	(44)	(40)	(41)
Malignant lymphoma, NOS		1 (3%)	
CIRCULATORY SYSTEM			
#Liver	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
#Uterus	(49)	(47)	(50)
Hemangiosarcoma	1 (2%)		
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Hepatocellular adenoma	2 (4%)	4 (8%)	4 (8%)
Hepatocellular carcinoma	1 (2%)	1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma, metastatic			1 (2%)
#Glandular stomach	(44)	(45)	(47)
Adenoma, NOS			1 (2%)
#Forestomach	(44)	(45)	(47)
Squamous cell papilloma	5 (11%)	1 (2%)	
#Pylorus	(44)	(45)	(47)
Adenomatous polyp, NOS			1 (2%)
#Duodenal gland	(44)	(40)	(41)
Adenoma, NOS	1 (2%)		
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Anterior pituitary	(45)	(44)	(43)
Adenoma, NOS	10 (22%)	4 (9%)	6 (14%)
#Adrenal	(49)	(46)	(48)
Cortical adenoma			1 (2%)
#Adrenal/capsule	(49)	(46)	(48)
Adenoma, NOS			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(45)	(43)	(43)
Follicular cell adenoma	4 (9%)	2 (5%)	
#Pancreatic islets	(44)	(41)	(43)
Islet cell adenoma	1 (2%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Squamous cell carcinoma			1 (2%)
#Uterus	(49)	(47)	(50)
Carcinoma, NOS	1 (2%)		
Adenoma, NOS	1 (2%)		
Adenocarcinoma, NOS	1 (2%)		
Endometrial stromal polyp			1 (2%)
#Ovary	(47)	(45)	(48)
Granulosa cell tumor		1 (2%)	1 (2%)
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	2 (4%)	2 (4%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	9	15	8
Moribund sacrifice	3	4	3
Terminal sacrifice	36	31	32
Dosing accident	2		7
TUMOR SUMMARY			
Total animals with primary tumors**	38	26	30
Total primary tumors	52	32	40
Total animals with benign tumors	26	12	15
Total benign tumors	29	15	19
Total animals with malignant tumors	21	16	18
Total malignant tumors	23	16	20
Total animals with secondary tumors##			1
Total secondary tumors			1
Total animals with tumors uncertain--benign or malignant		1	1
Total uncertain tumors		1	1

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

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

ANIMAL NUMBER	0049	0044	0039	0033	0001	0046	0024	0047	0016	0034	0008	0045	0019	0014	0002	0003	0004	0005	0006	0007	0009	0010	0011	0012	0013
WEEKS ON STUDY	012	016	043	073	078	080	083	093	095	095	097	098	101	102	104	104	104	104	104	104	104	104	104	104	104
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X		X	X												
Alveolar/bronchiolar carcinoma														X											
Trachea	+	−	−	−	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	−	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Thymus	+	+	+	+	+	+	+	−	+	−	−	+	−	−	+	+	−	+	+	+	+	+	+	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma																			X						
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	N	N	N	+	N	+	N	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+
Pancreas	+	−	−	−	−	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	−	−	−	+	+	−	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma						X											X								
Small intestine	+	+	−	−	−	+	+	−	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Malignant lymphoma, NOS										X															
Large intestine	+	+	−	−	−	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	−	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS															·	X		X		X					X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																		X							
Parathyroid	+	−	−	+	−	−	−	−	+	+	−	+	−	+	−	−	+	+	−	−	−	+	+	+	+
Pancreatic islets	+	−	−	−	−	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	N	N	+	N	+	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	N	N
Uterus	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																						X			
Adenoma, NOS																									
Adenocarcinoma, NOS																							X		
Hemangiosarcoma																									
Ovary	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																			X				X		
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS			X	X	X			X				X						X		X			X		
Malignant lymphoma, histiocytic type						X																			

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

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0015	0017	0018	0020	0021	0022	0023	0025	0026	0027	0028	0029	0030	0031	0032	0035	0036	0037	0038	0040	0041	0042	0043	0048	0050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										3
Alveolar/bronchiolar carcinoma																										1
Trachea	−	+	+	+	−	+	+	+	−	−	+	+	+	+	+	+	−	−	+	+	−	+	+	+	+	37
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Thymus	−	−	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	−	+	+	+	+	−	+	37
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma										X									X							2
Hepatocellular carcinoma																										1
Hemangiosarcoma																		X								1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Squamous cell papilloma						X	X	X																		5
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenoma, NOS																	X									1
Malignant lymphoma, NOS																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	45
Adenoma, NOS														X	X	X					X	X			X	10
Adrenal	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	−	+	+	+	+	+	+	+	+	45
Follicular cell adenoma								X																	X	4
Parathyroid	+	+	−	−	−	−	−	+	−	−	+	−	+	−	+	−	−	+	−	+	+	−	−	+	−	22
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Islet cell adenoma	X																									1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	*50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS																										1
Adenoma, NOS					X																					1
Adenocarcinoma, NOS																										1
Hemangiosarcoma														X												1
Ovary	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																										2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS		X							X		X	X			X							X	X			15
Malignant lymphoma, histiocytic type																										1

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF PENICILLIN VK: LOW DOSE

ANIMAL NUMBER	00038	00488	00255	00433	00055	00399	00455	00111	00286	00411	00022	00077	00311	00322	00110	00300	00388	00161	00011	00044	00066	00088	00099	00122	00133
WEEKS ON STUDY	05 54	05 55	07 75	07 77	08 84	08 88	09 90	09 91	09 91	09 92	09 95	09 97	09 97	09 97	09 99	09 99	10 00	10 01	10 04	10 04	10 04	10 04	10 04	10 04	10 04
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	N	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	−	+	+	+	+	+	+	−	−	+	+	−	+	+	+	−	+	−	−	+	−	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	−	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Thymus	+	+	−	−	−	+	−	−	−	+	+	−	−	+	−	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																					X	X			
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	+	+	N	N	N	N	+	N	N	+	+	N	+	+	+	+	+	+	+
Pancreas	+	−	−	−	+	−	+	−	−	−	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	−	+	−	+	−	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma					X																				
Small intestine	+	−	−	+	+	−	+	−	−	−	+	−	+	+	−	+	−	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS																									
Large intestine	−	−	+	+	+	−	+	−	−	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	−	+	+	+	−	+	−	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	−	+	+	−	+	+	+	+	+	−	+	−	+	+	+	+	+	−	+	+	+	+
Adenoma, NOS								X												X					
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	−	+	+	+	+	+	−	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																				X			X		
Parathyroid	−	+	−	−	+	+	+	−	+	−	−	−	+	−	−	−	+	−	−	−	−	−	−	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	N	+	N	N	+	+	+	N	+	+	+	N	N	+	+	+	+	+	+	N	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+
Ovary	−	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor																			X						
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS							X																		
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS				X		X	X			X														X	
Malignant lymphoma, histiocytic type	X										X														

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

ANIMAL NUMBER	0 1 4	0 1 5	0 1 7	0 1 8	0 1 9	0 2 0	0 2 1	0 2 2	0 2 3	0 2 4	0 2 7	0 2 8	0 2 9	0 3 3	0 3 4	0 3 5	0 3 6	0 3 7	0 4 0	0 4 2	0 4 4	0 4 6	0 4 7	0 4 9	0 5 0	TOTAL:
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Papilloma, NOS															X											1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																				X						1
Trachea	−	+	−	−	−	−	+	−	+	−	+	+	−	−	+	+	+	+	+	−	−	−	+	+	+	30
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymus	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	39
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma							X			X																4
Hepatocellular carcinoma										X																1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Malignant lymphoma, NOS																							X			1
Large intestine	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
ENDOCRINE SYSTEM																										
Pituitary	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenoma, NOS										X										X						4
Adrenal	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	46
Thyroid	+	+	−	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	43
Follicular cell adenoma																										2
Parathyroid	−	+	−	−	−	+	+	+	+	−	−	+	+	−	−	−	+	+	+	−	−	+	+	+	−	22
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	N	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	*50
Uterus	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
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
Adenoma, NOS											X															2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS			X								X	X		X		X			X					X	12
Malignant lymphoma, histiocytic type																										2

* Animals necropsied

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

ANIMAL NUMBER	00505	00440	01414	02525	01313	04141	03331	02626	02222	03838	00004	01616	03303	00202	01101	01100	00909	03535	00101	00003	00606	00707	00808	01212	01505
WEEKS ON STUDY	00404	00404	01707	01107	04101	06106	06606	07709	08101	08101	08505	08606	09101	09202	09808	09909	10000	10303	10404	10404	10404	10404	10404	10404	10404
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X				
Alveolar/bronchiolar carcinoma										X															
Trachea	+	+	−	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	−	+	−	+	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS															X										
Lymph nodes	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	−	+	+	+	−	+	+	−	−	−	+	+	+	−	−	+	−	+	−	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																			X		X				
Hepatocellular carcinoma																			X						
Alveolar/bronchiolar carcinoma, metastatic										X															
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	N	+	+	+	N	N	N	N	N	N	N	+	N	+	+	+	N	+	N	+	+	+	N
Pancreas	−	+	−	+	+	+	+	−	+	−	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	−	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	−	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									X
Adenomatous polyp, NOS																									
Small intestine	+	−	−	+	−	+	−	−	−	−	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	−	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adrenal	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									X
Cortical adenoma																									
Thyroid	+	−	−	+	+	+	+	+	+	−	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+
Parathyroid	−	−	−	+	+	−	+	+	+	−	−	+	−	+	+	−	+	+	+	+	−	+	−	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	+	N	+	+	N	+	N	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+
Squamous cell carcinoma											X														
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Adenoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS						X				X		X	X	X				X		X		X			X

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

ANIMAL NUMBER	0171	0181	0191	0201	0211	0231	0241	0271	0281	0291	0301	0321	0341	0361	0371	0391	0422	0433	0444	0455	0466	0477	0488	0499	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Malignant lymphoma, NOS									X																	1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma													X												X	3
Alveolar/bronchiolar carcinoma									X																	2
Trachea	+	−	+	+	+	−	+	−	−	+	+	−	+	+	+	−	+	+	+	−	+	+	−	+	−	34
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, NOS																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	−	−	+	+	+	+	−	+	−	+	+	+	−	+	+	−	+	+	+	+	35
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma											X													X		4
Hepatocellular carcinoma																										1
Alveolar/bronchiolar carcinoma, metasta																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	*50
Pancreas	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Esophagus	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS																										1
Adenomatous polyp, NOS																X										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Large intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	−	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	−	+	+	+	43
Adenoma, NOS		X		X								X			X				X					X		6
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS																										1
Cortical adenoma																				X						1
Thyroid	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Parathyroid	+	−	+	−	−	−	−	−	−	+	+	−	−	+	+	−	−	+	+	−	−	−	−	−	−	23
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	*50
Squamous cell carcinoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp												X														1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
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
Adenoma, NOS					X																					1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS	X			X		X				X							X									14

* Animals necropsied

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

	Vehicle Control	500 mg/kg	1,000 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	3/50 (6%)	1/49 (2%)	3/50 (6%)
Adjusted Rates (b)	7.4%	3.1%	9.4%
Terminal Rates (c)	0/36 (0%)	1/32 (3%)	3/32 (9%)
Week of First Observation	95	104	104
Life Table Tests (d)	P=0.540	P=0.343N	P=0.603
Incidental Tumor Tests (d)	P=0.474	P=0.273N	P=0.501
Cochran-Armitage Trend Test (d)	P=0.593		
Fisher Exact Test (d)		P=0.316N	P=0.661
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	1/49 (2%)	5/50 (10%)
Adjusted Rates (b)	9.9%	3.1%	14.6%
Terminal Rates (c)	0/36 (0%)	1/32 (3%)	4/32 (13%)
Week of First Observation	95	104	81
Life Table Tests (d)	P=0.366	P=0.219N	P=0.433
Incidental Tumor Tests (d)	P=0.340	P=0.139N	P=0.386
Cochran-Armitage Trend Test (d)	P=0.421		
Fisher Exact Test (d)		P=0.187N	P=0.500
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	17/50 (34%)	15/50 (30%)	16/50 (32%)
Adjusted Rates (b)	38.5%	37.3%	40.3%
Terminal Rates (c)	10/36 (28%)	9/32 (28%)	9/32 (28%)
Week of First Observation	43	54	61
Life Table Tests (d)	P=0.479	P=0.511N	P=0.516
Incidental Tumor Tests (d)	P=0.382N	P=0.290N	P=0.452N
Cochran-Armitage Trend Test (d)	P=0.457N		
Fisher Exact Test (d)		P=0.415N	P=0.500N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	5.6%	12.5%	12.5%
Terminal Rates (c)	2/36 (6%)	4/32 (13%)	4/32 (13%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.222	P=0.283	P=0.283
Incidental Tumor Tests (d)	P=0.222	P=0.283	P=0.283
Cochran-Armitage Trend Test (d)	P=0.274		
Fisher Exact Test (d)		P=0.339	P=0.339
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	8.3%	12.5%	12.5%
Terminal Rates (c)	3/36 (8%)	4/32 (13%)	4/32 (13%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.358	P=0.435	P=0.435
Incidental Tumor Tests (d)	P=0.358	P=0.435	P=0.435
Cochran-Armitage Trend Test (d)	P=0.424		
Fisher Exact Test (d)		P=0.500	P=0.500
Forestomach: Squamous Cell Papilloma			
Overall Rates (a)	5/44 (11%)	1/45 (2%)	0/47 (0%)
Adjusted Rates (b)	13.1%	2.2%	0.0%
Terminal Rates (c)	4/36 (11%)	0/32 (0%)	0/32 (0%)
Week of First Observation	80	84	
Life Table Tests (d)	P=0.015N	P=0.122N	P=0.044N
Incidental Tumor Tests (d)	P=0.004N	P=0.084N	P=0.023N
Cochran-Armitage Trend Test (d)	P=0.009N		
Fisher Exact Test (d)		P=0.096N	P=0.024N

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

	Vehicle Control	500 mg/kg	1,000 mg/kg
Anterior Pituitary Gland: Adenoma			
Overall Rates (a)	10/45 (22%)	4/44 (9%)	6/43 (14%)
Adjusted Rates (b)	29.4%	12.1%	22.2%
Terminal Rates (c)	10/34 (29%)	3/30 (10%)	6/27 (22%)
Week of First Observation	104	91	104
Life Table Tests (d)	P=0.271N	P=0.108N	P=0.368N
Incidental Tumor Tests (d)	P=0.224N	P=0.072N	P=0.368N
Cochran-Armitage Trend Test (d)	P=0.171N		
Fisher Exact Test (d)		P=0.078N	P=0.234N
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	4/45 (9%)	2/43 (5%)	0/43 (0%)
Adjusted Rates (b)	12.1%	6.9%	0.0%
Terminal Rates (c)	4/33 (12%)	2/29 (7%)	0/30 (0%)
Week of First Observation	104	104	
Life Table Tests (d)	P=0.047N	P=0.397N	P=0.075N
Incidental Tumor Tests (d)	P=0.047N	P=0.397N	P=0.075N
Cochran-Armitage Trend Test (d)	P=0.041N		
Fisher Exact Test (d)		P=0.360N	P=0.064N
Uterus: Adenoma, Adenocarcinoma, or Carcinoma			
Overall Rates (a)	3/49 (6%)	0/47 (0%)	0/50 (0%)
Adjusted Rates (b)	8.3%	0.0%	0.0%
Terminal Rates (c)	3/36 (8%)	0/31 (0%)	0/32 (0%)
Week of First Observation	104		
Life Table Tests (d)	P=0.047N	P=0.148N	P=0.142N
Incidental Tumor Tests (d)	P=0.047N	P=0.148N	P=0.142N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.129N	P=0.117N
All Sites: Benign Tumors			
Overall Rates (a)	26/50 (52%)	12/50 (24%)	15/50 (30%)
Adjusted Rates (b)	64.8%	32.9%	46.9%
Terminal Rates (c)	22/36 (61%)	9/32 (28%)	15/32 (47%)
Week of First Observation	80	84	104
Life Table Tests (d)	P=0.035N	P=0.012N	P=0.049N
Incidental Tumor Tests (d)	P=0.017N	P=0.002N	P=0.045N
Cochran-Armitage Trend Test (d)	P=0.014N		
Fisher Exact Test (d)		P=0.004N	P=0.021N
All Sites: Malignant Tumors			
Overall Rates (a)	21/50 (42%)	16/50 (32%)	18/50 (36%)
Adjusted Rates (b)	47.1%	40.1%	44.3%
Terminal Rates (c)	13/36 (36%)	10/32 (31%)	10/32 (31%)
Week of First Observation	43	54	61
Life Table Tests (d)	P=0.466N	P=0.319N	P=0.508N
Incidental Tumor Tests (d)	P=0.237N	P=0.129N	P=0.289N
Cochran-Armitage Trend Test (d)	P=0.302N		
Fisher Exact Test (d)		P=0.204N	P=0.341N
All Sites: All Tumors			
Overall Rates (a)	38/50 (76%)	26/50 (52%)	30/50 (60%)
Adjusted Rates (b)	84.3%	63.6%	74.7%
Terminal Rates (c)	29/36 (81%)	18/32 (56%)	22/32 (69%)
Week of First Observation	43	54	61
Life Table Tests (d)	P=0.241N	P=0.075N	P=0.281N
Incidental Tumor Tests (d)	P=0.053N	P=0.005N	P=0.096N
Cochran-Armitage Trend Test (d)	P=0.061N		
Fisher Exact Test (d)		P=0.011N	P=0.067N

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

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

TABLE D4. HISTORICAL INCIDENCE OF GLANDULAR STOMACH TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence of Adenomas in Vehicle Controls
Historical Incidence at Springborn Institute for Bioresearch, Inc.	
Ampicillin trihydrate	0/47 (0%)
Overall Historical Incidence	
TOTAL	(b) 2/1,709 (0.1%)
SD (c)	0.47%
Range (d)	
High	1/50
Low	0/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Includes one adenomatous polyp; no malignant tumors have been observed; one adenomatous polyp of the pylorus was also observed.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF PENICILLIN VK

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Ulcer, acute			2 (4%)
Inflammation, active chronic			1 (2%)
Inflammation, chronic focal			2 (4%)
Inflammation, chronic diffuse	1 (2%)		
Fibrosis, focal		1 (2%)	
Parasitism		1 (2%)	
Pigmentation, NOS			1 (2%)
Hyperplasia, epithelial		1 (2%)	1 (2%)
Hyperkeratosis		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Foreign body, NOS			1 (2%)
Inflammation, acute/chronic	1 (2%)		
Abscess, chronic			1 (2%)
Necrosis, fat	1 (2%)		
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Hemorrhage	3 (6%)		1 (2%)
Inflammation, acute focal	18 (36%)	16 (32%)	9 (18%)
Inflammation, acute/chronic	8 (16%)	3 (6%)	
Foreign material, NOS	23 (46%)	17 (34%)	7 (14%)
*Nasal gland	(50)	(50)	(50)
Dilatation, NOS			1 (2%)
*Nasal turbinate	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Crystals, NOS	1 (2%)		
#Trachea	(37)	(30)	(34)
Inflammation, acute focal		1 (3%)	
#Tracheal submucosa	(37)	(30)	(34)
Lymphocytic inflammatory infiltrate			1 (3%)
Inflammation, chronic focal			1 (3%)
#Lung	(50)	(49)	(50)
Congestion, acute passive	2 (4%)	2 (4%)	4 (8%)
Edema, NOS		1 (2%)	
Hemorrhage	5 (10%)	1 (2%)	3 (6%)
Lymphocytic inflammatory infiltrate		5 (10%)	2 (4%)
Inflammation, acute focal	1 (2%)	1 (2%)	
Inflammation, acute/chronic	1 (2%)		1 (2%)
Inflammation, chronic focal		2 (4%)	2 (4%)
Inflammation, granulomatous focal		1 (2%)	
Foreign material, NOS	1 (2%)		2 (4%)
Hyperplasia, alveolar epithelium		1 (2%)	
Histiocytosis	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hyperplasia, lymphoid	6 (12%)	7 (14%)	1 (2%)
#Bone marrow	(49)	(47)	(50)
Hyperplasia, focal			1 (2%)
Myelofibrosis	1 (2%)		
Hyperplasia, hematopoietic	21 (43%)	23 (49%)	13 (26%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF PENICILLIN VK (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Spleen	(50)	(48)	(50)
Hemosiderosis		1 (2%)	
Atrophy, diffuse		1 (2%)	
Leukemoid reaction		6 (13%)	1 (2%)
Hyperplasia, hematopoietic	8 (16%)	1 (2%)	4 (8%)
Hyperplasia, lymphoid	9 (18%)	7 (15%)	11 (22%)
#Lymph node	(45)	(47)	(48)
Hyperplasia, lymphoid	1 (2%)		2 (4%)
#Mandibular lymph node	(45)	(47)	(48)
Inflammation, acute/chronic	1 (2%)	1 (2%)	
Plasmacytosis	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid	1 (2%)	4 (9%)	3 (6%)
#Bronchial lymph node	(45)	(47)	(48)
Hyperplasia, lymphoid		1 (2%)	
#Pancreatic lymph node	(45)	(47)	(48)
Hyperplasia, lymphoid	1 (2%)		
#Mesenteric lymph node	(45)	(47)	(48)
Hemorrhage	1 (2%)		
Inflammation, acute diffuse		1 (2%)	
Abscess, NOS		1 (2%)	
Inflammation, acute/chronic	1 (2%)		
Amyloidosis			1 (2%)
Histiocytosis	2 (4%)		
Hyperplasia, lymphoid	1 (2%)	2 (4%)	
#Renal lymph node	(45)	(47)	(48)
Hyperplasia, lymphoid			1 (2%)
#Thymic lymph node	(45)	(47)	(48)
Hemorrhage		1 (2%)	
Inflammation, acute/chronic		2 (4%)	
Histiocytosis	1 (2%)		
Hyperplasia, lymphoid		1 (2%)	1 (2%)
*Cortex of bone	(50)	(50)	(50)
Myelofibrosis	17 (34%)	21 (42%)	15 (30%)
#Lung	(50)	(49)	(50)
Hyperplasia, lymphoid	2 (4%)		
#Salivary gland	(47)	(48)	(49)
Hyperplasia, lymphoid			1 (2%)
#Liver	(50)	(50)	(50)
Leukemoid reaction		2 (4%)	
Hyperplasia, lymphoid	1 (2%)		
Hematopoiesis	5 (10%)		3 (6%)
#Ovary/parovarian	(47)	(45)	(48)
Hyperplasia, lymphoid	1 (2%)		
#Adrenal	(49)	(46)	(48)
Hematopoiesis	1 (2%)		
#Thymus	(37)	(39)	(35)
Inflammation, acute/chronic	1 (3%)		
Hyperplasia, lymphoid	4 (11%)	2 (5%)	6 (17%)
CIRCULATORY SYSTEM			
#Heart	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate		1 (2%)	
#Myocardium	(50)	(50)	(50)
Inflammation, chronic focal			1 (2%)
Degeneration, NOS	2 (4%)	1 (2%)	1 (2%)
#Cardiac valve	(50)	(50)	(50)
Pigmentation, NOS		1 (2%)	
*Pulmonary artery	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF PENICILLIN VK (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM			
*Tooth	(50)	(50)	(50)
Dysplasia, NOS	23 (46%)	31 (62%)	27 (54%)
*Pulp of tooth	(50)	(50)	(50)
Abscess, NOS		1 (2%)	
#Salivary gland	(47)	(48)	(49)
Cyst, NOS		1 (2%)	
Lymphocytic inflammatory infiltrate		1 (2%)	2 (4%)
Inflammation, acute focal		1 (2%)	
Fibrosis, multifocal	1 (2%)		
#Liver	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
Inflammation, chronic focal	7 (14%)	2 (4%)	9 (18%)
Necrosis, focal		2 (4%)	3 (6%)
Basophilic cyto change		1 (2%)	
Focal cellular change			1 (2%)
Cell size alteration	3 (6%)	1 (2%)	1 (2%)
#Liver/Kupffer cell	(50)	(50)	(50)
Hyperplasia, diffuse		1 (2%)	
#Liver/hepatocytes	(50)	(50)	(50)
Cytoplasmic vacuolization	1 (2%)	1 (2%)	
Hyperplasia, focal			1 (2%)
*Gallbladder	(50)	(50)	(50)
Eosinophilic cyto change			2 (4%)
#Pancreas	(44)	(41)	(43)
Ectopia		2 (5%)	
Dilatation/ducts			1 (2%)
Cyst, NOS		1 (2%)	1 (2%)
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, chronic focal	1 (2%)		1 (2%)
#Pancreatic acinus	(44)	(41)	(43)
Cytoplasmic vacuolization			1 (2%)
Focal cellular change	1 (2%)		
Atrophy, focal	3 (7%)	3 (7%)	1 (2%)
Hyperplasia, focal		1 (2%)	
#Peripancreatic tissue	(44)	(41)	(43)
Necrosis, fat		1 (2%)	
#Gastric fundal gland	(44)	(45)	(47)
Dilatation, NOS	1 (2%)	5 (11%)	13 (28%)
Eosinophilic cyto change	3 (7%)	34 (76%)	41 (87%)
#Glandular stomach	(44)	(45)	(47)
Cyst, NOS		5 (11%)	15 (32%)
Inflammation, acute focal		2 (4%)	2 (4%)
Inflammation, chronic focal		10 (22%)	30 (64%)
Fibrosis		2 (4%)	11 (23%)
Hyperplasia, epithelial		19 (42%)	38 (81%)
Squamous metaplasia		1 (2%)	5 (11%)
#Forestomach	(44)	(45)	(47)
Inflammation, acute focal		2 (4%)	
Inflammation, chronic focal	3 (7%)	1 (2%)	2 (4%)
Hyperplasia, epithelial	2 (5%)	1 (2%)	2 (4%)
Hyperkeratosis			1 (2%)
#Jejunal submucosa	(44)	(40)	(41)
Amyloidosis	3 (7%)		1 (2%)
#Ileal mucosa	(44)	(40)	(41)
Amyloidosis			2 (5%)
#Ileal submucosa	(44)	(40)	(41)
Amyloidosis			4 (10%)
*Rectum	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate			1 (2%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF PENICILLIN VK (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney	(49)	(49)	(50)
Lymphocytic inflammatory infiltrate	3 (6%)		5 (10%)
Pyelonephritis, acute		1 (2%)	
Inflammation, acute/chronic		1 (2%)	
Pyelonephritis, chronic			1 (2%)
Nephropathy	1 (2%)		1 (2%)
Infarct, healed	1 (2%)		
Amyloidosis	1 (2%)		
#Perirenal tissue	(49)	(49)	(50)
Cyst, NOS		1 (2%)	
Inflammation, acute/chronic		1 (2%)	
#Kidney/tubule	(49)	(49)	(50)
Atrophy, focal	1 (2%)		
#Urinary bladder	(49)	(45)	(50)
Lymphocytic inflammatory infiltrate		1 (2%)	1 (2%)
#Urinary bladder/mucosa	(49)	(45)	(50)
Hyperplasia, diffuse	1 (2%)		
ENDOCRINE SYSTEM			
#Anterior pituitary	(45)	(44)	(43)
Hemorrhage	1 (2%)		
Hyperplasia, focal	9 (20%)	8 (18%)	5 (12%)
Angiectasis	3 (7%)		
#Adrenal	(49)	(46)	(48)
Angiectasis		1 (2%)	
#Adrenal/capsule	(49)	(46)	(48)
Hyperplasia, NOS	1 (2%)		1 (2%)
#Adrenal cortex	(49)	(46)	(48)
Focal cellular change	2 (4%)		
Hypertrophy, focal	1 (2%)	4 (9%)	
Hyperplasia, focal		1 (2%)	
#Adrenal medulla	(49)	(46)	(48)
Amyloidosis	1 (2%)		
#Thyroid	(45)	(43)	(43)
Follicular cyst, NOS		3 (7%)	
Inflammation, multifocal			1 (2%)
Inflammation, chronic focal		1 (2%)	
Hyperplasia, follicular cell	7 (16%)	3 (7%)	1 (2%)
#Pancreatic islets	(44)	(41)	(43)
Ectopia	1 (2%)		
Hyperplasia, focal	1 (2%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Hyperplasia, cystic	2 (4%)	4 (8%)	1 (2%)
*Vagina	(50)	(50)	(50)
Inflammation, acute focal	1 (2%)		2 (4%)
Inflammation, chronic diffuse			1 (2%)
Hyperplasia, epithelial	1 (2%)		
Dysplasia, NOS	1 (2%)		
#Uterus	(49)	(47)	(50)
Abscess, NOS		2 (4%)	1 (2%)
Angiectasis	2 (4%)	1 (2%)	1 (2%)
#Cervix uteri	(49)	(47)	(50)
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic focal			1 (2%)
#Uterus/endometrium	(49)	(47)	(50)
Inflammation, acute focal	2 (4%)	5 (11%)	3 (6%)
Hyperplasia, focal	1 (2%)		2 (4%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF PENICILLIN VK (Continued)

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM			
#Uterus/endometrium (Continued)	(49)	(47)	(50)
Hyperplasia, cystic	39 (80%)	34 (72%)	32 (64%)
Metaplasia, squamous		2 (4%)	1 (2%)
#Endometrial gland	(49)	(47)	(50)
Cyst, NOS	1 (2%)		
Hemorrhage	1 (2%)		
#Ovary/parovarian	(47)	(45)	(48)
Lymphocytic inflammatory infiltrate			3 (6%)
Inflammation, acute diffuse			1 (2%)
Inflammation, granulomatous focal		1 (2%)	
#Ovary	(47)	(45)	(48)
Cyst, NOS	4 (9%)	9 (20%)	7 (15%)
Parovarian cyst	3 (6%)	2 (4%)	6 (13%)
Hemorrhagic cyst			2 (4%)
Abscess, NOS	1 (2%)	7 (16%)	1 (2%)
Inflammation, chronic focal			1 (2%)
Necrosis, focal	1 (2%)		
Angiectasis	1 (2%)		
NERVOUS SYSTEM			
#Brain/thalamus	(49)	(50)	(50)
Mineralization	14 (29%)	1 (2%)	18 (36%)
*Facial nerve	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Inflammation, chronic focal			1 (2%)
Hyperplasia, focal	2 (4%)	1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Knee joint	(50)	(50)	(50)
Inflammation, chronic focal		1 (2%)	
*Abdominal muscle	(50)	(50)	(50)
Inflammation, acute focal		1 (2%)	
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Hemorrhage			1 (2%)
Lymphocytic inflammatory infiltrate		1 (2%)	
Inflammation, acute focal		1 (2%)	
Inflammation, acute/chronic	1 (2%)		2 (4%)
Inflammation, granulomatous focal		1 (2%)	
Foreign material, NOS	1 (2%)		
*Abdominal cavity	(50)	(50)	(50)
Cyst, NOS	1 (2%)	1 (2%)	
Inflammation, acute focal	1 (2%)	1 (2%)	
Inflammation, acute/chronic		2 (4%)	
*Pleura	(50)	(50)	(50)
Inflammation, acute focal			2 (4%)
Inflammation, acute/chronic	1 (2%)		
*Pericardium	(50)	(50)	(50)
Inflammation, chronic focal	1 (2%)		
*Mesentery	(50)	(50)	(50)
Inflammation, chronic focal			1 (2%)
Necrosis, fat	4 (8%)	4 (8%)	4 (8%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF PENICILLIN VK (Continued)

	Vehicle Control	Low Dose	High Dose
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		1 (2%)
Inflammation, acute focal		4 (8%)	1 (2%)
Inflammation, acute/chronic		1 (2%)	1 (2%)
Inflammation, chronic focal			2 (4%)
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

GENETIC TOXICOLOGY OF

PENICILLIN VK AND PENICILLIN V

TABLE E1. MUTAGENICITY OF PENICILLIN VK IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/plate (b) −S9 Trial 1	−S9 Trial 2	+S9 (hamster) Trial 1	+S9 (hamster) Trial 2	+S9 (rat) Trial 1	+S9 (rat) Trial 2
TA100	0	197 ± 13.9	135 ± 20.7	255 ± 30.2	130 ± 3.6	279 ± 21.0	144 ± 3.5
	100	187 ± 4.6	111 ± 13.1	265 ± 8.7	144 ± 5.5	272 ± 19.5	135 ± 3.8
	333	177 ± 9.9	109 ± 6.9	267 ± 6.7	135 ± 4.9	300 ± 15.0	141 ± 8.4
	1,000	168 ± 10.2	98 ± 9.5	246 ± 14.5	111 ± 6.9	244 ± 9.7	116 ± 6.8
	3,333	164 ± 2.9	98 ± 7.0	213 ± 4.5	119 ± 5.1	267 ± 6.4	129 ± 5.2
	10,000	166 ± 8.3	93 ± 10.5	190 ± 9.2	102 ± 3.3	267 ± 14.0	118 ± 10.5
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	985 ± 74.1	650 ± 34.8	2,292 ± 47.1	2,474 ± 27.6	1,509 ± 48.0	808 ± 59.0
TA1535	0	4 ± 1.2	6 ± 1.0	9 ± 0.9	10 ± 0.9	8 ± 1.3	10 ± 1.2
	10	--	7 ± 0.7	--	11 ± 0.7	--	7 ± 0.7
	33	--	6 ± 1.2	--	11 ± 0.3	--	5 ± 0.0
	100	3 ± 0.3	3 ± 0.9	8 ± 0.9	8 ± 0.7	7 ± 0.6	12 ± 1.7
	333	4 ± 0.6	3 ± 1.5	3 ± 0.6	2 ± 0.6	2 ± 0.0	6 ± 2.3
	1,000	Toxic	0 ± 0.0	Toxic	0 ± 0.0	Toxic	2 ± 0.3
	3,333	0 ± 0.0	--	0 ± 0.0	--	0 ± 0.0	--
	10,000	0 ± 0.0	--	0 ± 0.0	--	0 ± 0.0	--
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	961 ± 154.4	153 ± 18.9	229 ± 7.2	81 ± 4.2	290 ± 23.7	36 ± 7.5
TA1537	0	5 ± 1.5	4 ± 1.2	6 ± 0.3	7 ± 1.8	6 ± 0.7	7 ± 0.7
	10	--	6 ± 1.2	--	9 ± 0.7	--	11 ± 0.3
	33	--	3 ± 0.9	--	9 ± 1.0	--	12 ± 1.5
	100	3 ± 0.6	2 ± 0.3	3 ± 0.3	6 ± 1.7	5 ± 0.0	11 ± 2.7
	333	3 ± 0.6	3 ± 0.9	2 ± 0.3	2 ± 0.0	2 ± 0.6	4 ± 1.2
	1,000	Toxic	Toxic	Toxic	Toxic	Toxic	3 ± 1.5
	3,333	0 ± 0.0	--	0 ± 0.0	--	0 ± 0.0	--
	10,000	0 ± 0.0	--	0 ± 0.0	--	0 ± 0.0	--
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	176 ± 25.7	43 ± 2.3	131 ± 14.6	87 ± 4.6	148 ± 11.9	40 ± 5.8
TA98	0	22 ± 1.9	19 ± 1.8	28 ± 5.1	24 ± 2.6	36 ± 5.8	23 ± 1.8
	100	24 ± 0.9	15 ± 2.6	27 ± 1.5	21 ± 1.2	32 ± 4.8	23 ± 2.7
	333	25 ± 1.0	15 ± 3.0	35 ± 2.3	24 ± 3.8	35 ± 1.5	25 ± 4.3
	1,000	17 ± 2.3	12 ± 1.2	37 ± 3.7	26 ± 4.5	37 ± 1.8	20 ± 2.2
	3,333	14 ± 0.7	14 ± 1.2	33 ± 2.8	19 ± 4.4	36 ± 4.0	22 ± 0.3
	10,000	16 ± 3.5	10 ± 2.2	35 ± 4.7	11 ± 1.9	30 ± 2.8	20 ± 1.5
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	311 ± 13.8	309 ± 16.2	1,882 ± 152.6	1,729 ± 65.6	827 ± 37.6	466 ± 47.6

(a) Study performed at Case Western Reserve University. The detailed protocol is presented in Haworth et al. (1983). Cells and study compound or solvent (distilled water) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA1537.

TABLE E2. MUTAGENICITY OF PENICILLIN VK AND PENICILLIN V IN MOUSE L5178Y LYMPHOMA CELLS (a,b)

Compound	Concentration (μg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutant Count	Mutant Fraction (c)
PENICILLIN VK--Study performed at Litton Bionetics, Inc.					
-S9					
Trial 1					
Distilled water (d)		99.0 ± 5.8	100.0 ± 6.7	66.3 ± 2.6	22.5 ± 0.6
Penicillin VK	500	87.3 ± 7.2	78.7 ± 4.4	65.3 ± 3.8	25.0 ± 1.2
	1,000	91.3 ± 3.8	68.0 ± 6.0	69.3 ± 4.9	25.3 ± 2.3
	2,000	86.7 ± 3.0	65.3 ± 9.3	69.0 ± 10.2	26.3 ± 4.1
	3,000	83.0 ± 6.4	73.3 ± 4.4	53.3 ± 6.2	21.3 ± 1.5
	4,000	81.0 ± 3.5	66.0 ± 2.1	67.0 ± 5.6	27.3 ± 1.2
	5,000	92.7 ± 6.1	69.0 ± 3.5	75.0 ± 7.2	27.3 ± 0.9
Ethyl methanesulfonate	500	23.0 ± 3.6	6.0 ± 0.6	655.7 ± 56.6	(e) 990.3 ± 108.4
Trial 2					
Distilled water (d)		101.5 ± 6.2	100.0 ± 8.2	116.8 ± 6.7	38.5 ± 1.9
Penicillin VK	500	102.7 ± 7.0	76.7 ± 0.7	118.7 ± 7.1	38.3 ± 0.3
	1,000	88.7 ± 1.2	77.0 ± 2.5	108.0 ± 6.6	40.3 ± 1.9
	2,000	100.7 ± 10.8	77.7 ± 3.8	123.7 ± 23.2	40.3 ± 3.8
	3,000	95.3 ± 9.0	84.7 ± 4.1	92.0 ± 4.6	33.0 ± 2.0
	4,000	101.0 ± 6.2	84.0 ± 3.5	128.7 ± 15.1	43.0 ± 5.6
	5,000	92.7 ± 7.5	71.3 ± 5.8	105.3 ± 15.2	39.3 ± 8.0
Ethyl methanesulfonate	500	12.0 ± 0.6	2.0 ± 0.0	554.3 ± 15.0	(e) 1,521.3 ± 30.3
+S9 (induced) (f)					
Trial 1					
Distilled water (d)		87.5 ± 2.6	100.0 ± 7.1	123.5 ± 10.0	47.5 ± 4.8
Penicillin VK	(g) 125	80.5 ± 0.5	82.0 ± 0.0	120.5 ± 1.5	50.0 ± 1.0
	(g) 250	76.5 ± 4.5	84.5 ± 11.5	129.5 ± 3.5	57.0 ± 2.0
	(h) 500	97	73	235	81
	1,000	75.7 ± 3.3	67.7 ± 7.2	214.7 ± 20.0	(e) 95.3 ± 10.2
	1,500	95.3 ± 7.9	48.7 ± 6.4	259.3 ± 24.7	(e) 90.7 ± 4.7
	2,000	76.0 ± 4.7	14.0 ± 3.6	245.3 ± 15.0	(e) 108.3 ± 7.3
	3,000	Lethal	--	--	--
Methylcholanthrene	5	28.3 ± 1.9	2.7 ± 0.3	337.3 ± 14.9	(e) 394.7 ± 9.3
Trial 2					
Distilled water (d)		102.3 ± 4.2	100.0 ± 5.9	110.3 ± 16.1	35.5 ± 3.9
Penicillin VK	250	84.0 ± 2.6	65.0 ± 7.1	134.0 ± 15.3	(e) 52.7 ± 4.4
	500	74.0 ± 3.8	60.0 ± 6.4	123.3 ± 17.7	(e) 55.3 ± 6.3
	1,000	75.0 ± 10.0	48.0 ± 6.8	121.0 ± 5.3	(e) 55.3 ± 4.8
	1,500	76.0 ± 7.0	25.3 ± 5.5	218.3 ± 23.4	(e) 99.7 ± 20.5
	(i) 2,000	61	10	157	86
	2,500	Lethal	--	--	--
Methylcholanthrene	5	23.0 ± 0.6	3.7 ± 0.3	203.3 ± 14.3	(e) 294.3 ± 29.0

TABLE E2. MUTAGENICITY OF PENICILLIN VK AND PENICILLIN V IN MOUSE L5178Y LYMPHOMA CELLS (Continued)

Compound	Concentration (μg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutant Count	Mutant Fraction (c)
+S9 (noninduced) (j)					
Trial 1					
Distilled water (d)		100.3 ± 0.9	100.0 ± 7.5	178.8 ± 17.8	59.5 ± 6.2
Penicillin VK	500	92.7 ± 3.5	57.0 ± 4.2	217.0 ± 22.5	79.3 ± 11.0
	1,000	84.3 ± 5.8	55.0 ± 9.1	200.0 ± 12.3	80.0 ± 6.4
	(g) 2,000	64.0 ± 6.0	47.5 ± 5.5	321.5 ± 92.5	(e) 165.0 ± 34.0
	3,000	77.0 ± 7.4	37.0 ± 5.0	399.3 ± 40.8	(e) 173.7 ± 11.6
	4,000	72.3 ± 3.4	27.3 ± 2.3	531.0 ± 21.2	(e) 246.3 ± 11.8
	5,000	53.0 ± 18.0	10.3 ± 4.1	329.3 ± 94.1	(e) 237.3 ± 56.5
Methylcholanthrene	7	55.7 ± 8.9	15.3 ± 2.0	371.3 ± 31.6	(e) 228.7 ± 23.1
Trial 2					
Distilled water (d)		81.8 ± 1.8	100.0 ± 3.3	170.3 ± 12.0	70.0 ± 4.7
Penicillin VK	500	87.7 ± 6.4	96.3 ± 10.4	250.7 ± 9.1	96.0 ± 4.6
	1,000	84.0 ± 1.5	75.3 ± 6.2	241.3 ± 12.3	95.3 ± 3.9
	2,000	73.0 ± 6.0	60.0 ± 6.4	275.3 ± 20.7	(e) 126.3 ± 9.4
	3,000	75.3 ± 6.4	43.0 ± 2.1	404.3 ± 31.2	(e) 179.0 ± 6.0
	4,000	69.7 ± 1.9	26.0 ± 3.6	394.7 ± 11.0	(e) 189.3 ± 3.5
	5,000	Lethal	--	--	--
Methylcholanthrene	7	64.3 ± 6.1	33.0 ± 3.6	512.7 ± 3.8	(e) 270.7 ± 26.2
PENICILLIN VK--Study Performed at SRI International					
-S9					
Trial 1					
Distilled water (d)		69.8 ± 1.8	100.0 ± 2.7	142.8 ± 7.2	68.5 ± 2.8
Penicillin VK (g)	1,640	74.5 ± 16.5	104.0 ± 10.0	208.5 ± 47.5	92.5 ± 0.5
	2,050	74.5 ± 2.5	100.0 ± 5.0	240.5 ± 7.5	107.0 ± 0.0
	2,560	80.5 ± 3.5	111.0 ± 3.0	258.5 ± 11.5	107.5 ± 9.5
	3,200	70.0 ± 4.0	90.5 ± 11.5	258.5 ± 0.5	(e) 123.5 ± 7.5
	4,000	67.5 ± 4.5	82.5 ± 7.5	240.5 ± 7.5	(e) 119.0 ± 12.0
	5,000	69.5 ± 3.5	79.5 ± 4.5	212.0 ± 14.0	102.5 ± 12.5
Ethyl methanesulfonate	500	42.0 ± 2.6	35.7 ± 2.2	1,003.0 ± 26.1	(e) 797.0 ± 48.0
Trial 2					
Distilled water (d)		69.3 ± 2.4	100.0 ± 8.8	52.3 ± 5.0	25.3 ± 3.2
Penicillin VK (g)	2,050	73.0 ± 6.0	83.5 ± 12.5	62.5 ± 0.5	29.0 ± 3.0
	2,560	66.0 ± 11.0	103.5 ± 12.5	69.0 ± 2.0	36.0 ± 7.0
	3,200	68.0 ± 16.0	114.5 ± 19.5	61.5 ± 16.5	30.0 ± 1.0
	4,000	64.0 ± 1.0	93.5 ± 3.5	50.0 ± 9.0	26.0 ± 4.0
	5,000	64.5 ± 0.5	80.5 ± 12.5	58.0 ± 11.0	30.0 ± 6.0
Ethyl methanesulfonate	500	41.7 ± 2.3	40.7 ± 4.4	647.7 ± 26.9	(e) 523.0 ± 46.7

TABLE E2. MUTAGENICITY OF PENICILLIN VK AND PENICILLIN V IN MOUSE L5178Y LYMPHOMA CELLS (Continued)

Compound	Concentration (μg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutant Count	Mutant Fraction (c)
+S9 (induced) (f)					
Trial 1					
Distilled water (d)		78.5 ± 2.6	100.0 ± 5.5	227.3 ± 8.4	96.8 ± 4.3
Penicillin VK	(g) 840	77.0 ± 2.0	62.0 ± 2.0	560.5 ± 24.5	(e) 242.5 ± 17.5
	(g) 1,050	53.0 ± 24.0	38.5 ± 17.5	635.0 ± 32.0	(e) 494.5 ± 206.5
	(h) 1,310	65	43	587	302
	(g) 1,640	50.0 ± 22.0	15.0 ± 12.0	694.0 ± 1.0	(e) 577.5 ± 257.5
	(g) 2,050	52.5 ± 1.5	8.0 ± 1.0	742.5 ± 17.5	(e) 468.5 ± 2.5
	3,200	Lethal	--	--	--
Methylcholanthrene	5	31.3 ± 1.3	12.0 ± 1.2	690.0 ± 27.3	(e) 732.7 ± 6.6
Trial 2					
Distilled water (d)		70.8 ± 3.1	99.8 ± 6.1	122.0 ± 10.1	57.3 ± 2.6
Penicillin VK	(g) 838	68.5 ± 0.5	70.5 ± 3.5	297.5 ± 12.5	(e) 145.0 ± 7.0
	(g) 1,048	55.0 ± 5.0	51.5 ± 4.5	299.0 ± 3.0	(e) 182.5 ± 14.5
	(g) 1,310	55.0 ± 5.0	44.0 ± 6.0	272.0 ± 1.0	(e) 166.0 ± 15.0
	(g) 1,638	67.5 ± 9.5	33.5 ± 2.5	323.5 ± 6.5	(e) 162.0 ± 19.0
	(h) 2,048	32	6	283	298
Methylcholanthrene	5	57.3 ± 2.6	58.0 ± 2.5	434.7 ± 15.9	(e) 254.3 ± 16.2
PENICILLIN V--Study performed at Litton Bionetics, Inc.					
-S9					
Trial 1					
Acetone (d)		94.5 ± 2.5	100.0 ± 4.7	86.8 ± 3.4	30.8 ± 1.7
Penicillin V	(k) 250	86.3 ± 1.5	88.7 ± 1.2	58.7 ± 10.8	22.7 ± 4.4
	500	107.3 ± 4.7	87.0 ± 3.6	72.3 ± 10.2	22.7 ± 3.5
	750	104.3 ± 3.5	71.0 ± 2.3	81.3 ± 6.7	26.3 ± 2.7
	(l) 1,000	107.3 ± 1.2	72.3 ± 2.4	87.7 ± 13.4	27.3 ± 4.6
	(g) 1,500	104.0 ± 10.0	53.0 ± 6.0	71.5 ± 5.5	23.0 ± 4.0
	(g) 2,000	107.5 ± 2.5	38.5 ± 10.5	123.0 ± 37.0	37.5 ± 10.5
Methyl methanesulfonate	5	74.0 ± 6.4	59.0 ± 1.2	527.0 ± 29.5	(e) 240.0 ± 19.1
Trial 2					
Acetone (d)		92.0 ± 9.0	100.0 ± 4.7	74.5 ± 4.9	27.8 ± 3.2
Penicillin V	(e) 250	79.7 ± 1.3	85.3 ± 2.3	59.7 ± 1.2	25.0 ± 0.6
	500	90.7 ± 2.4	102.0 ± 7.6	73.3 ± 4.9	27.0 ± 1.7
	750	90.0 ± 4.5	84.3 ± 4.7	67.0 ± 7.2	24.7 ± 1.7
	(l) 1,000	93.7 ± 10.9	97.0 ± 4.0	92.7 ± 12.0	33.3 ± 0.9
	1,500	103.3 ± 2.9	86.3 ± 9.0	92.0 ± 7.8	29.7 ± 2.8
	2,000	92.3 ± 7.8	63.7 ± 11.3	96.7 ± 12.3	34.7 ± 1.9
Methyl methanesulfonate	5	43.0 ± 2.5	27.3 ± 4.8	467.7 ± 40.7	(e) 365.7 ± 43.5

TABLE E2. MUTAGENICITY OF PENICILLIN VK AND PENICILLIN V IN MOUSE L5178Y LYMPHOMA CELLS (Continued)

Compound	Concentration (μg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutant Count	Mutant Fraction (c)
+S9 (induced) (f)					
Trial 1					
Acetone (d)		98.8 ± 7.6	100.0 ± 15.7	97.0 ± 6.6	33.3 ± 3.5
Penicillin V	(k) 300	80.0 ± 3.5	83.3 ± 7.7	93.3 ± 13.9	38.7 ± 5.5
	400	87.0 ± 3.2	93.3 ± 5.6	80.0 ± 4.2	30.7 ± 2.6
	500	90.7 ± 3.4	83.7 ± 6.1	84.7 ± 5.0	31.0 ± 1.5
	(g) 600	98.5 ± 15.5	89.5 ± 14.5	82.5 ± 22.5	27.5 ± 3.5
	(l) 800	81.0 ± 3.2	90.0 ± 9.6	76.0 ± 3.0	31.3 ± 1.9
	1,000	91.0 ± 0.6	83.3 ± 4.4	95.0 ± 4.0	35.0 ± 1.5
Methylcholanthrene	2.5	48.3 ± 3.4	17.3 ± 0.7	741.7 ± 47.1	(e) 521.0 ± 58.1
Trial 2					
Acetone (d)		95.3 ± 5.8	100.0 ± 2.5	76.0 ± 9.3	26.8 ± 2.5
Penicillin V	(k) 300	84.3 ± 1.2	115.3 ± 0.9	96.3 ± 9.3	38.0 ± 3.1
	400	95.3 ± 12.6	120.3 ± 10.4	69.0 ± 0.6	25.3 ± 3.4
	500	87.7 ± 9.8	105.3 ± 14.4	81.3 ± 10.1	31.0 ± 4.0
	600	104.0 ± 6.0	78.7 ± 7.2	97.7 ± 7.3	31.7 ± 3.8
	(l) 800	97.0 ± 11.7	80.3 ± 14.6	79.3 ± 2.3	28.3 ± 3.8
	(g) 1,000	109.0 ± 3.0	77.5 ± 0.5	80.5 ± 3.5	24.5 ± 0.5
Methylcholanthrene	2.5	33.3 ± 6.6	7.3 ± 1.8	294.0 ± 10.0	(e) 316.7 ± 54.0

(a) The experimental protocol is presented in detail by Myhr et al. (1985) and follows the basic format of Clive et al. (1979). The highest dose of study compound is determined by solubility or toxicity and may not exceed 5 mg/ml. All doses are tested in triplicate; the average for the three tests (unless otherwise indicated) is presented in the table. 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 and soft agar supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency.

(b) Mean ± standard error of replicate trials for approximately 3×10^6 cells each. All data are evaluated statistically for both trend and peak response ($P<0.05$ for at least one of the three highest dose sets). Both responses must be significantly ($P<0.05$) positive for a chemical to be considered mutagenic. If only one of these responses is significant, the call is "questionable"; the absence of both trend and peak response results in a "negative" call.

(c) Mutant fraction (frequency) is a ratio of the mutant count to the cloning efficiency, divided by 3 (to arrive at MF per 1×10^6 cells treated); MF = mutant fraction.

(d) Results presented are the average of four tests.

(e) Significant positive response; occurs when the relative mutant fraction (average MF of treated culture/average MF of solvent control) is greater than or equal to 1.6.

(f) Tests conducted with metabolic activation were performed as described in (a) except that S9, prepared from the liver of Aroclor 1254-induced F344 rats, was added at the same time as the study chemical and/or solvent.

(g) Results presented are the average of two tests.

(h) Only one test was performed.

(i) Data presented are the results of one test; doses in two tests were lethal.

(j) Tests conducted with metabolic activation were performed as described in (a) except that noninduced S9, prepared from the liver of untreated F344 rats, was added at the same time as the study chemical and/or solvent.

(k) Acidic pH shift at this and all higher doses

(l) Precipitation of penicillin V at this and all higher doses

TABLE E3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY PENICILLIN VK (a)

Compound	Dose (µg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
-S9 (c)								
Trial 1--Summary: Positive								
Medium		50	1,035	526	0.51	10.5	26.0	--
Penicillin VK	500	50	1,037	538	0.52	10.8	26.0	102.9
	1,667	50	1,037	546	0.53	10.9	26.0	103.8
	5,000	50	1,029	759	0.74	15.2	26.0	144.8
Mitomycin C	0.001	50	1,036	828	0.80	16.6	26.0	158.1
	0.010	5	103	282	2.74	56.4	26.0	537.1
Trial 2--Summary: Positive								
Medium		50	1,046	468	0.45	9.4	26.5	--
Penicillin VK	5,000	50	1,045	716	0.69	14.3	26.5	152.1
	6,000	50	1,047	812	0.78	16.2	(d) 36.5	172.3
	7,000	50	1,044	831	0.80	16.6	(d) 36.5	176.6
	8,000	0						
Mitomycin C	0.001	50	1,042	771	0.74	15.4	26.5	163.8
	0.010	5	104	217	2.09	43.4	26.5	461.7
+S9 (e)								
Trial 1--Summary: Negative								
Medium		50	1,035	544	0.53	10.9	26.0	--
Penicillin VK	500	50	1,043	610	0.58	12.2	26.0	111.9
	1,667	50	1,038	513	0.49	10.3	26.0	94.5
	5,000	50	1,031	564	0.55	11.3	26.0	103.7
Cyclophosphamide	0.4	50	1,041	791	0.76	15.8	26.0	145.0
	2	5	105	169	1.61	33.8	26.0	310.1
Trial 2--Summary: Negative								
Medium		50	1,050	524	0.50	10.5	26.5	--
Penicillin VK	8,000	50	1,046	504	0.48	10.1	26.5	96.2
	9,000	50	1,047	513	0.49	10.3	26.5	98.1
	10,000	50	1,049	509	0.49	10.2	26.5	97.1
Cyclophosphamide	0.4	50	1,049	753	0.72	15.1	26.5	143.8
	2	5	104	186	1.79	37.2	26.5	354.3

(a) Study performed at Litton Bionetics, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (medium) as described in (c) or (e) below and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air-dried, and stained.
(b) SCEs/cell in treated culture expressed as a percent of the SCEs/cell in the control culture
(c) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours.
(d) Because some chemicals induce a delay in the cell division cycle, harvest times are occasionally extended to maximize the proportion of second division cells available for analysis.
(e) 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 BrdU was added. Cells were incubated for a further 26 hours, with colcemid present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

TABLE E4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY PENICILLIN VK (a)

Trial 1					Trial 2				
Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
−S9 (b) Harvest time 22.0 h (c)					−S9 (b) Harvest time 21.5 h (c)				
Medium					Medium				
	100	2	0.02	2		50	1	0.02	2
	100	2	0.02	2		50	2	0.04	4
Penicillin VK					Penicillin VK				
9,000	50	108	2.16	42	9,000	50	18	0.36	20
9,500	50	109	2.18	50	9,500	25	77	3.08	64
10,000	50	95	1.90	50	10,000	25	28	1.12	40
Summary: Positive					Summary: Positive				
Mitomycin C					Cyclophosphamide				
0.025	100	25	0.25	18	0.025	50	9	0.18	16
0.063	50	41	0.82	52	0.063	25	23	0.92	48
+S9 (d) Harvest time 11.0 h									
Medium									
	100	1	0.01	1					
	100	1	0.01	1					
Penicillin VK									
9,000	100	3	0.03	2					
9,500	100	1	0.01	1					
10,000	100	2	0.02	2					
Summary: Negative									
Cyclophosphamide									
7.5	100	11	0.11	10					
37.5	50	34	0.68	38					

(a) Study performed at Litton Bionetics, Inc. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (medium) as indicated in (b) or (d). Cells were arrested in first metaphase by addition of colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.
(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent (medium) for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid was added for an additional 2-3 hours followed by harvest.
(c) Because of significant chemically induced cell cycle delay, incubation time before addition of colcemid was lengthened to provide sufficient metaphases at harvest.
(d) In the presence of S9, cells were incubated with study compound or solvent (medium) for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid was added for the last 2-3 hours of incubation before harvest. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

APPENDIX F

SENTINEL ANIMAL PROGRAM

APPENDIX F. 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 were selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group were killed at 6, 12, and 18 months on study. The blood from each animal was collected and clotted, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests were performed:

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

II. Results

Results are presented in Table F1.

TABLE F1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF PENICILLIN VK (a)

Interval (months)	No. of Animals	Positive Serologic Reaction for
RATS		
6	10/10	PVM
	10/10	RCV
12	10/10	PVM
	10/10	RCV
MICE		
6	3/10	PVM
12	9/9	PVM
	1/9	MHV
18	5/5	PVM

(a) Blood samples were taken from sentinel animals at 6, 12, and 18 months after the start of dosing; samples were sent to Microbiological Associates (Bethesda, MD) for determination of antibody titers.

APPENDIX G

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

Pelleted Diet: September 1980 to October 1982

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

TABLE G1. 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
Dried brewer's 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 G2. 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
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 G3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	23.91 ± 0.79	22.7-25.3	24
Crude fat (percent by weight)	4.99 ± 0.43	4.2-5.7	24
Crude fiber (percent by weight)	3.32 ± 0.23	2.9-3.8	24
Ash (percent by weight)	6.49 ± 0.47	5.7-7.43	24
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)	10,920 ± 1,824	8,300-15,000	24
Vitamin D (IU/kg)	6,300		1
α-Tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm)	17.2 ± 1.8	14.0-21.0	(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)	1.28 ± 0.18	1.08-1.69	24
Phosphorus (percent)	0.99 ± 0.06	0.88-1.10	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 (7/22/81) was not analyzed for thiamine.

TABLE G4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.44 ± 0.19	<0.05-1.06	24
Cadmium (ppm) (a)	< 0.10		24
Lead (ppm)	1.00 ± 0.73	0.42-3.37	24
Mercury (ppm) (a)	< 0.05		24
Selenium (ppm)	0.31 ± 0.07	0.14-0.52	24
Aflatoxins (ppb) (a,b)	< 10	< 5.0-< 10.0	24
Nitrate nitrogen (ppm) (c)	8.70 ± 3.67	2.1-17.0	24
Nitrite nitrogen (ppm) (d)	2.20 ± 1.59	0.4-6.9	24
BHA (ppm) (d,e)	6.02 ± 4.57	<0.5-16.0	24
BHT (ppm) (d)	3.03 ± 1.82	0.8-7.0	24
Aerobic plate count (CFU/g) (f)	35,950 ± 27,857	4,900-88,000	24
Coliform (MPN/g) (g)	27.4 ± 52.6	<3-240	22
Coliform (MPN/g) (h)	90.0 ± 237.9	<3-1,100	24
E. coli (MPN/g) (i)	< 3		24
Total nitrosamines (ppb) (j,k)	6.48 ± 5.82	<0.8-18.5	21
Total nitrosamines (ppb) (j,l)	28.76 ± 64.88	<0.8-273.2	24
N-Nitrosodimethylamine (ppb) (j,k)	5.24 ± 5.66	<0.8-16.5	21
N-Nitrosodimethylamine (ppb) (j,l)	27.29 ± 64.45	<0.8-272	24
N-Nitrosopyrrolidine (ppb)	1.23 ± 0.79	<0.3-3.5	24
Pesticides (ppm)			
α-BHC (a,m)	<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 (n)	<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 (n)	<0.1	0.2 (4/27/81)	24
Methyl parathion (a)	<0.02		24
Ethyl parathion (a)	<0.02		24
Malathion (o)	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 G4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) All values were less than the detection limit, given in the table as the mean.
(b) Detection limit 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) CFU = Colony-forming unit
(g) Mean, standard deviation, and range exclude one very high value of 1,100 obtained for the batch produced on 12/16/80 and one high value of 460 obtained for the batch produced on 9/23/82 (MPN = most probable number).
(h) Mean, standard deviation, and range include the high values listed in footnote (g).
(i) All values were less than 3 MPN/g.
(j) All values were corrected for percent recovery.
(k) 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.
(l) Mean, standard deviation, and range include the very high values given in footnote (k).
(m) BHC = hexachlorocyclohexane or benzene hexachloride
(n) There was one observation above the detection limit; the value and the date it was obtained are given under the range.
(o) Ten batches contained more than 0.05 ppm.

APPENDIX H

AUDIT SUMMARY

APPENDIX H. AUDIT SUMMARY

The experimental data, documents, and pathology specimens for the 2-year toxicology and carcinogenesis studies of penicillin VK in rats and mice were audited for accuracy, consistency, completeness, and compliance with Good Laboratory Practice (GLP) regulations of the Food and Drug Administration (fully implemented by the NTP on October 1, 1981). The studies were conducted for the NTP by Springborn Institute for Bioresearch, Inc., Spencerville, Ohio, under a subcontract with Tracor Jitco, Inc., until May 2, 1983, and then under contract with the NIEHS. Animal dosing began December 1, 1980, for rats and December 8, 1980, for mice. The retrospective audit was conducted at the NTP Archives, Research Triangle Park, North Carolina, from March 2 to March 27, 1987, by Program Resources, Inc. (W.L. Oller, Ph.D., Principal Investigator). Others involved in the conduct of the audit are listed in the full audit report, which is on file at the NIEHS. The audit included a review of:

(1) All chemistry records.
(2) All records concerning animal receipt, quarantine, randomization, and disposition prior to study start.
(3) Body weight and clinical observation data for 10% of the study animals.
(4) All inlife records concerning environmental conditions, masses, mortality, and animal identification.
(5) All postmortem records for individual animals concerning identification, disposition codes, condition codes, and correlation between gross and microscopic diagnoses.
(6) Residual formalin-fixed tissues from rats and mice to resolve potential noncorrelations between gross observations and microscopic diagnoses, to confirm animal identification, and to detect untrimmed potential lesions.
(7) Slides and blocks of tissues from all animals to verify proper match and accurate labeling.
(8) Tabulated pathology diagnoses for study animals to verify computer data entry.
(9) Correlation between the data, results, and procedures presented in the preliminary Board Draft (July 1987) of NTP Technical Report 336 and the records available at the NTP Archives.

The audit of inlife toxicology documents and data showed that procedures were implemented per the Tracor Jitco Basic Ordering Agreement during the conduct of the studies. Seventeen rats and 30 mice were underdosed by 10%-21% one time during the study. Mean body weights for all study groups were recalculated and corrected as needed.

The audit of the analytical chemistry documents and data showed that microfiche documentation from the Midwest Research Institute for purity, identity, stability, and chemical/vehicle referee analyses was present and complete. Records and raw data from Springborn Institute's analyses of the bulk chemical and dose mixtures were present and complete.

The audit of pathology documents, data, and specimens revealed 22 noncorrelations between gross observations and microscopic diagnoses in nontarget organs in rats and 52 noncorrelations between gross observations and microscopic diagnoses in nontarget organs in mice. These were determined to have no impact on the interpretation of the pathology data. Wet tissues were examined for untrimmed potential lesions. Those untrimmed potential lesions involving target organs were subsequently trimmed, embedded, and examined microscopically, and the diagnoses were incorporated into the final pathology data. A random sample of wet tissues was examined for animal identification, and there was no indication that animals were exchanged among groups. Carcasses and/or residual wet tissues of one rat and two mice were incorrectly identified.

In conclusion, the study records at the NTP Archives support the data and results presented in this Technical Report.

 * U.S. GOVERNMENT PRINTING OFFICE 1988; 201-778/80312

NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS
PUBLISHED AS OF APRIL 1988

TR No.	CHEMICAL
200	2,6-Toluenediamine Dihydrochloride
201	2,3,7,8-Tetrachlorodibenzo-p-dioxin (Dermal)
202	1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin and 1,2,3,7,8,9-Hexachlorodibenzo-p-dioxin (Dermal)
203	Phenol
204	Benzoin
205	4,4'-Oxydianiline
206	Dibromochloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane (Inhalation)
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butylbenzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-ethylhexyl)phthalate
219	2,6-Dichloro-*p*-phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C.I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
228	Vinylidene Chloride
229	Guar Gum
230	Agar
231	Stannous Chloride
232	Pentachloroethane
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	D-Mannitol
237	1,1,1,2-Tetrachloroethane
238	Ziram
239	Bis(2-chloro-1-methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
247	L-Ascorbic Acid
248	4,4'-Methylenedianiline Dihydrochloride
249	Amosite Asbestos
250	Benzyl Acetate
251	Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
267	Propylene Oxide
269	Telone II®
271	HC Blue No. 1
272	Propylene
273	Trichloroethylene (Four strains of rats)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
281	H.C. Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethy)phosphonium Sulfate and Tetrakis(hydroxymethy)phosphonium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane
307	Ephedrine Sulfate
308	Chlorinated Paraffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
320	Rotenone
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonate
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate
329	1,2-Epoxybutane
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol

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.