NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 395

TOXICOLOGY AND CARCINOGENESIS STUDIES OF PROBENECID

(CAS NO. 57-66-9)

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

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were 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 Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

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.

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NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

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NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
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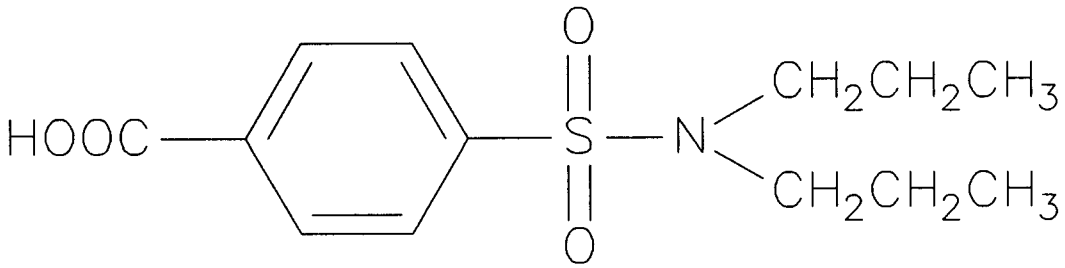
ABSTRACT



PROBENECID

CAS No. 57-66-9
Chemical Formula: $C_{13}H_{19}NO_4S$ Molecular Weight: 285.4

Synonyms: 4-[(Dipropylamino)sulfonyl]benzoic acid; *p*-(dipropylsulfamoyl)benzoic acid; *p*-(dipropylsulfamyl)benzoic acid
Trade Names: Benacen; Benemid; Benemide; Benn; Probalan; Probecid; Proben; Probenid; Robenecid; Uricocid

Probenecid is a white crystalline solid commonly used as a uricosuric agent in the treatment of gout. Because of its inhibitory effects on renal tubule transport processes, probenecid is also used as a therapeutic adjunct to enhance blood levels of penicillin and its action. Toxicology and carcinogenicity studies were conducted by administering probenecid (>99% pure) in corn oil by gavage to groups of F344/N rats and B6C3F$_1$ mice of each sex once daily, 5 days per week in 14-day, 13-week, and 2-year studies. Genetic toxicology studies were conducted in *Salmonella typhimurium* and Chinese hamster ovary cells.

14-Day Studies
Doses used in the 14-day studies for both rats and mice were 0, 200, 400, 800, 1,600, or 3,200 mg/kg. Of the animals receiving 3,200 mg/kg, all rats, all female mice, and two of five male mice died during the studies. No deaths occurred among the other dose groups. There was a significant reduction in body weight gain in male and female rats receiving 1,600 mg/kg and in female rats receiving 800 mg/kg. No gross lesions were attributed to probenecid administration in rats or mice of either sex.

13-Week Studies
Doses used in the 13-week studies were 0, 50, 100, 200, 400, or 800 mg/kg for rats and 0, 100, 200, 400, 800, or 1,600 mg/kg for mice. No rats died during the 13-week studies. In mice, 5 of 10 males and 3 of 10 females receiving 1,600 mg/kg and 1 of 10 males receiving 800 mg/kg died during the study. Significant reductions in body weight gain occurred in male rats administered 800 mg/kg, male mice administered 1,600 mg/kg, and female mice administered 800 or 1,600 mg/kg. All dose groups of male rats and all groups of female rats receiving 100 mg/kg or more showed significant increases in absolute and/or relative liver weights compared to control groups. This change was also seen in mice receiving 200 mg/kg and greater, except female mice in the 400 mg/kg group. No compound-related lesions occurred in rats or mice of either sex.

Based on compound-related deaths and suppression of body weight gains observed at higher doses in the 13-week studies, doses of 0, 100, and 400 mg/kg were used for the 2-year studies in rats and mice. These doses were administered once daily, 5 days a week for up to 103 weeks to groups of 50 males or 50 females of each species.

Body Weight and Survival in the 2-Year Studies

The mean body weight of high-dose female rats was 10% to 20% lower than that of controls throughout the studies. Mean body weights for all other dosed rats and for all dosed mice were similar to those of controls throughout the 2-year studies.

Survival of high-dose male rats and high-dose and low-dose male mice was significantly lower than that of controls. Survival rates after 2 years were: male rats—control, 37/50; 100 mg/kg, 34/50; 400 mg/kg, 22/50; female rats—24/50; 35/50; 19/50; male mice—38/50; 23/50; 24/50; female mice—32/49; 32/49; 32/50.

Neoplasms and Nonneoplastic Lesions in the 2-Year Studies

No chemical-related histopathologic toxic effects or increased incidence of tumors attributable to probenecid were observed in male or female rats receiving probenecid by corn oil gavage for up to 2 years. Mammary gland fibroadenomas and combined thyroid C-cell adenomas or carcinomas exhibited significant negative trends in female rats. These decreased tumor rates were associated with lower body weights. The incidence of adrenal medullary pheochromocytomas was significantly decreased in high-dose male rats. No compound-related increase in nonneoplastic lesions was observed in rats of either sex.

No compound-related neoplastic effects were observed in male mice. In high-dose female mice, there were significant increases in the incidences of hepatocellular adenomas (3/48; 2/49; 14/49), but there was no corresponding increase in carcinomas (2/48; 2/49; 3/49). Treatment-related increased incidences of ovarian abscesses in female mice were causally related to *Klebsiella* species infection rather than directly related to chemical administration.

Genetic Toxicology

Probenecid was not mutagenic in *Salmonella typhimurium* strain TA100, TA1535, TA1537, or TA98 with or without metabolic activation. In cytogenetic tests with Chinese hamster ovary cells, probenecid induced sister chromatid exchanges in the absence, but not in the presence of S9 activation. No induction of chromosomal aberrations was observed with or without S9.

Conclusions

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of probenecid for male or female F344/N rats receiving 100 or 400 mg/kg in corn oil. There was *no evidence of carcinogenic activity* of probenecid for male $B6C3F_1$ mice given 100 or 400 mg/kg probenecid in corn oil. There was *some evidence of carcinogenic activity* of probenecid for female $B6C3F_1$ mice based on an increased incidence of hepatocellular adenomas.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 8. A summary of peer review comments and the public discussion on this Technical Report appears on page 10.

Summary of the 2-Year and Genetic Toxicology Studies of Probenecid

Variable	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 100, or 400 mg/kg in corn oil by gavage 5 days a week at a volume of 5 mL/kg	0, 100, or 400 mg/kg in corn oil by gavage 5 days a week at a volume of 5 mL/kg	0, 100, or 400 mg/kg in corn oil by gavage 5 days a week at a volume of 10 mL/kg	0, 100, or 400 mg/kg in corn oil by gavage 5 days a week at a volume of 10 mL/kg
Body weights	No effect	Body weight depression in high dose	No effect	No effect
2-Year survival rates	37/50, 34/50, 22/50	24/50, 35/50, 19/50	38/50, 23/50, 24/50	32/49, 32/49, 32/50
Nonneoplastic effects	None attributed to probenecid	None attributed to probenecid	None attributed to probenecid	None attributed to probenecid
Neoplastic effects	None attributed to probenecid	None attributed to probenecid	None attributed to probenecid	Liver: hepatocellular adenomas (3/48, 2/49, 14/49)
Level of evidence of carcinogenic activity	No evidence	No evidence	No evidence	Some evidence
Genetic toxicology				
Salmonella typhimurium				
Gene mutation:	Negative with and without S9 in strains TA100, TA1535, TA1537, and TA98			
Sister chromatid exchange				
Chinese hamster ovary cells *in vitro*:	Positive without S9			
Chromosomal aberrations				
Chinese hamster ovary cells *in vitro*:	Negative with and without S9			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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. 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. 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 cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report 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 five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to 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. Such consideration 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:

- 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 to neoplastic 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);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- 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.

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on probenecid on November 20, 1990 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:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS

On November 20, 1990, the draft Technical Report on the toxicology and carcinogenesis studies of probenecid received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Committee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. K.M. Abdo, NIEHS, introduced the toxicology and carcinogenesis studies of probenecid by discussing the uses, experimental design, survival, body weight, and liver weight effects in rats and mice. He commented that the only compound-related lesions were hepatocellular tumors in female mice. The proposed conclusions were *no evidence of carcinogenic activity* for male or female F344/N rats or for male B6C3F$_1$ mice, and *some evidence of carcinogenic activity* for female B6C3F$_1$ mice.

Dr. Carlson, a principal reviewer, agreed with the conclusions. He commented on the statement that no chemical-related toxic effects were observed in male or female rats as being contradictory to statements in the results that "the moribund condition of these animals was presumed to be the result of chemical toxicity" and "these deaths were therefore presumed to be related to chemical toxicity."

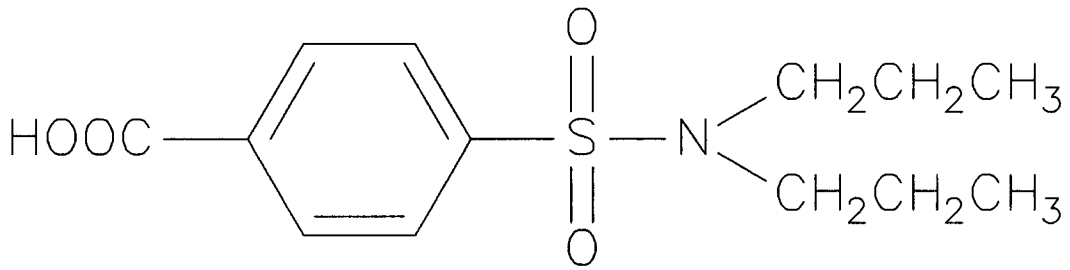
Dr. Scala said the issue of moribund animals and the relationship of their condition to chemical toxicity needed to be clarified in the report.

Dr. Garman, the second principal reviewer, agreed with the conclusions. However, he questioned the combination of female mice hepatocellular adenomas and carcinomas in the summary table when the frequency of carcinoma was obviously not treatment related. Dr. Eustis, NIEHS, said the carcinomas would be separated out from the table.

Dr. Gold, the third principal reviewer, agreed with the conclusions. She suggested that the conclusions read "benign hepatocellular neoplasms," since the level of *some* rather than *clear evidence* in female mice was due to an increase in benign tumors only. Dr. Abdo said the conclusion would say "hepatocellular adenomas."

Dr. Carlson moved that the Technical Report on probenecid be accepted with the conclusions as written for male and female rats and male mice, *no evidence of carcinogenic activity*, and for female mice, *some evidence of carcinogenic activity*, with the last sentence being changed to emphasize that the conclusion was based on adenomas. Dr. Garman seconded the motion, which was accepted unanimously with eleven votes.

INTRODUCTION



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PHYSICAL AND CHEMICAL PROPERTIES, USE, AND HUMAN EXPOSURE

Probenecid is a white crystalline, almost odorless powder (melting point: 194° to 196° C) commonly used as an uricosuric agent in the treatment of gout. It is soluble in ethanol, acetone, and dilute solutions of alkali hydroxides but is practically insoluble in water (Al-Badr and El-Obeid, 1981; *The Merck Index*, 1983). The pK_a of probenecid is 3.4 in aqueous medium (Cunningham *et al.*, 1981) and the maximum wavelength of absorption is 244 nm (Israili *et al.*, 1972).

Probenecid was first synthesized by condensation of *p*-carboxybenzene-sulfonyl chloride with di-*n*-propylamine (Miller, 1952). Because of its inhibitory effects on renal tubule transport processes, probenecid blocks the renal tubule secretion of a number of acidic drugs in humans, including antibiotics, analgesics, antiarthritic agents, and diuretics (Cunningham *et al.*, 1981). Therefore, probenecid is used as a therapeutic adjunct to increase blood levels and to prolong the action of penicillin in humans (Beyer *et al.*, 1951). Furthermore, because probenecid inhibits the active reabsorption of uric acid at the proximal tubule (Beyer *et al.*, 1951), it is an effective uricosuric agent for the treatment of chronic gout and gouty arthritis (Cunningham *et al.*, 1981; Weiner and Mudge, 1985). Probenecid also inhibits the active transport of acidic metabolites of catecholamines in the brain (Bowman and Rand, 1980). Currently, the primary therapeutic use of probenecid is to lower uric acid blood levels in patients with gout.

Probenecid is marketed as a prescription drug product. In the treatment of chronic gout, adult daily dosages of 1 to 2 g are given in 500 mg doses. To effectively block the renal excretion of penicillin, the daily adult dosage of probenecid is 2 g, which is given in four 500 mg doses; for children weighing less than 50 kg, a probenecid dose of 25 mg/kg is given initially, followed by maintenance doses of 10 mg/kg four times daily (Weiner and Mudge, 1985).

METABOLISM AND DISPOSITION

Probenecid is efficiently absorbed from the human gastrointestinal tract, and peak plasma levels in

adults are reached 1 to 5 hours after oral administration (Dayton *et al.*, 1963; Selen *et al.*, 1982). An oral dose of 2 g resulted in peak probenecid plasma concentrations of 150 to 200 μg/mL. Absorption was considered to be essentially complete because, once peak plasma levels were reached, the plasma decay rate was the same after oral or intravenous administration. Furthermore, the bioavailability of probenecid was found to be 100% at oral doses of 0.5 to 2 g (Emanuelsson *et al.*, 1987). Urinary elimination of approximately 80% of the radiolabel from single oral doses of ^{14}C-probenecid (Perel *et al.*, 1970, 1971; Melethil and Conway, 1976) further demonstrated the nearly complete absorption of probenecid from the human intestinal tract. Melethil and Conway (1976) suggested that incomplete recovery of the administered dose was due to some excretion of the drug in bile and feces. Probenecid does not appear to accumulate in organs at concentrations higher than the plasma levels of this drug (Dayton *et al.*, 1963).

The plasma half-life of probenecid is variable, ranging from 4 to 12 hours in humans, 3 to 8 hours in dogs, 3 to 4 hours in rats, and 1 hour in monkeys (Dayton and Perel, 1971; Dayton *et al.*, 1963, 1973). The rate at which probenecid is cleared from plasma is dose dependent; the plasma half-life of probenecid increased with increasing oral doses of 0.5 to 2 g in humans (Dayton *et al.*, 1963; Selen *et al.*, 1982) or with increasing intravenous doses of 8 to 160 mg/kg in monkeys (Chiang and Benet, 1981) and 40 to 160 mg/kg in dogs (Dayton *et al.*, 1967). Nonlinear elimination of probenecid has also been observed in rats (Emanuelsson *et al.*, 1987).

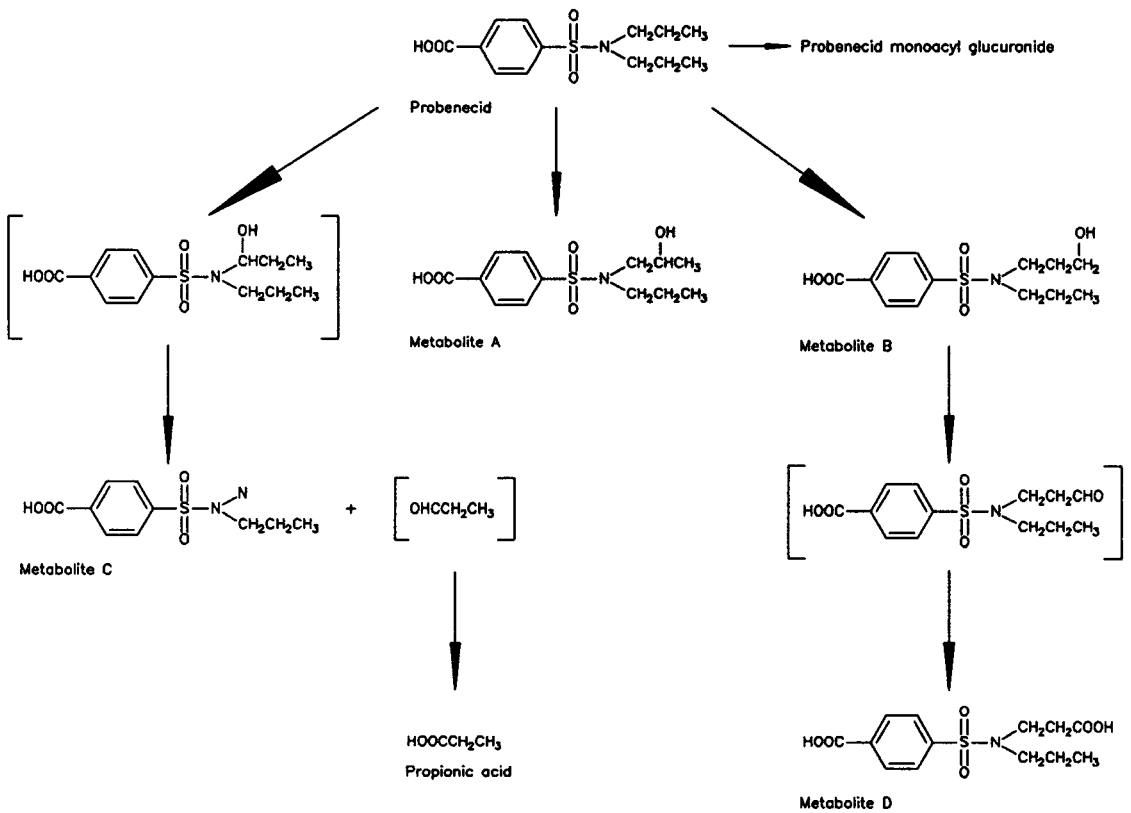
Probenecid is extensively bound (80% to 90%) to plasma proteins in humans, dogs, rats (Dayton *et al.*, 1963; Dayton and Perel, 1971; Israili *et al.*, 1972), and monkeys (Chiang and Benet, 1981). The unbound fraction of probenecid in rat plasma increased nonlinearly with increasing plasma concentrations of the drug from 10 to 650 μg/mL; however, because the unbound volume of distribution decreased when the dose was increased from 50 to 100 mg/kg, Emanuelsson and Paalzow (1988) concluded that the drug is distributed almost exclusively in the extracellular fluid.

Probenecid is extensively metabolized in humans (Perel *et al.*, 1970; Dayton and Perel, 1971; Melethil and Conway, 1976), dogs (Dayton *et al.*, 1973) and rats (Dayton *et al.*, 1973; Guarino *et al.*, 1969; Conway and Melethil, 1974). The major pathways of biotransformation of probenecid, presented in Figure 1, involve oxidation of the N-propyl side chain and glucuronide conjugation (Guarino *et al.*, 1969; Perel *et al.*, 1970; Israili *et al.*, 1972). Oxidation of the phenyl ring, decarboxylation of probenecid, or covalent binding to microsomal proteins have not been observed (Dayton *et al.*, 1973).

As detailed in Figure 1, identified metabolic products resulting from side chain oxidation are the monohydroxylated derivatives at the secondary (metabolite A) and terminal (metabolite B) positions, the N-depropyl compound (metabolite C), the carboxy compound (metabolite D), as well as glucuronide conjugates of metabolites A and C. Metabolite C is presumably formed via the unstable 1-hydroxylated intermediate, and metabolite D is formed by further oxidation of metabolite B (Israili *et al.*, 1972). The metabolites of probenecid are less lipid soluble and less tightly bound to plasma albumin than is the parent compound. The renal clearance of the monoacyl glucuronide of probenecid is greater than that of probenecid (Perel *et al.*, 1971). Propionic acid is also a product of probenecid metabolism (Israili *et al.*, 1972).

In humans, the major urinary metabolite of probenecid metabolism excreted in 48 hours is the acyl glucuronide conjugate of probenecid, accounting for about 41% of a given dose (Perel *et al.*, 1970). The amount of unchanged probenecid excreted is only about 4% of the dose. The other metabolites excreted within 48 hours by humans are the products of oxidative attack of the N-propyl side chain: metabolite A (7% to 13%), metabolite B (2% to 4%), metabolite C (5% to 8%), and metabolite D (6% to 9%).

Elimination of probenecid occurs by renal and biliary excretion. Renal excretion of unchanged drug probably has no significant effect on the clearance of probenecid since it accounts for only about 5% to 13% of the total elimination of the drug (Perel *et al.*, 1970; Melethil and Conway, 1976; Chiang and Benet, 1981). Saturation of metabolic pathways has also been discounted as the cause for the nonlinear kinetics of elimination, because the pattern of urinary excretion of probenecid metabolites was essentially unchanged in humans receiving oral doses of 0.5, 1.0, or 2.0 g of probenecid (Melethil and Conway, 1976) or in monkeys



Identified Metabolites:

A: p-(N-propyl-N-2-hydroxypropylsulfamoyl) benzoic acid

B: p-(N-propyl-N-3-hydroxypropylsulfamoyl) benzoic acid

C: p-(propylsulfamoyl) benzoic acid

D: p-(n-propyl-N-2-carboxyethylsulfamoyl) benzoic acid

[ ] putative intermediates

FIGURE 1
Pathways of Probenecid Metabolism

receiving from 8 to 160 mg/kg intravenously (Chiang and Benet, 1981). The rate-limiting process, accounting for the saturable elimination kinetics of probenecid at therapeutic doses, has not been identified with certainty. The slower rate of probenecid metabolism at higher doses may be due to product inhibition of the oxidative metabolic pathways (Ho *et al.*, 1986) or biliary recycling (Chiang and Benet, 1981).

In the bile of renal-ligated Sprague-Dawley rats, unchanged drug, N-depropylated probenecid (metabolite B), and glucuronides of the side chain oxidized compounds (glucuronide conjugates of metabolites A, B, and D) were detected; however, the major urinary metabolite in humans, the acyl glucuronide of probenecid, was present in lesser amounts than the glucuronide conjugates of the hydroxy metabolites (Guarino *et al.*, 1969; Conway and Melethil, 1974). In the rat, biliary excretion appears to be the major pathway of excretion of probenecid and its metabolites; metabolites in the urine may arise as a result of enterohepatic circulation. Oxidation of the N-propyl side chain is also the predominant metabolic pathway in monkeys, whereas in dogs, glucuronide conjugation of the parent compound is the predominant pathway (Dayton *et al.*, 1973). Rat, mouse, and human liver preparations produced the same N-propyl side chain metabolites as those formed *in vivo* (Cunningham *et al.*, 1977).

Mechanism of Renal Transport

The mechanism of renal transport of probenecid and its inhibition of renal tubule secretion of organic anions has been studied in kidney cortical slices and in isolated kidney tubules (Berndt, 1966; Sheikh and Stahl, 1977, Sheikh *et al.*, 1979). Probenecid is accumulated by renal tissue under both aerobic and anaerobic incubation conditions. The active aerobic uptake is enhanced by metabolic substrates (acetate or succinate) and is suppressed by metabolic inhibitors (cyanide or iodoacetamide) or other organic anions (*p*-aminohippurate, phenol red, and other substituted phenolsulfonphthalein dyes) (Sheikh and Stahl, 1977). Anaerobic uptake of probenecid was not sensitive to metabolic inhibitors and therefore was attributed to the passive binding of probenecid to tissue constituents. Demonstration of competitive inhibition of probenecid uptake by other organic anions (*p*-aminohippurate, chlorothiazide, salicylate, and penicillins) established that the aerobic active renal transport of this drug occurs by the common organic anion transport system (Sheikh and Stahl, 1977; Sheikh and Maxild, 1978). Uptake of probenecid by rat liver slices also occurs by passive diffusion followed by nonspecific tissue binding and by an active organic acid transport mechanism (Gigon and Guarino, 1970).

Toxicity

Human Effects

Twelve adult patients with elevated serum uric acid levels were given probenecid at daily doses of 500 to 1,500 mg for 48 weeks (Bassett *et al.*, 1977). Treatment with probenecid induced a rapid and sustained decline (30%) in serum uric acid levels, as well as slight reductions in serum albumin, hemoglobin, and systolic and diastolic pressure. Huge overdoses of probenecid result in stimulation of the central nervous system, convulsions, and death from respiratory failure (Weiner and Mudge, 1985).

Patients receiving probenecid have experienced nausea, vomiting, frequent urination, hypersensitivity reactions, sore gums, flushing, dizziness, and anemia. Nephrotic syndrome, hepatic necrosis, and aplastic anemia have occurred rarely (Osol and Hoover, 1975). A single fatality has been attributed to hypersensitivity to probenecid. Jaundice, asthma, skin rash, and eosinophilia preceded massive hepatic necrosis in this patient (Gosselin *et al.*, 1976). Most cases of severe allergic reactions and anaphylaxis reportedly occurred within several hours after administration to patients who had previously received probenecid (Huff, 1986).

Animal Toxicity

Acute toxic effects of probenecid administration in laboratory animals include increased respiration, muscular twitching, vomiting, micturition, and tonic convulsions followed by death due to respiratory arrest (McKinney *et al.*, 1951). LD_{50} values for probenecid in rats, mice, rabbits, and dogs are presented in Table 1. No microscopic lesions were observed in animals exposed to a single lethal dose of this drug. The acute toxicity of probenecid after oral administration is similar in rats and mice.

Oral administration of probenecid to rats at doses of 100, 200, or 400 mg/kg 5 days per week for 12 weeks did not cause any apparent hematologic

TABLE 1
LD_{50} Values of Probenecid in Rats, Mice, Rabbits, and Dogs[a]

Species	Route of Administration			
	Oral	Subcutaneous	Intravenous	Intraperitoneal
Rats	1,604	611		394
Mice	1,666	1,156	458	1,000[b]
Rabbits			304	
Dogs			270	

[a] LD_{50} values are reported in mg/kg. Data reported by McKinney *et al.* (1951) except where noted.
[b] Data reported by Hoshi *et al.* (1968).

changes or gross or microscopic lesions (McKinney *et al.*, 1951). In addition, probenecid did not produce any local or generalized sensitization responses in guinea pigs. Oral administration of 640 mg/kg of probenecid to rats caused an increase in the levels of aldolase activity but not alkaline phosphatase activity in 24-hour urine samples, suggesting that this treatment induced slight renal tubule cell damage (Raab and Moerth, 1976). No studies have been reported on the potential carcinogenicity of probenecid in laboratory animals.

Reproductive and Developmental Toxicity

Probenecid was not teratogenic in New Zealand rabbits when administered orally in gelatin capsules at doses of 0, 25, 50, 100, or 200 mg/kg on days 8 through 16 of gestation (Merck Sharp & Dohme, unpublished); the percentage of resorptions was increased in the 25 (14%), 100 (15%), and 200 (17%) mg/kg groups compared to controls (5%). There were no adverse effects on reproductive parameters in groups of male and female Sprague-Dawley rats that were fed diets containing probenecid at daily doses adjusted to provide approximately 10, 50, and 100 mg/kg from 10 weeks prior to breeding and through the breeding of two successive litters (Merck Sharp & Dohme, unpublished).

Genetic Toxicity

Probenecid was negative in tests for mutagenicity in *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, and TA1537 in the presence or absence of rat or hamster liver S9 (Mortelmans *et al.*, 1986).

STUDY RATIONALE

Probenecid was recommended by the Food and Drug Administration for 2-year oral toxicology and carcinogenesis studies because of its widespread use as a uricosuric agent in the treatment of chronic gout and because there was a lack of carcinogenicity data. The gavage route of administration was selected because human exposure occurs by the oral route. The corn oil vehicle was used because of low palatability of probenecid in feed and its insolubility in water. Poor palatability of dosed feed containing probenecid was indicated from the results of 14-day dosed feed studies conducted with rats at the same laboratory. The only effects observed in these studies were body weight depression and reduced feed consumption.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF PROBENECID

Probenecid was obtained from Ganes Chemical, Inc. (New York City, NY) in one lot (lot number 9L008892). Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (MRI, Kansas City, MO), and then confirmed by the study laboratory (Appendix G).

The study chemical, a fine, white, fluffy crystalline powder, was identified as probenecid by elemental analysis and infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. Its purity was found to be greater than 99% by Karl Fischer water analysis, weight loss on drying, titration of the carboxylic acid group, thin-layer chromatography, and high performance liquid chromatography (HPLC). As a supplement to the solubility and purity analyses, the complete battery of USP tests were performed. All test results met the USP specifications. Stability studies performed with HPLC found that probenecid was stable as a bulk chemical when stored protected from light for 2 weeks at temperatures up to 60° C. Throughout the studies the bulk chemical was stored in sealed containers protected from the light at 0° ± 5° C. Stability of the bulk chemical was monitored by the study laboratory with infrared spectroscopy and carboxylic acid titration and no change in the study material was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

Dose formulation studies were initially performed in feed. The homogeneity and stability of the formulations were confirmed by HPLC analyses. Due to palatability problems, however, the administration route and formulation vehicle were changed to gavage with corn oil. Dose formulations were prepared by mixing appropriate amounts of probenecid with corn oil (Appendix G, Table G1). Studies were conducted by the analytical chemistry laboratory to determine the homogeneity and stability of probenecid in corn oil. Homogeneity was confirmed using a spectroscopic method and HPLC analyses of corn oil suspensions of probenecid at a concentration of 20 mg/mL. Stability for 2 weeks in the dark at room temperature (20° to 24° C) and under simulated dosing conditions (exposed to air and light for 3 hours) was confirmed. During the toxicology studies the dose formulations were stored at 0° ± 5° C for no more than 2 weeks.

Dose formulations were analyzed once during the 14-day studies and twice during the 13-week studies. The results of the analyses for both studies were within ± 10% of the target concentrations (Appendix G, Tables G2 and G3).

During the 2-year studies, the study laboratory conducted analyses of formulation room samples every 8 weeks and animal room samples every 24 weeks using ultraviolet spectroscopy. These analyses indicated that the dose formulations were within ± 10% of target concentrations 99% (73/74) of the time (Appendix G, Table G4). Results of periodic referee analyses performed by the analytical chemistry laboratory were in agreement with those conducted by the study laboratory (Appendix G, Table G5).

14-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice from the Charles River Laboratories (Kingston, NY) were observed for 19 days before being placed on study. The rats were 10 weeks old when the study began, and the mice were 11 weeks old.

Groups of five animals of each species and sex were administered 0, 200, 400, 800, 1,600, or 3,200 mg/kg probenecid in corn oil by gavage daily at a volume of 5 mL/kg for rats and 10 mL/kg for mice, 5 days per week so that 12 doses were given over 17 days. Animals in the high-dose group (3,200 mg/kg) received 1,600 mg/kg probenecid in corn oil by gavage two times a day administered at least 5 hours apart. Feed consumption by cage was recorded weekly. Animals were housed five per cage, with

water available *ad libitum*. The rats and mice were observed twice daily for signs of toxicity; they were weighed at study initiation, weekly, and the end of the studies. Details of study design and animal maintenance are summarized in Table 2. A gross necropsy was performed on all animals.

13-WEEK STUDIES

To evaluate the cumulative toxic effects of repeated exposure to probenecid and to determine appropriate doses for the 2-year studies, 13-week studies were conducted. Male and female F344/N rats from the Charles River Laboratories (Kingston, NY) were observed for 15 days before being placed on study; male and female $B6C3F_1$ mice from the same source were observed for 13 days. The rats were 6 to 7 weeks old when the study began, and the mice were 7 to 8 weeks old.

Groups of ten rats of each sex were administered 0, 50, 100, 200, 400, or 800 mg/kg probenecid in corn oil by gavage daily at a volume of 5 mL/kg, 5 days per week for 13 weeks. Groups of ten mice of each sex were administered 0, 100, 200, 400, 800, or 1,600 mg/kg probenecid by gavage daily at a volume of 10 mL/kg, 5 days per week for 13 weeks.

Animals were housed five per cage, with feed and water available *ad libitum*. They were observed twice daily, and signs of toxicity were recorded. Individual animal weights were recorded weekly throughout the studies. Feed and water consumption were not recorded. Table 2 summarizes further experimental details.

Complete necropsies with tissue collection were performed on all animals. Organ weights were recorded for the brain, liver, right kidney, thymus, heart, and lungs of all animals, and the right testes of all males. Tissues were preserved in 10% neutral buffered formalin, dehydrated, embedded in paraffin in sections from 4 to 6 μm thick, and stained with hematoxylin and eosin. Microscopic examination was conducted on organs and tissues from all control animals, all animals receiving the highest dose including the five early deaths, and all male mice in the second highest dose group (800 mg/kg). Further details are presented in Table 2.

2-YEAR STUDIES

Study Design

Groups of 50 rats and mice of each sex were administered 0, 100, or 400 mg/kg probenecid in corn oil by gavage at a volume of 5 mL/kg for rats and 10 mL/kg for mice, 5 days a week for 103 weeks.

Source and Specifications of Animals

The male and female F344/N rats and $B6C3F_1$ mice used in these studies were obtained from the Frederick Cancer Research Facility (Frederick, MD). After all animals were quarantined for 14 to 20 days, five animals of each species and sex were randomly selected and sacrificed for parasite evaluation and gross observation of disease. The animals' health was monitored throughout the studies by serologic analyses performed at 6-month intervals after study initiation according to the protocols of the NTP Sentinel Animal Program (Appendix J). The rats were placed on study when they were 8 to 9 weeks old; mice were 8 weeks old.

Animal Maintenance

Both rats and mice were housed five per cage with feed and water available *ad libitum*. Cages were rotated every two weeks. Feed analyses are presented in Appendix H. Further details of animal maintenance are given in Table 2.

Clinical Examinations and Pathology

All animals were observed twice daily for signs of toxicity. Clinical findings and body weights were recorded once a week for the first 13 weeks of the studies and once a month thereafter.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were fixed in 10% neutral buffered formalin and processed for microscopic examination (embedded in paraffin in sections from 4 to 6 μm thick and stained with hematoxylin and eosin). A complete histopathologic examination was conducted on all animals found dead, on all control and high-dose animals, and on all low-dose male mice. In the other low-dose groups, specific organs as well as gross lesions were subjected to histopathologic examination.

Organs examined included: adrenal gland and kidney in low-dose male rats; kidney, pituitary gland, and thyroid gland in low-dose female rats; and liver, ovary, stomach, and thyroid gland in low-dose female mice. Table 2 lists those tissues and organs that were examined microscopically.

After pathology evaluations were completed by the study laboratory pathologist and the pathology data had been entered into the Toxicology Data Management System, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit for accuracy of labeling and animal identification and for thoroughness of tissue trimming. 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. A quality assessment pathologist reviewed selected tissues for accuracy and consistency of lesion diagnosis. All neoplasms and nonneoplastic lesions in the kidneys of all male and female rats and in the livers of all male and female mice were reviewed. Additionally, neoplasms diagnosed in tissues other than those mentioned were reviewed in all animals, and all diagnoses (neoplastic and nonneoplastic) were reviewed from a randomly selected 10% of animals from each control and high-dose group.

The quality assessment report and slides were submitted to the Pathology Working Group (PWG) chair, who reviewed tissues for which there was a disagreement in diagnosis between the laboratory and quality assessment pathologists. Representative examples of potential chemical-related nonneoplastic lesions and neoplasms and examples of disagreements in diagnosis between the laboratory and quality assessment pathologists were selected by the PWG chair for review by the PWG. The PWG included both the laboratory pathologist and the quality assessment pathologist as well as other pathologists experienced in rodent toxicologic pathology, who examined the tissues without knowledge of dose group or previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the final diagnosis was changed to reflect the opinion of the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are evaluated separately or combined according to the guidelines of McConnell *et al.* (1986).

Statistical Methods

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in graphs located in the results section of this report. Animals were censored from the survival analyses at the time they were found to be dead from other than natural causes; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test for dose-related trends. When significant survival differences were detected, additional analyses using these procedures were carried out to determine the point in time 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) before tissue sampling for histopathology, 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

The majority of tumors in this study were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was a logistic regression analysis, which assumed that the diagnosed tumors were discovered as the result of death from an unrelated cause and, thus, did not affect the risk of death. In this approach, tumor prevalence was modeled as a

logistic function of chemical exposure and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if it did not significantly enhance the fit of the model. The dosed and control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). When tumors are incidental, this comparison of the time-specific tumor prevalences also provides a comparison of the time-specific tumor incidences (McKnight and Crowley, 1984).

In addition to logistic regression, alternative methods of statistical analysis were used, and the results of these tests are summarized in the appendixes. These include the life table test (Cox, 1972; Tarone, 1975), appropriate for rapidly lethal tumors, and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart *et al.*, 1979), procedures based on the overall proportion of tumor-bearing animals.

Tests of significance include pairwise comparisons of each dosed group with controls and a test for an overall dose-response trend. Continuity-corrected tests were used in the analysis of tumor incidence, and reported P values are one-sided. The procedures described above also were used to evaluate selected nonneoplastic lesions.

Analysis of Continuous Variables

For all end points, dosed groups were compared with the control group using the nonparametric multiple comparison test of Dunn (1964) or Shirley (1977). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose response trends and to determine whether Dunn's or Shirley's test was more appropriate for pairwise comparisons.

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can often 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.

QUALITY ASSURANCE METHODS

The 13-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR Part 58). In addition, as study records were submitted to the NTP Archives, they were audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and preliminary review draft of this NTP Technical Report were conducted. Audit procedures are presented in the reports, which are on file at the NIEHS. The audit findings were reviewed and assessed by the NTP staff so that all had been resolved or were otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

The genetic toxicity of probenecid was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium* and to induce sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells. The methods and materials employed in these studies are given in Appendix F.

TABLE 2
Experimental Design and Materials and Methods in the Gavage Studies of Probenecid

14-Day Studies	13-Week Studies	2-Year Studies
Study Laboratory		
EG&G Mason Research Institute (Worcester, MA)	EG&G Mason Research Institute (Worcester, MA)	EG&G Mason Research Institute (Worcester, MA)
Strain and Species		
Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$
Animal Source		
Charles River Laboratories (Kingston, NY)	Charles River Laboratories (Kingston, NY)	Frederick Cancer Research Facility (Frederick, MD)
Time Held Before Study		
19 days	Rats: 15 days Mice: 13 days	Male rats: 20 days Female rats: 14 days Mice: 20 days
Age When Placed on Study		
Rats: 10 weeks Mice: 11 weeks	Rats: 6-7 weeks Mice: 7-8 weeks	Rats: 8-9 weeks Mice: 8 weeks
Date of First Dose		
3 March 1981	Rats: 20 May 1981 Mice: 18 May 1981	Male rats: 27 May 1982 Female rats: 4 June 1982 Male mice: 10 May 1982 Female mice: 18 May 1982
Duration of Dosing		
17 days (5 days/week for 12 dose days)	13 weeks (5 days/week)	103 weeks (5 days/week)
Date of Last Dose		
20 March 1981	Rats: 19 August 1981 Mice: 17 August 1981	Male rats: 17 May 1984 Female rats: 25 May 1984 Male mice: 30 April 1984 Female mice: 8 May 1984
Necropsy Dates		
20 March 1981 - 1 April 1981	Rats: 19-24 August 1981 Mice: 17-19 August 1981	Male rats: 25 May 1984 - 4 June 1984 Female rats: 1-8 June 1984 Male mice: 9-11 May 1984 Female mice: 16-22 May 1984
Age When Killed		
Rats: 12 weeks Mice: 13 weeks	Rats: 19-20 weeks Mice: 20-21 weeks	Rats: 112-114 weeks Mice: 113 weeks
Size of Study Groups		
5 males and 5 females	10 males and 10 females	50 males and 50 females
Animals per Cage		
5	5	5

TABLE 2
Experimental Design and Materials and Methods in the Gavage Studies of Probenecid (continued)

14-Day Studies	13-Week Studies	2-Year Studies
Method of Animal Distribution		
After culling for outliers, animals were assigned to test and control groups so that within a given dose group all initial animal weights were approximately equal (± 2 g).	Same as 14-day studies	After culling for outliers, animals of a species and sex were randomized to individual cages and cages were assigned to dose and control groups using random number tables. Initial rack placement was randomly determined.
Method of Animal Identification		
Ear punch	Ear punch	Ear punch
Diet		
NIH-07 (Zeigler Bros., Gardners, PA), available *ad libitum*	Same as 14-day studies	Same as 14-day studies
Feeders		
Stainless steel (Scientific Cages, Bryan, TX), filled as needed, changed weekly	Stainless steel (Scientific Cages, Bryan, TX), filled twice weekly, changed weekly	Same as 13-week studies
Water		
Chlorinated tap water (Worcester Public Water Supply, Worcester, MA), available *ad libitum*	Same as 14-day studies	Same as 14-day studies
Cages		
Polycarbonate (Lab Products, Rochelle Park, NJ), changed twice weekly	Same as 14-day studies	Same as 14-day studies
Bedding		
Hardwood chips (American Excelsior, Baltimore, MD), changed twice weekly	Same as 14-day studies	Hardwood chips (American Excelsior, Baltimore, MD, or Northeastern Products, Warrensburg, NY), changed twice weekly
Cage Filters		
Nonwoven fiber (Snow Filtration, Cincinnati, OH), changed biweekly	Nonwoven fiber (Lab Products, Rochelle Park, NJ, or Snow Filtration, Cincinnati, OH), changed biweekly	Same as 13-week studies
Racks		
Stainless steel (Lab Products, Rochelle Park, NJ), changed biweekly	Same as 14-day studies	Same as 14-day studies
Animal Room Environment		
Temperature: 23.3°-23.8° C Humidity: 34%-61% Fluorescent light: 12 hours/day Room air changes: 12-15 changes/hour	Temperature: 20.6°-24.4° C Humidity: 32%-78% Fluorescent light: 12 hours/day Room air changes: >12 changes/hour	Temperature: 21.1°-28.3° C Humidity: 18%-62% Fluorescent light: 12 hours/day Room air changes: ≈13 changes/hour

TABLE 2
Experimental Design and Materials and Methods in the Gavage Studies of Probenecid (continued)

14-Day Studies	13-Week Studies	2-Year Studies
Doses 0, 200, 400, 800, 1,600, or 3,200 mg/kg in corn oil by gavage at a volume of 5 mL/kg for rats and 10 mL/kg for mice. The high dose was divided into two doses of 1,600 mg/kg administered at least 5 hours apart.	Rats: 0, 50, 100, 200, 400, or 800 mg/kg in corn oil by gavage at a volume of 5 mL/kg Mice: 0, 100, 200, 400, 800, or 1,600 mg/kg in corn oil by gavage at a volume of 10 mL/kg	0, 100, or 400 mg/kg in corn oil by gavage at a volume of 5 mL/kg for rats and 10 mL/kg for mice
Type and Frequency of Observation Observed twice daily; body weights taken initially, weekly, and at termination; clinical observations recorded as needed. Feed consumption by cage recorded weekly.	Observed twice daily; body weights taken initially, weekly throughout the studies, and at termination; clinical observations recorded as needed.	Observed twice daily; body weights initially, weekly through week 13, monthly thereafter; clinical observations recorded as needed.
Necropsy Necropsy performed on all animals.	**Necropsy** Necropsy performed on all animals. Organ weights recorded for the brain, liver, right kidney, thymus, heart, and lungs of all animals, and the right testis of all males.	**Necropsy** Necropsy performed on all animals
Histopathology None required	**Histopathology** In addition to tissue masses, gross lesions, and associated regional lymph nodes, the following organs and/or tissues were examined histologically for all control animals, all male mice in the second highest dose group (800 mg/kg), and all animals in the highest dose groups: adrenal gland, bone (sternebrae including marrow), brain (frontal cortex and basal ganglia, parietal cortex and thalamus, cerebellum and pons), bronchi, clitoral gland (rats only), esophagus, gallbladder (mice only), heart, kidney, large intestine (cecum, colon, rectum), liver, lung, lymph nodes (mandibular, mesenteric), mammary gland, nasal cavity and turbinates, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland (rats only), prostate gland, salivary gland, seminal vesicle, skin, small intestine (duodenum, jejunum, ileum), spleen, stomach, testis, thymus, thyroid gland, trachea, urinary bladder, and uterus.	**Histopathology** Complete histopathologic examination performed on all control and high-dose animals, as well as all low-dose male mice. The following organs and/or tissues were included in complete histopathologic examinations, as well as any tissue masses, gross lesions, and associated regional lymph nodes: adrenal gland, bone (sternebrae including marrow), brain, bronchi, clitoral gland (rats only), epididymis, esophagus, gallbladder (mice only), heart, kidney, large intestine (cecum, colon, rectum), liver, lung, lymph nodes (mesenteric), mammary gland, nasal cavity and turbinates, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, skin, small intestine (duodenum, ileum, jejunum), spleen, stomach, testis, thymus, thyroid, trachea, urinary bladder, and uterus. In low-dose rats and low-dose female mice, all gross lesions and the following organs were examined histologically: adrenal gland (male rats); kidney (male and female rats); liver (female mice); ovary (female mice); pituitary gland (female rats); stomach (female mice); thyroid gland (female rats and mice).

RESULTS

RATS

14-Day Studies

All rats receiving 3,200 mg/kg died within 8 days (Table 3). Initial mean body weights for females in the four highest dose groups were significantly higher than for the control group because of improper assignment of animals to groups. Although animals within a dose group weighed ± 2 g of a group mean, the body weight means among all dose groups varied more than ± 2 g. Mean body weight gain of males and females in the 1,600 mg/kg group and females in the 800 mg/kg group was significantly lower than that of the controls. Signs of toxicity were observed in the three highest dose groups. Those reported for males in the two highest surviving dose groups (800 and 1,600 mg/kg) included ataxia, hunched posture, lethargy, and periorbital porphyrin staining. In addition, males in the 1,600 mg/kg dose group exhibited dyspnea.

There were no gross lesions attributable to probenecid administration.

TABLE 3
Survival and Mean Body Weights of Rats in the 14-Day Gavage Studies of Probenecid

Dose (mg/kg)	Survival[a]	Mean Body Weights[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	151 ± 3	211 ± 6	60 ± 6	
200	5/5	156 ± 2	217 ± 4	61 ± 3	103
400	5/5	154 ± 2	216 ± 4	62 ± 5	102
800	5/5	153 ± 3	207 ± 2	54 ± 3	98
1,600	5/5	152 ± 4	160 ± 2**	8 ± 4**	76
3,200	0/5[c]	151 ± 3	–	–	–
Female					
0	5/5	104 ± 2	143 ± 2	39 ± 2	
200	5/5	105 ± 2	147 ± 3	42 ± 2	103
400	5/5	120 ± 3**	150 ± 4	30 ± 2	105
800	5/5	121 ± 2**	139 ± 3	18 ± 2**	97
1,600	5/5	123 ± 2**	129 ± 4	6 ± 2**	90
3,200	0/5[d]	122 ± 1**	–	–	–

** Significantly different (P≤0.01) from the control group by Dunn's or Shirley's test
[a] Number surviving/number initially on study
[b] Mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
[c] Day of death: 2,4,5,7,8; no final group mean body weight calculated due to 100% mortality in this group.
[d] Day of death: 2,2,2,2,2; no final group mean body weight calculated due to 100% mortality in this group.

13-Week Studies

All rats lived to the end of the studies, and body weight gain of high-dose males was significantly less than that of the controls (Table 4). There was yellow-brown staining of the perineum of all males and females receiving the highest dose and two females receiving the second highest dose. All high-dose females also had periorbital porphyrin staining.

Organ weights and organ-weight-to-body-weight ratios are presented in Appendix E. All treated female groups showed statistically significant increases in mean liver weights and all except the 50 mg/kg group also showed significant increases in mean liver-weight-to-body-weight ratios. Mean liver weights were slightly increased in all groups of treated males, and that of the group receiving 200 mg/kg was significantly increased compared to controls. The lack of statistical significance in the 400 and 800 mg/kg groups is likely due to the reductions in body weight gain of these groups since the liver-weight-to-body-weight ratios were significantly increased in all treated groups of male rats.

There were no gross or histologic lesions attributable to probenecid administration.

Based on decreased body weight gains in rats receiving 800 mg/kg probenecid in the 13-week studies, probenecid doses of 0, 100, and 400 mg/kg were selected for use in the 2-year studies. The 400 mg/kg dose is equivalent to 10 times the daily human adult dose; the 100 mg/kg dose is equivalent to 2.5 times the maintenance dose given to patients to block renal excretion of penicillin.

TABLE 4
Survival and Mean Body Weights of Rats in the 13-Week Gavage Studies of Probenecid

Dose (mg/kg)	Survival[a]	Mean Body Weights[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	98 ± 3	363 ± 9	265 ± 9	
50	10/10	99 ± 3	350 ± 7	252 ± 9	96
100	10/10	98 ± 3	344 ± 8	246 ± 8	95
200	10/10	98 ± 3	351 ± 6	253 ± 6	97
400	10/10	99 ± 4	348 ± 10	250 ± 10	96
800	10/10	99 ± 4	311 ± 7**	212 ± 6**	86
Female					
0	10/10	100 ± 2	202 ± 3	102 ± 3	
50	10/10	100 ± 2	213 ± 5	113 ± 3	106
100	10/10	100 ± 2	209 ± 4	109 ± 4	104
200	10/10	101 ± 2	202 ± 4	101 ± 3	100
400	10/10	100 ± 2	197 ± 2	97 ± 2	98
800	10/10	100 ± 2	191 ± 3	92 ± 3	95

** Significantly different ($P \leq 0.01$) from the control group by Dunn's or Shirley's test
[a] Number surviving/number initially on study
[b] Mean ± standard error.

2-Year Studies

Body Weights and Clinical Findings

Mean body weights of dosed male rats were within 5% of that of the controls throughout the studies (Figure 2 and Table 5). Although the mean body weight of low-dose female rats was similar to that of the control throughout the studies, high-dose female rats had over 10% lower mean body weights than controls from week 41 to the end of the studies (Table 6 and Figure 2).

No clinical findings attributed to probenecid administration were observed during the 2-year studies.

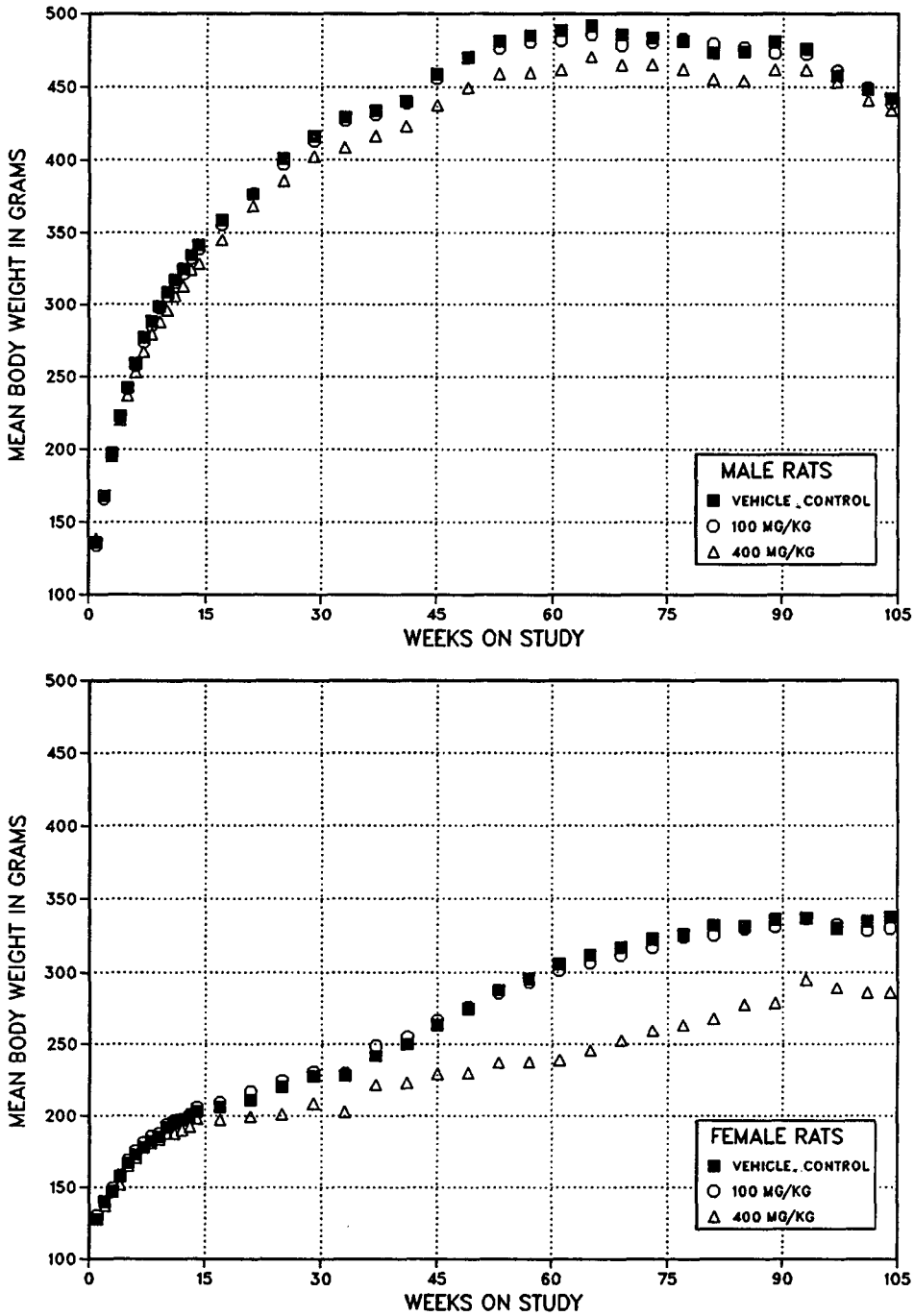


FIGURE 2
Growth Curves for Male and Female Rats Administered Probenecid by Gavage for 2 Years

TABLE 5
Mean Body Weights and Survival of Male Rats in the 2-Year Gavage Studies of Probenecid

Weeks on Study	Vehicle Control		100 mg/kg			400 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	136	50	134	99	50	139	102	50
2	168	50	166	99	50	168	100	50
3	197	50	196	100	50	195	99	50
4	223	50	222	99	50	220	99	50
5	243	50	242	100	50	237	98	50
6	259	50	258	99	50	253	98	50
7	277	50	274	99	50	268	97	50
8	288	50	286	99	50	280	97	50
9	299	50	298	100	50	288	97	50
10	309	50	306	99	50	296	96	50
11	317	50	315	99	50	306	96	50
12	325	50	321	99	50	313	96	50
13	334	50	332	99	50	324	97	50
14	342	50	339	99	50	329	96	50
17	359	50	356	99	50	345	96	50
21	377	50	377	100	50	369	98	50
25	401	50	397	99	50	386	96	50
29	416	50	413	99	50	403	97	50
33	429	50	427	100	50	409	95	50
37	434	50	431	99	50	417	96	50
41	440	50	439	100	50	423	96	50
45	459	49	456	99	49	438	95	50
49	470	49	470	100	49	450	96	49
53	481	49	477	99	49	459	95	49
57	485	49	481	99	49	460	95	48
61	489	49	482	99	49	462	95	48
65	492	48	486	99	49	471	96	48
69	486	48	478	99	48	465	96	47
73	484	48	481	99	46	465	96	45
77	481	48	483	100	45	462	96	44
81	473	47	479	101	45	455	96	44
85	474	47	477	101	44	454	96	40
89	481	45	473	98	43	462	96	38
93	476	44	473	99	42	462	97	38
97	458	41	461	101	37	453	99	34
101	449	41	450	100	35	441	98	31
104	442	39	439	99	35	434	98	24
Terminal sacrifice		37			34			22
Mean for weeks								
1-13	260		258	99		253	97	
14-52	413		411	100		397	96	
53-104	475		473	100		458	96	

TABLE 6
Mean Body Weights and Survival of Female Rats in the 2-Year Gavage Studies of Probenecid

Weeks on Study	Vehicle Control		100 mg/kg			400 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	128	50	131	102	50	128	100	50
2	140	50	140	100	50	137	98	50
3	148	50	150	101	50	147	100	50
4	158	50	159	101	50	152	96	50
5	167	50	169	101	50	165	99	50
6	173	50	176	102	50	171	99	50
7	178	50	182	102	50	178	100	50
8	183	50	186	102	50	181	99	50
9	186	50	188	101	50	184	99	50
10	192	50	194	101	50	188	98	50
11	195	50	197	101	50	188	96	50
12	197	50	198	100	50	190	96	50
13	199	50	201	101	49	192	97	50
14	203	50	206	101	49	198	98	50
17	206	50	209	102	48	198	96	49
21	211	50	217	103	48	200	95	48
25	221	50	224	102	48	201	91	48
29	228	50	230	101	48	209	92	48
33	228	50	230	101	48	203	89	46
37	242	50	249	103	48	222	92	46
41	250	50	255	102	48	223	89	43
45	264	50	267	101	48	229	87	42
49	275	50	277	101	48	230	84	42
53	288	49	286	99	48	237	82	42
57	296	49	294	99	48	238	80	42
61	306	49	302	99	48	239	78	42
65	312	49	307	98	48	246	79	42
69	317	49	312	98	48	253	80	42
73	323	48	317	98	48	260	81	41
77	326	46	324	100	48	264	81	39
81	332	45	326	98	46	268	81	38
85	331	44	330	100	45	278	84	35
89	336	43	331	99	42	279	83	32
93	337	38	336	100	41	295	88	29
97	330	32	333	101	41	290	88	25
101	335	29	329	98	39	286	86	22
104	338	24	330	98	35	287	85	19
Terminal sacrifice		24			35			19
Mean for weeks								
1-13	173		175	101		169	98	
14-52	233		236	101		211	91	
53-104	322		318	99		266	83	

Survival

Estimates of the probabilities of survival of male and female rats administered probenecid in corn oil by gavage at the doses used in these studies and those of the vehicle controls are illustrated in Kaplan-Meier curves (Figure 3). The survival of rats occurred with a significant dose-related trend and that of high-dose males was significantly less than that of the controls (Table 7). There were approximately twice as many high-dose males killed while moribund (23/50) as low-dose (13/50) or controls (12/50). In each group, approximately equal numbers of animals were killed because of large external neoplasms, mainly fibromas, fibrosarcomas, or preputial gland neoplasms; advanced nonneoplastic disease, especially nephropathy; and mononuclear cell leukemia or various other malignant neoplasms (Table 8 and Appendix A, Table A1). There were, however, more high-dose males than control males without definitive gross or microscopic lesions to account for their moribund condition. The moribund condition of these animals was presumed to be the result of chemical toxicity.

Survival of control and high-dose females was less than that of the low-dose females (Table 7). Nearly all unscheduled early deaths in the control and low-dose groups were rats killed while moribund, whereas in the high-dose group, there was a large number of natural deaths which contributed to the overall mortality. The majority of the natural deaths occurred during the first 52 weeks of the studies while most of the moribund sacrifices occurred after week 88.

This unusual mortality pattern is the result of several independent factors. Compared to the low-dose group, more control females were moribund because of large external neoplasms, primarily mammary gland fibroadenomas, or because of debilitation as a result of mononuclear cell leukemia or other miscellaneous neoplasms (Table 8 and Appendix B, Table B1). On the other hand, the lower survival of the high-dose females was attributed to the large number of natural deaths. In these animals there were no gross or histologic findings which could be clearly implicated as the cause of death; these deaths were therefore presumed to be related to chemical toxicity.

Pathology and Statistical Analysis of Results

Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one study group are presented in Appendix A for male rats and in Appendix B for female rats. No statistically significant increased tumor incidences were found in rats of either sex. In the 2-year studies, several statistically significant negative trends in the incidences of neoplasms were seen in male and female rats (Appendix A, Table A3 and Appendix B, Table B3). These included adrenal gland pheochromocytoma (20/49; 19/50; 8/50) in male rats and mammary gland fibroadenoma (24/50; 23/50; 5/50) and thyroid C-cell tumors (12/49; 4/50; 3/47) in female rats.

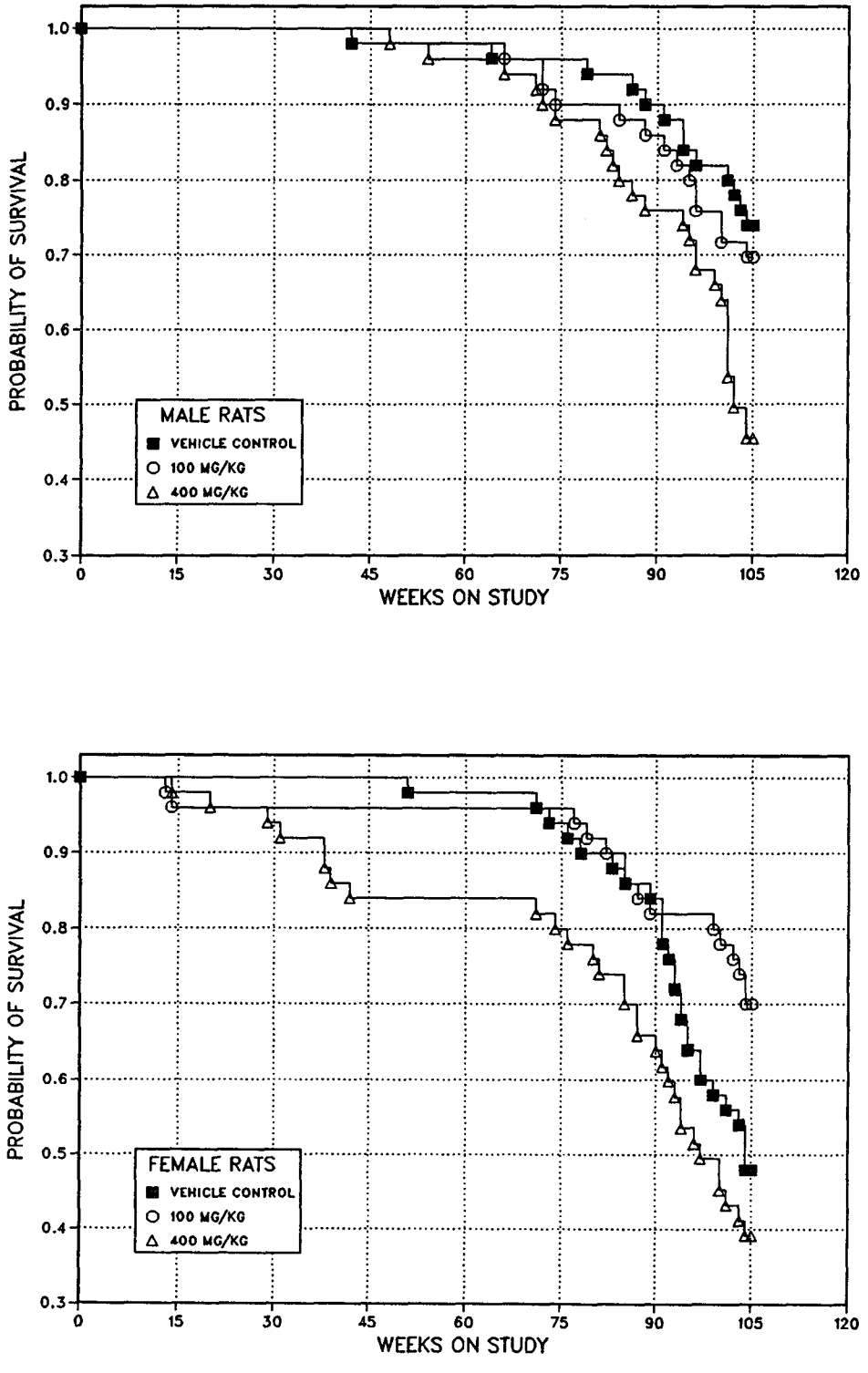


FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Rats Administered Probenecid by Gavage for 2 Years

TABLE 7
Survival of Rats in the 2-Year Gavage Studies of Probenecid

	Vehicle Control	100 mg/kg	400 mg/kg
Male			
Animals initially in study	50	50	50
Natural deaths	3	4	5
Moribund kills	10	11	22
Accidental deaths[a]	0	1	1
Animals surviving to study termination[b]	37	34	22
Percent survival at end of study[c]	74	69	45
Mean survival (days)[d]	700	687	667
Survival P values[e]	0.003	0.722	0.006
Female			
Animals initially in study	50	50	50
Natural deaths	1	0	10
Moribund kills	25	15	20
Accidental deaths[a]	0	0	1
Animals surviving to study termination[b]	24	35	19
Percent survival at end of study[c]	48	70	39
Mean survival (days)[d]	677	681	600
Survival P values[e]	0.041	0.048N	0.231

[a] Censored from survival analyses
[b] Rats found moribund during the last week of the studies were considered survivors.
[c] Kaplan-Meier determinations. Survival rates are adjusted for accidental deaths.
[d] Mean of all deaths (uncensored, censored, terminal sacrifice)
[e] The entry in the control column is the trend test result. Subsequent entries are the results of pairwise tests.

TABLE 8
Causes of Death in Rats in the 2-Year Gavage Studies of Probenecid

	Vehicle Control	100 mg/kg	400 mg/kg
Male			
Found moribund[a]			
External masses	5	2	5
Mononuclear cell leukemia	2	4	3
Miscellaneous neoplasia	1	4	6
Nonneoplastic disease	3	2	1
Undetermined cause	1	1	8
Totals	12	13	23
Found dead			
Mononuclear cell leukemia	1	2	2
Miscellaneous neoplasia	1	1	1
Nonneoplastic disease	0	0	1
Undetermined cause	2	1	1
Totals	4[b]	4	5
Female			
Found moribund[a]			
External masses	12	7	3
Mononuclear cell leukemia	8	5	8
Miscellaneous neoplasia	5	1	3
Nonneoplastic disease	0	1	3
Undetermined cause	1	1	3
Totals	26	15	20
Found dead			
Mononuclear cell leukemia	0	0	1
Miscellaneous neoplasia	0	0	0
Nonneoplastic disease	0	0	0
Undetermined cause	1	0	9
Totals	1	0	10

[a] Includes animals found moribund during the last week of the studies.
[b] Includes an animal that died during the last week of the studies.

MICE

14-Day Studies

Of the animals receiving 3,200 mg/kg, all females and two of five males died during the studies (Table 9). Mean body weight gain of surviving high-dose males was slightly lower than that of the controls. Male and female mice receiving 3,200 mg/kg exhibited convulsions, hyperpnea, prostration, and periorbital porphyrin staining.

There were no gross lesions attributable to probenecid administration.

13-Week Studies

Five males and three females receiving 1,600 mg/kg and one male receiving 800 mg/kg died during the studies (Table 10). Body weight gain of surviving 1,600 mg/kg mice and 800 mg/kg female mice were significantly reduced relative to controls. Mice in the two highest dose groups showed a dose-related behavioral response to probenecid administration. Animals receiving the highest dose became hyperactive during the first week of the studies, whereas those in the second highest dose groups showed similar responses beginning the second week and continuing throughout the studies.

TABLE 9
Survival and Mean Body Weights of Mice in the 14-Day Gavage Studies of Probenecid

Dose (mg/kg)	Survival[a]	Mean Body Weights[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	23.1 ± 0.3	28.0 ± 0.2	4.9 ± 0.4	
200	5/5	23.2 ± 0.3	28.3 ± 0.3	5.1 ± 0.1	101
400	5/5	23.0 ± 0.2	27.7 ± 0.5	4.8 ± 0.5	99
800	5/5	23.0 ± 0.1	27.4 ± 0.3	4.5 ± 0.2	98
1,600	5/5	23.0 ± 0.3	27.2 ± 0.3	4.2 ± 0.2	97
3,200	3/5[c]	22.6 ± 0.6	26.0 ± 1.2	3.6 ± 0.7	93
Female					
0	5/5	17.9 ± 0.1	22.0 ± 0.2	4.0 ± 0.1	
200	5/5	18.2 ± 0.2	22.4 ± 0.4	4.2 ± 0.3	102
400	5/5	17.9 ± 0.2	22.0 ± 0.6	4.1 ± 0.5	100
800	5/5	18.0 ± 0.1	22.1 ± 0.3	4.1 ± 0.2	101
1,600	5/5	18.3 ± 0.2	22.6 ± 0.2	4.3 ± 0.2	103
3,200	0/5[d]	18.2 ± 0.3	–	–	–

[a] Number surviving/number initially on study. Differences from the control group are not significant by Dunn's or Shirley's test.
[b] Mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
[c] Day of death: 2,3
[d] Day of death: 3,4,4,8,9; no final group mean body weight calculated due to 100% mortality in this group.

TABLE 10
Survival and Mean Body Weights of Mice in the 13-Week Gavage Studies of Probenecid

Dose (mg/kg)	Survival[a]	Mean Body Weights[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	21.1 ± 0.4	33.0 ± 0.8	11.9 ± 0.7	
100	10/10	21.0 ± 0.3	34.2 ± 0.6	13.2 ± 0.6	104
200	10/10	21.2 ± 0.4	33.9 ± 0.6	12.7 ± 0.6	103
400	10/10	20.9 ± 0.5	34.3 ± 0.7	13.4 ± 0.5	104
800	9/10[c]	21.2 ± 0.6	33.1 ± 0.6	11.9 ± 0.5	100
1,600	5/10[d]	21.4 ± 0.3	29.3 ± 0.6*	8.0 ± 0.7*	89
Female					
0	10/10	16.7 ± 0.3	26.6 ± 0.6	9.9 ± 0.4	
100	10/10	16.9 ± 0.2	26.0 ± 0.7	9.1 ± 0.6	98
200	9/10[e]	16.8 ± 0.3	25.7 ± 0.4	8.9 ± 0.4	97
400	10/10	16.9 ± 0.3	27.1 ± 0.6	10.3 ± 0.6	102
800	10/10	16.9 ± 0.2	25.1 ± 0.4	8.2 ± 0.4*	94
1,600	7/10[f]	17.2 ± 0.4	23.7 ± 0.6**	6.5 ± 0.4**	89

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Number surviving/number initially on study
[b] Mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
[c] Week of death: 9
[d] Week of death: 1,7,10,10,10
[e] During week 2, one female was found to be pregnant and was removed from the study.
[f] Week of death: 1,1,10

Organ weights and organ-weight-to-body-weight ratios are presented in Appendix E (Tables E3 and E4). Statistically significant increases were seen in mean liver weights from the two highest dose groups of males and females. Liver-weight-to-body weight ratios were statistically significantly different from controls for all dose groups, except males receiving 100 mg/kg and females receiving 400 mg/kg. Other differences in absolute and relative organ weights were not considered biologically significant.

There were no gross or histologic lesions attributable to probenecid administration.

Based on decreased body weight gains in mice receiving 800 and 1,600 mg/kg probenecid in the 13-week studies, probenecid doses of 0, 100, and 400 mg/kg were selected for use in the 2-year studies. The 400 mg/kg dose is equivalent to 10 times the daily human adult dose; the 100 mg/kg dose is equivalent to 2.5 times the maintenance dose given to patients to block renal excretion of penicillin.

2-Year Studies

Body Weights and Clinical Findings

Mean body weights of male and female mice receiving probenecid were similar to those of the controls throughout the studies (Tables 11 and 12 and Figure 4).

No clinical findings attributed to probenecid administration were observed during the 2-year studies.

TABLE 11
Mean Body Weights and Survival of Male Mice in the 2-Year Gavage Studies of Probenecid

Weeks on Study	Vehicle Control		100 mg/kg			400 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	23.2	50	23.2	100	50	23.0	99	50
2	24.9	49	24.9	100	48	24.7	99	49
3	25.5	49	25.6	100	48	25.7	101	49
4	26.5	49	26.8	101	48	26.2	99	49
5	27.2	49	26.8	99	48	26.9	99	49
6	27.8	49	27.7	100	48	28.1	101	48
7	27.8	49	28.4	102	48	28.2	101	48
8	29.1	49	28.8	99	48	28.8	99	48
9	29.6	49	29.7	100	48	29.0	98	48
10	30.6	49	30.4	99	48	30.5	100	48
11	30.5	49	30.9	101	48	30.6	100	48
12	31.2	49	31.1	100	48	31.1	100	48
13	31.7	49	31.7	100	48	31.5	99	48
14	31.1	49	31.3	101	48	31.7	102	48
17	32.9	49	32.2	98	48	32.2	98	48
21	33.4	49	32.3	97	48	32.4	97	48
25	35.1	49	34.1	97	47	35.2	100	48
29	35.9	49	35.2	98	47	36.1	101	48
37	37.7	49	36.3	96	45	35.8	95	48
41	38.7	49	36.4	94	45	37.5	97	48
45	38.0	49	37.0	97	44	37.7	99	46
49	38.4	48	37.6	98	44	37.8	98	46
53	39.9	48	38.3	96	44	38.7	97	45
57	40.2	47	38.8	97	43	38.9	97	45
61	39.9	46	38.3	96	42	39.0	98	44
65	40.4	46	38.1	94	39	38.9	96	43
69	39.5	46	37.6	95	37	38.1	97	43
73	39.9	46	38.6	97	36	38.6	97	43
77	38.9	45	37.5	96	35	38.4	99	41
81	39.1	44	38.1	97	34	38.5	99	41
85	38.3	42	37.7	98	34	37.7	98	39
89	37.9	40	37.7	100	33	37.6	99	36
93	37.4	40	36.5	98	31	36.9	99	31
97	36.6	40	37.4	102	27	37.2	102	29
101	36.3	38	36.3	100	26	36.4	100	28
104	37.5	38	37.0	99	24	37.8	101	24
Terminal sacrifice		38			23			24
Mean for weeks								
1-13	28.1		28.2	100		28.0	99	
14-52	35.7		34.7	97		35.2	98	
53-104	38.7		37.7	97		38.1	98	

TABLE 12
Mean Body Weights and Survival of Female Mice in the 2-Year Gavage Studies of Probenecid

Weeks on Study	Vehicle Control		100 mg/kg			400 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	18.7	50	18.9	101	50	18.6	100	50
2	19.5	50	19.4	100	50	19.5	100	50
3	20.5	49	20.8	102	50	20.4	100	50
4	20.9	49	20.5	98	50	20.9	100	50
5	21.4	49	21.4	100	50	21.4	100	50
6	21.8	48	21.7	100	49	21.9	101	50
7	22.5	48	22.8	101	49	23.0	102	50
8	22.9	48	22.9	100	49	22.6	99	50
9	23.9	48	23.8	100	49	23.8	100	50
10	24.0	48	23.9	100	49	24.0	100	50
11	24.7	48	24.3	98	49	24.2	98	50
12	24.8	48	24.5	99	49	24.7	100	50
13	24.7	48	24.8	100	49	24.4	99	50
14	25.2	48	25.1	100	49	25.5	101	50
17	26.2	48	26.0	99	48	25.4	97	50
21	27.0	48	26.8	99	48	26.8	99	50
25	28.9	48	28.9	100	48	28.8	100	50
29	29.4	48	29.6	101	48	29.6	101	50
33	31.9	48	31.2	98	48	31.2	98	50
37	31.7	48	32.6	103	48	32.4	102	50
41	34.5	48	34.8	101	48	34.5	100	50
45	34.9	48	34.9	100	48	34.5	99	49
49	35.4	48	35.9	101	47	35.7	101	49
53	36.7	48	37.4	102	46	36.9	101	47
57	38.6	48	38.9	101	46	38.0	98	47
61	38.9	48	39.3	101	46	37.6	97	46
65	39.7	48	40.3	102	46	39.1	99	45
69	40.2	48	40.6	101	46	38.2	95	44
73	40.6	48	41.1	101	45	39.6	98	43
77	39.6	48	41.1	104	45	39.7	100	41
81	39.7	47	41.0	103	42	39.0	98	41
85	38.6	46	40.8	106	41	38.8	101	37
89	39.4	42	40.6	103	39	40.2	102	36
93	38.2	42	40.4	106	37	38.6	101	35
97	38.8	39	41.2	106	36	39.6	102	34
101	37.5	37	39.8	106	33	39.2	105	34
104	38.6	33	39.8	103	32	39.8	103	32
Terminal sacrifice		32			32			32
Mean for weeks								
1-13	22.3		22.3	100		22.3	100	
14-52	30.5		30.6	100		30.4	100	
53-104	38.9		40.2	103		38.9	100	

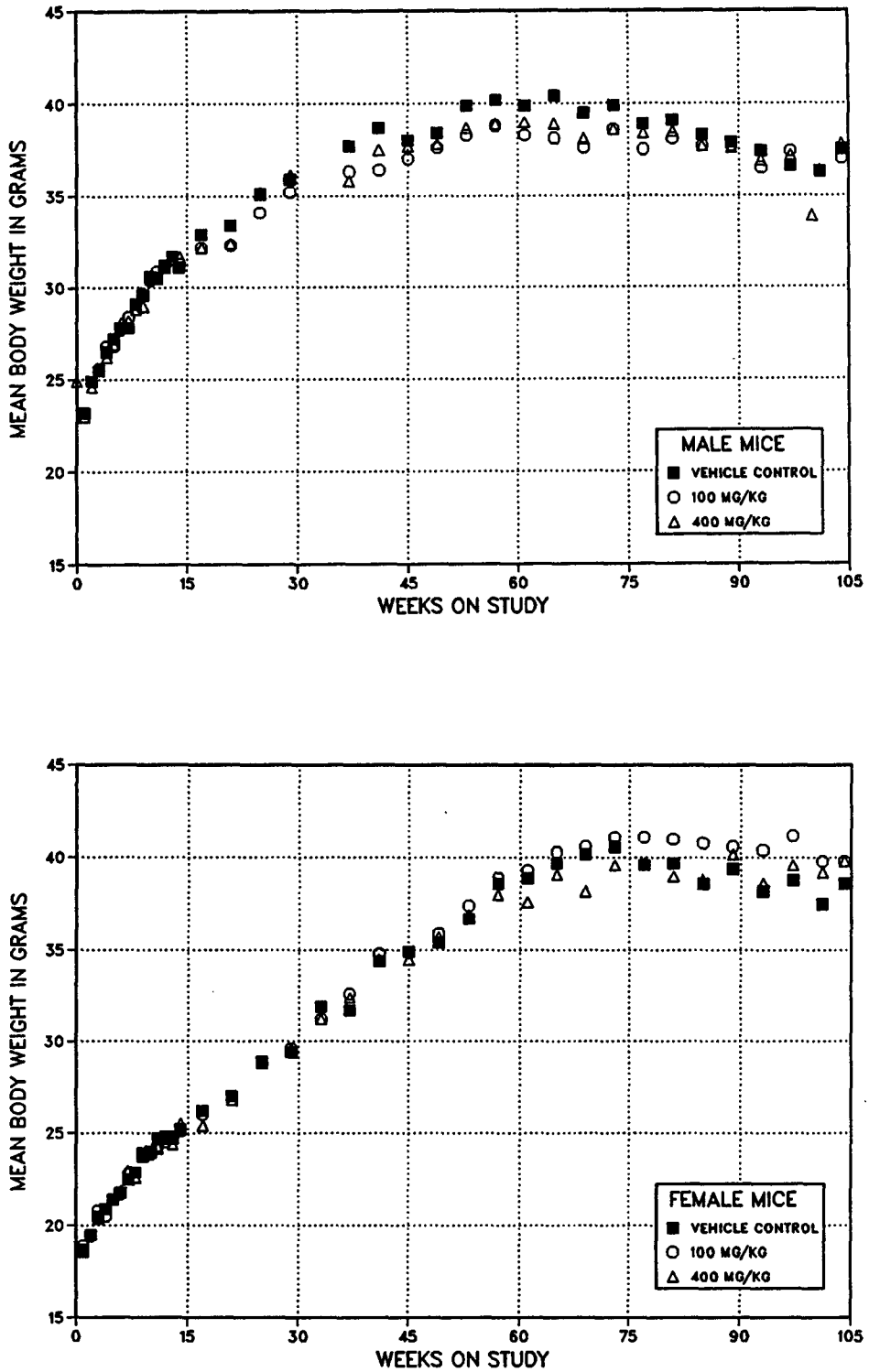


FIGURE 4
Growth Curves for Male and Female Mice Administered Probenecid by Gavage for 2 Years

Survival

Overall survival information is given in Table 13. Estimates of the probabilities of survival of male and female mice administered probenecid in corn oil by gavage at the doses used in these studies and those of the vehicle controls are illustrated in Kaplan-Meier curves (Figure 5). Both treated groups of male mice had significantly lower survival (48%) than controls (76%), whereas survival of female mice was similar among all groups. Clinical observations, gross necropsy findings, and histopathologic lesions were reviewed for animals that died before terminal sacrifice, and the probable and contributory causes of death or reasons for moribund sacrifice were determined. The increased number of moribund sacrifices or natural deaths in the low- and high-dose males was clearly attributable to several pathologic conditions including various malignant neoplasms such as rhabdomyosarcoma, lymphoma, hemangiosarcoma, anorectal squamous cell carcinoma, histiocytic sarcoma, and hepatocellular carcinomas (Table 14). Other males died or were killed moribund because of fight wounds or severe nonneoplastic disease such as pyelonephritis. None of these conditions were related to compound administration. The numbers of males for which the cause of death or moribund condition could not be determined were similar among control and treated groups.

TABLE 13
Survival of Mice in the 2-Year Gavage Studies of Probenecid

	Vehicle Control	100 mg/kg	400 mg/kg
Male			
Animals initially in study	50	50	50
Natural deaths	7	6	13
Moribund kills	5	19	13
Accidental deaths[a]	0	2	0
Animals surviving to study termination	38	23	24
Percent survival at end of study[b]	76	48	48
Mean survival (days)[c]	674	592	628
Survival P values[d]	0.050	0.009	0.011
Female			
Animals initially in study	50	50	50
Natural deaths	8	7	9
Moribund kills	9	9	9
Accidental deaths[a]	0	1	0
Other[e]	1	1	0
Animals surviving to study termination	32	32[f]	32
Percent survival at end of study[b]	65	67	64
Mean survival (days)[c]	690	668	657
Survival P values[d]	0.679	0.929	0.759

[a] Censored from survival analyses.
[b] Kaplan-Meier determinations. Survival rates adjusted for accidental deaths.
[c] Mean of all deaths (uncensored, censored, terminal sacrifice).
[d] The entry in the control column is the trend test result. Subsequent entries are the results of pairwise tests.
[e] These animals were found to be pregnant and were removed from the study.
[f] One of these animals was found moribund on the last day of the study.

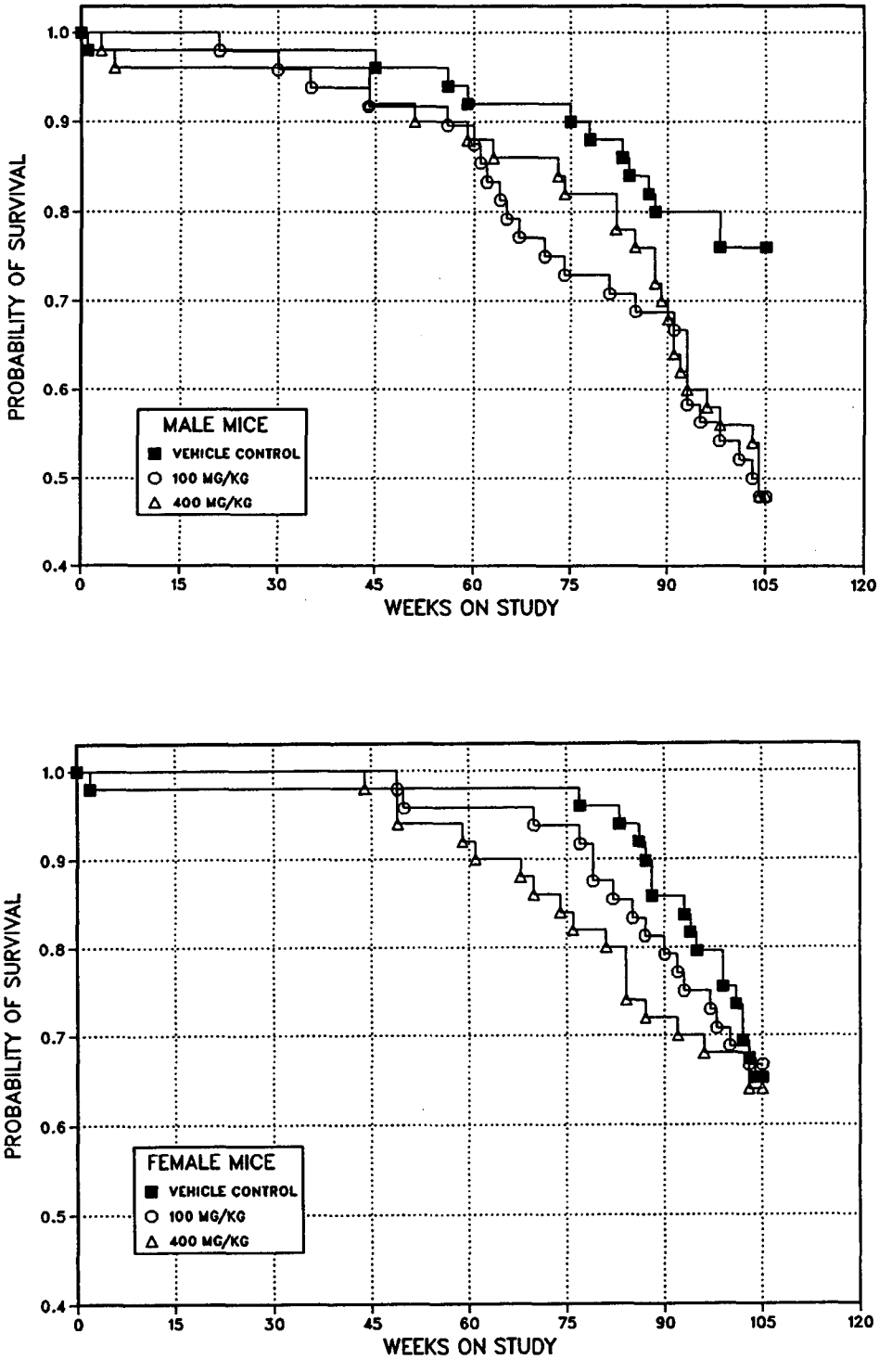


FIGURE 5
Kaplan-Meier Survival Curves for Male and Female Mice Administered Probenecid by Gavage for 2 Years

TABLE 14
Causes of Death in Mice in the 2-Year Gavage Studies of Probenecid

	Vehicle Control	100 mg/kg	400 mg/kg
Male			
Found moribund			
External masses	1	5	3
Fight wounds	1	2	0
Miscellaneous neoplasia	3	5	8
Nonneoplastic disease	0	2	1
Undetermined cause	0	5	1
Totals	5	19	13
Found dead			
Fight wounds	0	1	1
Miscellaneous neoplasia	2	2	5
Nonneoplastic disease	1	0	0
Undetermined cause	5	3	7
Totals	7	6	13
Female			
Found moribund			
External masses	0	1	1
Miscellaneous neoplasia	4	4	1
Ovarian abscesses	0	3	4
Nonneoplastic disease	1	0	1
Undetermined cause	4	2	2
Totals	9	10[a]	9
Found dead			
Miscellaneous neoplasia	2	2	1
Ovarian abscesses	1	3	6
Nonneoplastic disease	1	1	0
Undetermined cause	4	1	2
Totals	8	7	9

[a] Includes an animal found moribund on the last day of the studies.

In females, the overall survival and ratio of moribund sacrifices to natural deaths did not vary significantly among groups (Table 14). There were only a few early deaths for which the cause of death or reason for moribund sacrifice could not be determined; the incidences of these cases was not related to treatment. The natural death or moribund condition of most females was attributed to ovarian abscesses and miscellaneous neoplasms including histiocytic sarcoma, malignant lymphoma, harderian gland carcinoma, hemangiosarcoma, and fibrosarcoma. None of these neoplasms were significantly increased in dosed females although ovarian abscesses increased in a dose-related manner.

Pathology and Statistical Analysis of Results

Summaries of the incidence of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one study group, and historical control incidence for the neoplasms mentioned in this section are presented in Appendix C for male mice and Appendix D for female mice.

Liver: The incidences of hepatocellular adenoma (single and multiple: control, 3/48; low-dose, 2/49; high-dose, 14/49) and combined hepatocellular adenoma or carcinoma (5/48; 3/49; 16/49) occurred with a significant positive trend in female mice, and the incidences in the high-dose group were significantly higher than those of the controls (Table 15). The incidence of hepatocellular adenomas in the high-dose group was also outside the range of historical controls at the study laboratory (31/496; mean, 6.3%; range, 2%-6%). Adenomas were nodular masses composed of well-differentiated hepatocytes with eosinophilic or vacuolated cytoplasm. Carcinomas were larger neoplasms that sometimes involved entire liver lobes. These masses consisted of cells arranged in acinar or trabecular patterns or in cords. Cells had basophilic cytoplasm, large nuclei with coarsely stippled chromatin and numerous mitotic figures. Areas of necrosis and mineralization were common in some carcinomas.

In male mice, the incidences of primary hepatocellular neoplasms were similar among control and dose groups. The incidence of liver necrosis was increased in dosed male mice (4/50; 9/50; 14/50). The necrosis was focal and generally located within or adjacent to large neoplasms of varying histogenesis including hemangiosarcoma, histiocytic sarcoma, and hepatocellular carcinoma. Therefore, liver necrosis was considered secondary to invasive growth of liver neoplasms rather than related to compound administration.

Skin: There was a slight increase in subcutaneous mesenchymal neoplasms in dosed male mice (Table 16). Fibromas, fibrosarcomas, neurofibromas, and neurofibrosarcomas principally consisted of neoplastic fibroblasts and the intercellular collagen produced by these cells. Neurofibromas and neurofibrosarcomas were distinguished from the fibromas and fibrosarcomas by a pattern of growth similar to the nerve sheath neoplasms of humans. Unlike the neurofibromas and neurofibrosarcomas of humans, the origin of these neoplasms from nerves has not been clearly demonstrated in $B6C3F_1$ mice and the histogenesis of these neoplasms may be similar to that of fibromas and fibrosarcomas. The neoplasms diagnosed as sarcomas were so poorly differentiated that their cell of origin could not be determined, though some are likely to be anaplastic fibrosarcomas. The overall incidence of mesenchymal neoplasms in the control group is lower than the mean of the historical controls and the incidence in the dosed groups is well within the range of historical controls at the study laboratory (56/349; mean, 16%; range, 2% to 32%). Because of these reasons and the lack of a clear dose-related increase, these mesenchymal neoplasms are not considered related to compound administration.

Ovary: Combined unilateral and bilateral abscesses occurred in a dose-related increased incidence in female mice (1/47; 7/48; 11/50). Ovarian abscesses were considered causally related to bacterial infection (*Klebsiella oxytoca* and *Klebsiella pneumoniae*) rather than directly related to probenecid.

TABLE 15
Liver Tumors in Female Mice in the 2-Year Gavage Studies of Probenecid

	Vehicle Control	100 mg/kg	400 mg/kg
Hepatocellular Adenoma[e]			
Overall rates[a]	3/48 (6%)	2/49 (4%)	14/49 (29%)
Adjusted rates[b]	7.6%	5.5%	41.0%
Terminal rates[c]	1/32 (3%)	1/32 (3%)	12/32 (38%)
First incidence (days)	612	595	586
Logistic regression tests[d]	P<0.001	P=0.447N	P=0.002
Hepatocellular Carcinoma			
Overall rates	2/48 (4%)	2/49 (4%)	3/49 (6%)
Adjusted rates	5.3%	5.5%	9.0%
Terminal rates	0/32 (0%)	1/32 (3%)	2/32 (6%)
First incidence (days)	687	595	716
Logistic regression tests	P=0.395	P=0.683N	P=0.448
Hepatocellular Adenoma or Hepatocellular Carcinoma			
Overall rates	5/48 (10%)	3/49 (6%)	16/49 (33%)
Adjusted rates	12.5%	8.5%	45.6%
Terminal rates	1/32 (3%)	2/32 (6%)	13/32 (41%)
First incidence (days)	612	595	586
Logistic regression tests	P<0.001	P=0.329N	P=0.003

[a] Number of tumor-bearing animals/number of animals examined at site
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard these lesions as nonfatal. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] 2-year historical incidence for vehicle control groups in NTP corn oil gavage studies (mean ± standard deviation): 114/2,336 (4.9% ± 3.9%); range 0%-20%

TABLE 16
Incidences of Subcutaneous Mesenchymal Neoplasms in Male Mice in the 2-Year Gavage Studies of Probenecid[a]

	Vehicle Control	100 mg/kg	400 mg/kg
Fibroma	0/50	0/50	3/50
Fibrosarcoma	1/50	4/50	3/50
Neurofibroma	0/50	1/50	1/50
Neurofibrosarcoma	0/50	1/50	0/50
Sarcoma	0/50	1/50	0/50
Combined incidence[b]	1/50	7/50	6/50
Life table tests[c]	P=0.100	P=0.014	P=0.031
Logistic regression tests[c]	P=0.158	P=0.043	P=0.064

[a] Incidences based on the number of animals necropsied
[b] 2-year historical incidence for fibroma or fibrosarcoma for vehicle control groups in NTP corn oil gavage studies (mean ± standard deviation): 168/2,340 (7.2% ± 7.1%); range 0%-29%
[c] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal.

GENETIC TOXICITY

Tabular results of genetic toxicity testing are presented in Appendix F. Probenecid (33 to 10,000 μg/plate) was tested for induction of gene mutations in *Salmonella typhimurium* strains TA100, TA1535, TA1537, and TA98 using a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9. No increase in mutant colonies was observed in any of these four tester strains (Mortelmans *et al.*, 1986; Appendix F, Table F1).

In cytogenetic tests with Chinese hamster ovary (CHO) cells, probenecid induced sister chromatid exchanges (SCE) over a concentration range of 5 to 160 μg/mL in two of three trials conducted in the absence of S9. The results of this SCE test were variable among trials: in the first trial, a clear dose-response relationship was apparent; the second trial was negative; and the third trial had significant increases in SCE at the lowest and highest doses tested, with smaller increases observed at intermediate doses. Overall, the assay was judged to be positive. No increase in SCE was observed with Aroclor 1254-induced male Sprague-Dawley rat liver S9 (Appendix F, Table F2).

Probenecid (500 to 1,250 μg/mL) was negative for induction of chromosomal aberrations in CHO cells, with or without S9 (Appendix F, Table F3).

DISCUSSION AND CONCLUSIONS

Probenecid was recommended by the Food and Drug Administration for 2-year toxicology and carcinogenesis studies because of its widespread use as a uricosuric agent in the treatment of chronic gout and because there was a lack of carcinogenicity data. Probenecid was identified as a therapeutic agent during a planned approach to find an organic acid that would inhibit the renal tubule secretion of penicillin (Beyer *et al.*, 1951). Probenecid, a highly lipid-soluble benzoic acid derivative, inhibits the transport of a wide variety of organic acids across epithelial barriers, particularly the renal tubule. The renal effect of probenecid is to reduce the concentration of certain compounds in the urine and to elevate their plasma levels. In contrast, probenecid increases the excretion of uric acid by inhibiting reabsorption.

The NTP toxicity and carcinogenicity studies were conducted by administering the chemical in corn oil by gavage to F344/N rats and B6C3F_1 mice of each sex. The toxic effects of probenecid in the 14-day studies included ataxia in rats and convulsions in mice, reduced survival in rats of each sex and female mice receiving the 3,200 mg/kg, and reduced body weight gain in male and female rats receiving 800 mg/kg, and female rats receiving 1,600 mg/kg.

In the 13-week studies, deaths occurred in mice receiving 1,600 mg/kg, but not in dosed rats. Final mean body weights were reduced by 14% for high-dose male rats, by 5% for high dose female rats, and by 11% for male and female mice as compared to controls. Mice at the two highest dose groups, 800 and 1,600 mg/kg, showed signs of hyperactivity.

Large overdoses of probenecid in humans are reported to produce stimulation of the central nervous system, convulsions, and death from respiratory failure (Weiner and Mudge, 1985). Similar signs of toxicity were observed in treated rats and mice in the NTP 14-day and 13-week studies. Although the precise cause of the stimulating effects on the central nervous system and the physiological alterations leading to death are unknown, they may be related to the inhibitory effects of probenecid on the active transport of organic anions from the choroid plexus into the plasma (Bowman and Rand, 1980). Probenecid has been shown to cause the accumulation of homovanillic acid and 5-hydroxyindoleacetic acid, acidic metabolites of dopamine and serotonin in the cerebrospinal fluid. Dopamine and serotonin are synaptic neurotransmitters involved in the normal functioning of a wide variety of neurons in the brain. Alterations in the activity of these neurotransmitters is known or suspected to affect behavior, motor activity, regulation of body temperature, neuroendocrine control, and other essential physiological activities (Bloom, 1985).

In the NTP 13-week studies, female rats and male and female mice receiving 800 and 1,600 mg/kg showed significant increases in liver weight compared to controls. The increase in liver weights could be attributed to the fact that probenecid is an inducer of liver microsomal enzymes (Welch *et al.*, 1967). No compound-related lesions were observed in rats or mice. The lack of compound-related lesions was reported previously in rats receiving 100, 200, or 400 mg/kg, 5 days a week for 13 weeks and in rats receiving a single dose of 1,600 mg/kg (McKinney *et al.*, 1951). The half-life of probenecid has been reported to be 3 to 4 hours in rats (Dayton *et al.*, 1973). The ability of animals to rapidly eliminate probenecid may have contributed to this lack of compound-related toxic lesions.

Based on mortalities and body weight depression observed at higher doses in the 13-week studies, doses of 0, 100, and 400 mg/kg of probenecid were used in the 2-year studies for both rats and mice. The 400 mg/kg dose is equivalent to 5 times the daily human dose; and the 100 mg/kg dose is equivalent to 2.5 times the maintenance dose given to patients to block renal excretion of penicillin.

In the 2-year studies, the final mean body weights of both groups of dosed male rats and low-dose female rats were similar to those of the controls. The mean body weights of high-dose female rats, however, were lower than control values throughout the second year of the study. The final mean body weight for this group was 15% lower than the control value.

The survival of high-dose male rats was significantly less than controls (control, 37/50; low-dose, 34/50; high-dose, 22/50). The reduced survival of high-dose rats was attributed to increased number of animals that were sacrificed in a moribund state. However, in a number of these animals there were no microscopic lesions found that could account for their moribund condition. Survival in control and high-dose female rats was decreased compared to that in low-dose females (24/50; 35/50; 19/50). The lower survival in the control group was attributed to an increased number of animals sacrificed in a moribund state due to large external tumors or due to debilitation as a result of mononuclear cell leukemia or other neoplasms. As in the case of high-dose male rats, no gross or microscopic lesions were found that could account for many of the deaths in high-dose female rats.

The absence of gross or histopathologic lesions in many high-dose rats that were sacrificed in a moribund state or that died naturally suggests that probenecid caused subtle toxicity that was not detected in these animals by standard pathology procedures. This is consistent with the short-term studies, in which no lesions were detected at necropsy or by light microscopic examination of tissue sections. It is also consistent with findings in humans who have succumbed to overdoses of the drug. Moreover, probenecid has caused fatal hypersensitivity in one patient and immune hemolytic anemia in another (Gosselin *et al.*, 1976; Kickler *et al.*, 1986). Based on the reduced survival in high-dose rats due to chemical toxicity and reduced body weight in females, it is concluded that higher doses would not have been tolerated. Despite the slightly reduced final survival in the high-dose groups, the studies were considered adequate for assessing the carcinogenic potential of probenecid, as a sufficient number of animals lived long enough to be at risk for development of neoplasia (60% survival after 101 weeks in high-dose males, after 89 weeks in high-dose females).

There were no increases in the incidences of neoplasms at any site in the rats that could be attributed to the administration of probenecid. However, the incidence of mammary gland fibroadenoma in female rats occurred with a statistically significant negative trend. A statistically significant negative trend occurred for thyroid C-cell adenomas and combined thyroid C-cell adenomas or carcinomas in female rats. Although the factors leading to the decreased incidence of these lesions in female rats are not known, they may be related, in part, to the decreases in body weight observed in this group. Rao *et al.* (1987) have shown a direct association between body weight and the incidence of mammary gland tumors in female F344/N rats. Alternatively, the possible effect of probenecid on dopaminergic activity in the brain may have contributed to the decreased incidence of mammary gland fibroadenomas. Dopamine is responsible for inhibiting the release of prolactin from the pituitary gland, and drugs which stimulate dopaminergic activity inhibit prolactin release and subsequently the development and growth of mammary gland tumors. As mentioned above, probenecid has been shown to increase the level of homovanillic acid, a metabolite of dopamine, in the cerebral spinal fluid. However, it remains to be demonstrated if probenecid has a significant biological effect on dopaminergic activity in the brain at sublethal doses.

Mean body weights of male and female mice receiving probenecid were similar to controls. Survival of dosed male mice was significantly lower than controls (control, 38/50; low-dose, 23/50; high-dose, 24/50). The cause of death or moribund sacrifice in the majority of cases was attributed to the presence of malignant neoplasms, fight wounds or non-neoplastic disease condition such as pyelonephritis. None of these conditions or the reduced survival were considered to be related to chemical administration. A sufficient number of males (62%) in these dose groups survived long enough (93 weeks) to be at risk to develop neoplasia, and the studies were considered adequate for determining the carcinogenic potential of probenecid. Survival of dosed female mice was similar to controls and was unaffected by probenecid treatment.

In male mice there was no increase in the incidence of tumors at any site that could be attributed to the administration of probenecid. In female mice, however, hepatocellular adenomas and combined hepatocellular adenomas or carcinomas occurred with a significant positive trend and the incidence in the high-dose group was significantly greater than that in controls. Furthermore, the incidence in the high-dose female mice (adenoma: 14/49, 29%; combined adenoma or carcinoma: 16/49, 33%) exceeded the historical incidence for corn oil gavage studies (all NTP laboratories: adenoma, 114/2336 (4.9%), range 0%-20%; combined adenoma or carcinoma: 176/2336 (7.5%), range 0%-30%). Since

the increase in liver neoplasms consisted principally of benign tumors, it was considered to be some evidence of carcinogenic activity rather than clear evidence. There are only two other chemicals, studied by NCI/NTP that produced carcinogenic effects only in the liver of female mice. These are 2-nitro-*p*-phenylenediamine which caused an increase in the incidence of liver adenoma (NCI, 1979) and tris(2-ethylhexyl) phosphate which caused an increase in the incidence of liver carcinoma (NTP, 1984). Both are structurally unrelated to probenecid.

The dose-related increase in the incidence of mice with ovarian abscesses caused by *Klebsiella* species may have been related to probenecid administration. This drug is known to retard the transport of organic anions across epithelial cells including the renal tubule, liver, and choroid plexus; it may also affect the transport of organic anions across the epithelium of the urogenital tract. Thus, probenecid may have altered the vaginal or utero-ovarian microenvironment and provided conditions that were more favorable for infection by this organism. Alternatively, probenecid may have affected local or systemic immunity in such a way that female mice became more susceptible to infection. These hypotheses need to be examined experimentally.

Conclusions

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of probenecid for male or female F344/N rats receiving 100 or 400 mg/kg in corn oil. There was *no evidence of carcinogenic activity* of probenecid for male $B6C3F_1$ mice given 100 or 400 mg/kg probenecid in corn oil. There was *some evidence of carcinogenic activity* of probenecid for female $B6C3F_1$ mice based on an increased incidence of hepatocellular adenomas.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 8. A summary of peer review comments and the public discussion on this Technical Report appears on page 10.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR GAVAGE STUDY OF PROBENECID

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Probenecid

	Vehicle Control	100 mg/kg	400 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Moribund	10	11	22
Dead	3	4	5
Gavage death		1	1
Survivors			
Terminal sacrifice	34	32	21
Moribund	2	2	1
Died last week of study	1		
Animals examined microscopically	50	50	50
Alimentary System			
Intestine large, colon	(47)	(8)	(48)
Intestine small, duodenum	(48)	(9)	(49)
Adenocarcinoma			1 (2%)
Intestine small, jejunum	(46)	(8)	(47)
Adenocarcinoma		1 (13%)	
Leiomyoma			1 (2%)
Liver	(50)	(41)	(50)
Fibrous histiocytoma, metastatic, skin		1 (2%)	
Hepatocellular carcinoma		1 (2%)	
Neoplastic nodule	1 (2%)	1 (2%)	
Mesentery	(9)	(4)	(5)
Hepatocellular carcinoma, metastatic, liver		1 (25%)	
Pancreas	(50)	(20)	(49)
Acinus, adenoma			1 (2%)
Salivary glands	(49)	(16)	(49)
Stomach	(50)	(12)	(50)
Stomach, forestomach	(50)	(12)	(50)
Papilloma squamous		1 (8%)	
Cardiovascular System			
Heart	(50)	(8)	(50)
Schwannoma malignant			1 (2%)
Endocrine System			
Adrenal gland	(49)	(50)	(50)
Adrenal gland, cortex	(49)	(50)	(50)
Adenoma	2 (4%)		
Adrenal gland, medulla	(49)	(50)	(50)
Pheochromocytoma malignant	1 (2%)	1 (2%)	
Pheochromocytoma benign	14 (29%)	16 (32%)	6 (12%)
Bilateral, pheochromocytoma benign	5 (10%)	2 (4%)	2 (4%)
Islets, pancreatic	(49)	(19)	(49)
Adenoma	2 (4%)	2 (11%)	3 (6%)
Carcinoma		1 (5%)	1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Probenecid
(continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Endocrine System (continued)			
Pituitary gland	(50)	(26)	(50)
Pars distalis, adenoma	15 (30%)	12 (46%)	17 (34%)
Pars distalis, adenoma, multiple		2 (8%)	
Thyroid gland	(49)	(12)	(49)
Carcinoma			1 (2%)
C-cell, adenoma	9 (18%)	3 (25%)	10 (20%)
C-cell, carcinoma	1 (2%)		
Follicular cell, adenoma			1 (2%)
Follicular cell, carcinoma			1 (2%)
General Body System			
None			
Genital System			
Epididymis	(49)	(26)	(48)
Preputial gland	(49)	(15)	(50)
Adenoma	6 (12%)	2 (13%)	7 (14%)
Carcinoma		2 (13%)	1 (2%)
Bilateral, adenoma		1 (7%)	2 (4%)
Seminal vesicle	(49)	(30)	(50)
Testes	(49)	(44)	(50)
Bilateral, interstitial cell, adenoma	42 (86%)	33 (75%)	37 (74%)
Bilateral, interstitial tissue, adenoma		1 (2%)	
Interstitial cell, adenoma	3 (6%)	5 (11%)	7 (14%)
Hematopoietic System			
Blood	(31)	(1)	(21)
Bone marrow	(50)	(8)	(49)
Lymph node	(50)	(27)	(48)
Bronchial, mediastinal, fibrosarcoma, metastatic, skin	1 (2%)		
Mediastinal, fibrous histiocytoma, metastatic, skin		1 (4%)	
Lymph node, mesenteric	(50)	(20)	(47)
Mediastinal, hepatocellular carcinoma, metastatic, liver		1 (5%)	
Spleen	(50)	(19)	(49)
Thymus	(46)	(14)	(46)
Fibrosarcoma, metastatic, skin	1 (2%)		
Epithelial cell, thymoma benign	1 (2%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Probenecid
(continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Integumentary System			
Mammary gland	(26)	(9)	(27)
Fibroadenoma	3 (12%)	2 (22%)	
Skin	(49)	(20)	(50)
Basal cell adenoma	1 (2%)	1 (5%)	
Basal cell carcinoma		1 (5%)	1 (2%)
Fibrous histiocytoma		1 (5%)	
Keratoacanthoma	2 (4%)	1 (5%)	
Papilloma squamous		1 (5%)	1 (2%)
Squamous cell carcinoma		1 (5%)	
Trichoepithelioma	1 (2%)	1 (5%)	
Subcutaneous tissue, fibroma	5 (10%)	3 (15%)	3 (6%)
Subcutaneous tissue, fibrosarcoma	2 (4%)	1 (5%)	
Subcutaneous tissue, sarcoma		1 (5%)	2 (4%)
Subcutaneous tissue, schwannoma malignant		1 (5%)	
Musculoskeletal System			
Skeletal muscle	(2)	(1)	(3)
Fibrosarcoma, metastatic, skin	1 (50%)		
Fibrous histiocytoma, metastatic, skin		1 (100%)	
Nervous System			
Brain	(50)	(8)	(50)
Astrocytoma malignant			1 (2%)
Granular cell tumor benign			1 (2%)
Respiratory System			
Lung	(50)	(18)	(50)
Alveolar/bronchiolar adenoma	3 (6%)	2 (11%)	6 (12%)
Fibrosarcoma, metastatic, skin	1 (2%)		
Fibrous histiocytoma, metastatic, skin		1 (6%)	
Hepatocellular carcinoma, metastatic, liver		1 (6%)	
Nose	(49)	(9)	(49)
Basosquamous tumor benign	1 (2%)		
Special Senses System			
Ear	(1)	(3)	(3)
Fibrosarcoma	1 (100%)	1 (33%)	
Urinary System			
Kidney	(50)	(50)	(50)
Fibrosarcoma, metastatic, skin	1 (2%)		
Renal tubule, adenoma		1 (2%)	
Urinary bladder	(48)	(10)	(47)
Fibrous histiocytoma, metastatic, skin		1 (10%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Probenecid
(continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Systemic Lesions			
Multiple organs[a]	(50)	(50)	(50)
Leukemia mononuclear	6 (12%)	10 (20%)	7 (14%)
Lymphoma malignant undifferentiated cell			1 (2%)
Mesothelioma benign	1 (2%)		
Mesothelioma malignant	4 (8%)	2 (4%)	5 (10%)
Tumor Summary			
Total animals with primary neoplasms[b]	48	48	48
Total primary neoplasms	132	118	128
Total animals with benign neoplasms	47	46	47
Total benign neoplasms	119	93	105
Total animals with malignant neoplasms	15	23	21
Total malignant neoplasms	15	25	23
Total animals with secondary neoplasms[c]	1	2	1
Total secondary neoplasms	5	8	1

[a] The number in parentheses is the number of animals with any tissue examined microscopically.
[b] Primary tumors: all tumors except metastatic tumors
[c] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Probenecid: Vehicle Control

Number of Days on Study	2 9 3	4 4 7	5 5 1	5 9 7	6 1 0	6 3 6	6 5 3	6 5 8	6 7 1	7 0 7	7 0 8	7 2 0	7 2 7	7 3 0	7 3 0	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7
Carcass ID Number	0 0 4 5	0 1 5	0 8 5	0 5 5	0 1 4	0 3 5	0 7 5	0 9 5	1 0 5	0 1 3	0 4 4	0 3 4	0 7 4	1 0 3	1 0 4	0 1 1	0 2 2	0 2 3	0 2 4	0 2 5	0 3 3	0 6 3	0 6 4	0 6 5	0 7 3
Alimentary System																									
Esophagus	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Intestine large, cecum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Intestine large, colon	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Intestine large, rectum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	A	+
Intestine small	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Intestine small, duodenum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Intestine small, ileum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Intestine small, jejunum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	A	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																	X								
Mesentery	+					+	+						+								+	+			+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																			X						
Pheochromocytoma benign										X			X		X		X								
Bilateral, pheochromocytoma benign																								X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Adenoma																					X				
Parathyroid gland	M	M	M	+	M	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X	X				X	X	X				X			X			X			
Thyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																X						X			
C-cell, carcinoma																									
General Body System																									
None																									

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Probenecid: Vehicle Control (continued)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	
Carcass ID Number	0 2 1	0 3 1	0 3 2	0 4 1	0 4 2	0 5 1	0 5 2	0 5 3	0 5 4	0 6 1	0 7 1	0 7 2	0 8 1	0 8 2	0 8 3	0 9 1	0 9 2	0 9 3	1 0 1	1 0 2	0 1 2	0 4 3	0 6 2	0 8 4	0 9 4	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	47
Intestine small, jejunum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										1
Mesentery				+			+																			9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Adenoma			X																							2
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant																										1
Pheochromocytoma benign						X				X		X			X			X	X	X			X	X	X	14
Bilateral, pheochromocytoma benign			X	X				X			X															5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																X										2
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma				X		X				X						X	X			X			X			15
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma					X		X										X	X				X	X	X		9
C-cell, carcinoma																	X									1
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Probenecid: Vehicle Control (continued)

Number of Days on Study	2 9 3	4 4 7	5 5 1	5 9 7	6 1 0	6 3 6	6 5 3	6 5 8	6 7 1	7 0 7	7 0 8	7 2 0	7 2 7	7 3 0	7 3 0	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7
Carcass ID Number	0 4 5	0 1 5	0 8 5	0 5 5	0 1 4	0 3 5	0 7 5	0 9 5	1 0 5	0 1 3	0 4 4	0 3 4	0 7 4	0 0 3	1 0 4	1 0 1	0 2 2	0 2 3	0 2 4	0 2 5	0 3 3	0 6 3	0 6 4	0 6 5	0 7 3
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Preputial gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X	X							X														
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Bilateral, interstitial cell, adenoma			X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Interstitial cell, adenoma																									
Hematopoietic System																									
Blood																+	+	+	+	+	+	+	+	+	+
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bronchial, mediastinal, fibrosarcoma, metastatic, skin		X																							
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	M
Fibrosarcoma, metastatic, skin		X																							
Epithelial cell, thymoma benign																									
Integumentary System																									
Mammary gland	M	M	M	+	+	+	M	M	+	+	+	+	+	+	+	+	M	M	+	M	+	+	M	M	M
Fibroadenoma											X														
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Keratoacanthoma																									
Trichoepithelioma															X										
Subcutaneous tissue, fibroma					X				X										X						
Subcutaneous tissue, fibrosarcoma		X	X																						
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle		+											+												
Fibrosarcoma, metastatic, skin		X																							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Probenecid: Vehicle Control (continued)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	
Carcass ID Number	0 2 1	0 3 1	0 3 2	0 4 1	0 4 2	0 5 1	0 5 2	0 5 3	0 5 4	0 6 1	0 7 1	0 7 2	0 8 1	0 8 2	0 8 3	0 9 1	0 9 2	0 9 3	1 0 1	1 0 2	0 1 2	0 4 3	0 6 2	0 8 4	0 9 4	**Total Tissues/ Tumors**
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma				X													X		X							6
Prostate	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	42
Interstitial cell, adenoma								X									X	X								3
Hematopoietic System																										
Blood		+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	31
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bronchial, mediastinal, fibrosarcoma, metastatic, skin																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	46
Fibrosarcoma, metastatic, skin																										1
Epithelial cell, thymoma benign																		X								1
Integumentary System																										
Mammary gland	M	M	M	+	M	+	M	M	+	+	+	M	+	+	M	M	M	M	+	M	+	+	+	M	+	26
Fibroadenoma											X										X					3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Basal cell adenoma										X																1
Keratoacanthoma					X								X													2
Trichoepithelioma																										1
Subcutaneous tissue, fibroma					X	X																				5
Subcutaneous tissue, fibrosarcoma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Fibrosarcoma, metastatic, skin																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Probenecid: Vehicle Control (continued)

Number of Days on Study	2 9 3	4 4 7	5 5 1	5 9 7	6 1 0	6 3 6	6 5 3	6 5 8	6 7 1	7 0 7	7 0 8	7 2 0	7 2 7	7 3 0	7 3 0	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7
Carcass ID Number	0 4 5	0 1 5	0 8 5	0 5 5	0 1 4	0 3 5	0 7 5	0 9 5	1 0 5	0 1 3	0 4 4	0 3 4	0 7 4	1 0 3	1 0 4	0 1 1	0 2 2	0 2 3	0 2 4	0 2 5	0 3 3	0 6 3	0 6 4	0 6 5	0 7 3
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma									X					X											
Fibrosarcoma, metastatic, skin		X																							
Nose	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor benign																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Fibrosarcoma																									
Eye		+				+						+	+	+											
Harderian gland						+						+	+	+											
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin		X																							
Urinary bladder	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear														X	X								X	X	
Mesothelioma benign																								X	
Mesothelioma malignant							X			X			X												

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Probenecid: Vehicle Control (continued)

Number of Days on Study	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	
Carcass ID Number	0 2 1	0 3 1	0 3 2	0 4 1	0 4 2	0 5 1	0 5 2	0 5 3	0 5 4	0 6 1	0 7 1	0 7 2	0 8 1	0 8 2	0 8 3	0 9 1	0 9 2	0 9 3	1 0 1	1 0 2	0 1 2	0 4 3	0 6 2	0 8 4	0 9 4	**Total Tissues/ Tumors**
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																						X				3
Fibrosarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Basosquamous tumor benign																	X									1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																		+								1
Fibrosarcoma																		X								1
Eye																										5
Harderian gland																										4
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X				X																				6
Mesothelioma benign																										1
Mesothelioma malignant								X																		4

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Probenecid: 100 mg/kg

Number of Days on Study	2 9 2	4 6 2	4 9 9	5 0 3	5 1 7	5 8 2	6 1 6	6 3 1	6 5 0	6 5 1	6 6 4	6 6 7	6 7 2	6 9 4	6 9 9	7 2 3	7 3 0	7 3 0	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	1 2 5	1 8 5	1 5 5	1 7 5	1 6 4	1 8 4	1 4 5	1 3 5	1 5 4	1 6 2	1 1 5	1 1 4	2 0 5	1 9 5	1 9 4	1 1 3	1 4 4	2 0 4	1 1 1	1 1 2	1 2 1	1 2 2	1 2 3	1 2 4	1 3 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+		+			+												
Intestine large	+	+	+	+	+	+	+	+								+									
Intestine large, cecum	A	+	+	+	+	+	+	+																	
Intestine large, colon	+	+	+	+	+	+	+	+																	
Intestine large, rectum	+	+	+	+	+	+	+	+								+									
Intestine small	+	+	+	+	+	+	+	+				+													
Intestine small, duodenum	+	+	+	+	+	+	+	+				+													
Intestine small, ileum	+	+	+	+	+	+	+	+																	
Intestine small, jejunum	+	+	+	M	+	+	+	+				+													
Adenocarcinoma					X																				
Liver	+	+	+	+	+	+	+	+		+	+	+	+				+	+	+	+	+	+		+	+
Fibrous histiocytoma, metastatic, skin								X																	
Hepatocellular carcinoma																					X				
Neoplastic nodule																									
Mesentery							+								+						+				
Hepatocellular carcinoma, metastatic, liver																					X				
Pancreas	+	+	+	+	+	+	+	+				+			+		+				+	+			
Pharynx																+									
Salivary glands	+	+	+	+	+	+	+	+				+						+			+	+			
Stomach	+	+	+	+	+	+	+	+						+	+										
Stomach, forestomach	+	+	+	+	+	+	+	+						+	+										
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+						+	+										
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+																	
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																		X							
Pheochromocytoma benign								X		X			X		X		X		X				X		X
Bilateral, pheochromocytoma benign																X									
Islets, pancreatic	+	+	+	+	+	+	+	+				+		+	+		+				+	+			
Adenoma															X		X								
Carcinoma																									
Parathyroid gland	+	+	+	M	+	+	+	+					+									+			
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+				+		+		+		+	+	+		
Pars distalis, adenoma		X						X	X	X							X				X	X	X		
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+					+									+			
C-cell, adenoma																						X			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Probenecid: 100 mg/kg (continued)

Number of Days on Study	735	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	13 4	13 1	13 2	14 1	14 2	14 3	15 1	15 2	15 3	16 3	16 1	16 5	17 1	17 2	17 3	17 4	18 1	18 2	18 3	19 1	19 2	19 3	20 1	20 2	20 3	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+																			+						12
Intestine large																										9
Intestine large, cecum																										7
Intestine large, colon																										8
Intestine large, rectum																										9
Intestine small																										9
Intestine small, duodenum																										9
Intestine small, ileum																										8
Intestine small, jejunum																										8
Adenocarcinoma																										1
Liver	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+		+	+	+		+	41
Fibrous histiocytoma, metastatic, skin																										1
Hepatocellular carcinoma																										1
Neoplastic nodule											X															1
Mesentery																	+									4
Hepatocellular carcinoma, metastatic, liver																										1
Pancreas		+	+	+		+		+									+				+					20
Pharynx																										1
Salivary glands		+	+		+										+											16
Stomach																	+	+								12
Stomach, forestomach																	+	+								12
Papilloma squamous																		X								1
Stomach, glandular																		+								11
Cardiovascular System																										
Heart																										8
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign			X	X			X	X		X		X					X	X								16
Bilateral, pheochromocytoma benign																				X						2
Islets, pancreatic			+	+		+			+												+					19
Adenoma																										2
Carcinoma						X																				1
Parathyroid gland	+																			+						11
Pituitary gland					+	+		+				+			+						+	+	+		+	26
Pars distalis, adenoma					X	X		X							X											12
Pars distalis, adenoma, multiple												X												X		2
Thyroid gland	+																			+						12
C-cell, adenoma	X																			X						3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Probenecid: 100 mg/kg (continued)

Number of Days on Study	2 9 2	4 6 2	4 9 9	5 0 3	5 1 7	5 8 2	6 1 6	6 3 1	6 5 0	6 5 1	6 6 4	6 6 7	6 7 2	6 9 4	6 9 9	7 2 3	7 3 0	7 3 0	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	1 2 5	1 8 5	1 5 5	1 7 5	1 6 4	1 8 4	1 4 5	1 3 5	1 5 4	1 6 2	1 1 5	1 1 4	2 0 5	1 9 5	1 9 4	1 1 3	1 4 4	2 0 4	1 1 1	1 1 2	1 2 1	1 2 2	1 2 3	1 2 4	1 3 3
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+			+			+			+								+
Preputial gland	+	+	+	+	+	+	+				+					+					+		+		
Adenoma																									
Carcinoma																							X		
Bilateral, adenoma						X																			
Prostate	+	+	+	+	+	+	+	+							+										
Seminal vesicle	+	+	+	+	+	+	+	+	+	+		+		+		+	+	+							
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+			+		+	+
Bilateral, interstitial cell, adenoma							X		X	X	X	X	X	X		X	X	X	X			X		X	X
Bilateral, interstitial tissue, adenoma																									
Interstitial cell, adenoma				X		X																			
Hematopoietic System																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+																	
Lymph node	+	+	+	+	+	+	+	+			+	+	+		+	+		+			+	+			
Mediastinal, fibrous histiocytoma, metastatic, skin								X																	
Lymph node, mesenteric	+	+	+	+	+	+	+	+			+	+			+	+		+			+				
Mediastinal, hepatocellular carcinoma, metastatic, liver																					X				
Spleen	+	+	+	+	+	+	+	+				+	+		+										
Thymus	+	+	+	+	+	+	+	+			+			+	+	+					+				
Integumentary System																									
Mammary gland	M	+	+	M	+	+	M	M	+						+										
Fibroadenoma									X																
Skin	+	+	+	+	+	+	+	+			+			+		+									
Basal cell adenoma																									
Basal cell carcinoma																									
Fibrous histiocytoma								X																	
Keratoacanthoma														X											
Papilloma squamous																									
Squamous cell carcinoma																									
Trichoepithelioma																									
Subcutaneous tissue, fibroma																X									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, sarcoma											X														
Subcutaneous tissue, schwannoma malignant														X											

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Probenecid: 100 mg/kg (continued)

Number of Days on Study	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	1 3 4	1 3 1	1 3 2	1 4 1	1 4 2	1 4 3	1 5 1	1 5 2	1 5 3	1 6 3	1 6 1	1 6 5	1 7 1	1 7 2	1 7 3	1 7 4	1 8 1	1 8 2	1 8 3	1 9 1	1 9 2	1 9 3	2 0 1	2 0 2	2 0 3	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Epididymis	+	+				+					+		+	+	+	+	+	+	+			+		+	+	26
Preputial gland			+								+				+					+						15
Adenoma			X												X											2
Carcinoma																				X						2
Bilateral, adenoma																										1
Prostate				+																						10
Seminal vesicle			+	+	+	+			+		+		+		+	+	+	+		+	+	+		+		30
Testes	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+		+	+	+	+	+	44
Bilateral, interstitial cell, adenoma		X		X	X		X	X	X	X	X		X	X	X	X	X		X		X	X	X	X	X	33
Bilateral, interstitial tissue, adenoma			X																							1
Interstitial cell, adenoma	X					X												X								5
Hematopoietic System																										
Blood																	+									1
Bone marrow																										8
Lymph node	+	+	+			+			+		+				+		+		+		+		+			27
Mediastinal, fibrous histiocytoma, metastatic, skin																										1
Lymph node, mesenteric	+					+			+		+						+						+			20
Mediastinal, hepatocellular carcinoma, metastatic, liver																										1
Spleen				+							+	+		+			+	+		+					+	19
Thymus															+											14
Integumentary System																										
Mammary gland						+									+								+			9
Fibroadenoma						X																				2
Skin			+		+						+				+	+	+	+					+	+		20
Basal cell adenoma			X																							1
Basal cell carcinoma																							X			1
Fibrous histiocytoma																										1
Keratoacanthoma																										1
Papilloma squamous																	X									1
Squamous cell carcinoma											X															1
Trichoepithelioma			X																							1
Subcutaneous tissue, fibroma					X											X										3
Subcutaneous tissue, fibrosarcoma																								X		1
Subcutaneous tissue, sarcoma																										1
Subcutaneous tissue, schwannoma malignant																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Probenecid: 100 mg/kg (continued)

Number of Days on Study	2 9 2	4 6 2	4 9 9	5 0 3	5 1 7	5 8 2	6 1 6	6 3 1	6 5 0	6 5 1	6 6 4	6 6 7	6 7 2	6 9 4	6 9 9	7 2 3	7 3 0	7 3 0	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	1 2 5	1 8 5	1 5 5	1 7 5	1 6 4	1 8 4	1 4 5	1 3 5	1 5 4	1 6 2	1 1 5	1 1 4	1 0 5	1 9 5	1 9 4	1 1 3	1 4 4	2 0 4	1 1 1	1 1 2	1 2 1	1 2 2	1 2 3	1 3 4	1 3 3
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+																	
Skeletal muscle								+																	
Fibrous histiocytoma, metastatic, skin								X																	
Nervous System																									
Brain	+	+	+	+	+	+	+	+																	
Respiratory System																									
Lung	+	+	+	+	+	+	+	+		+	+			+		+					+		+		
Alveolar/bronchiolar adenoma		X																							
Fibrous histiocytoma, metastatic, skin								X																	
Hepatocellular carcinoma, metastatic, liver																					X				
Nose	+	+	+	+	+	+	+	+		+															
Trachea	+	+	+	+	+	+	+	+			+			+		+					+	+	+		
Special Senses System																									
Ear		+					+												+						
Fibrosarcoma																			X						
Eye		+				+	+	+					+		+						+				
Harderian gland						+	+	+				+			+						+				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+													+				
Fibrous histiocytoma, metastatic, skin								X																	
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X	X				X				X	X		X										
Mesothelioma malignant							X																		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Probenecid: 100 mg/kg (continued)

Number of Days on Study	735	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	13 4	13 1	13 2	14 1	14 2	14 3	15 1	15 2	15 3	16 3	16 1	16 5	17 1	17 2	17 3	17 4	18 1	18 2	18 3	19 1	19 2	19 3	20 1	20 2	20 3	**Total Tissues/ Tumors**
Musculoskeletal System																										
Bone																										8
Skeletal muscle																										1
Fibrous histiocytoma, metastatic, skin																										1
Nervous System																										
Brain																										8
Respiratory System																										
Lung											+		+	+				+								18
Alveolar/bronchiolar adenoma													X													2
Fibrous histiocytoma, metastatic, skin																										1
Hepatocellular carcinoma, metastatic, liver																										1
Nose																										9
Trachea	+										+		+	+												18
Special Senses System																										
Ear																										3
Fibrosarcoma																										1
Eye																			+							8
Harderian gland																			+							7
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma															X											1
Urinary bladder				+																						10
Fibrous histiocytoma, metastatic, skin																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear											X	X		X												10
Mesothelioma malignant																	X									2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Probenecid: 400 mg/kg

Number of Days on Study	3 3 6	3 7 2	4 5 7	4 9 1	4 9 9	5 1 3	5 6 2	5 7 4	5 8 0	5 8 8	6 0 0	6 1 1	6 1 2	6 6 0	6 6 6	6 7 0	6 9 0	6 9 5	7 0 0	7 0 3	7 0 4	7 0 4	7 0 6	7 0 7	7 0 8
Carcass ID Number	2 8 5	2 9 5	2 2 5	2 3 5	2 5 5	3 0 5	3 0 4	2 6 5	3 0 1	2 1 5	2 3 4	2 2 4	2 9 4	2 9 3	2 3 3	2 3 3	2 7 5	2 1 4	2 8 4	2 4 5	2 5 3	2 5 4	2 4 4	2 9 2	2 1 3
Alimentary System																									
Esophagus	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Adenocarcinoma							X																		
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+
Leiomyoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																					+				+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic																									
Schwannoma malignant															X										
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign							X																		
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Adenoma																				X		X			
Carcinoma																						X			
Parathyroid gland	+	M	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X	X	X	X					X							X	X		X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Carcinoma																									
C-cell, adenoma								X		X												X			
Follicular cell, adenoma																									
Follicular cell, carcinoma										X															

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Probenecid: 400 mg/kg (continued)

Number of Days on Study	7 1 3	7 2 3	7 2 7	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	2 5 2	2 3 2	2 2 3	2 1 1	2 1 2	2 2 1	2 2 2	2 3 1	2 4 3	2 5 1	2 8 3	2 4 1	2 4 2	2 6 1	2 6 2	2 6 3	2 6 4	2 7 1	2 7 2	2 7 3	2 7 4	2 8 1	2 8 2	2 9 1	3 0 2	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leiomyoma	X																									1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery	+				+			+																		5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinus, adenoma												X														1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic															X											1
Schwannoma malignant																										1
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign						X													X			X		X	X	6
Bilateral, pheochromocytoma benign		X													X											2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma								X																		3
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	M	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X			X			X			X					X		X	X						X	17
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma												X														1
C-cell, adenoma	X			X										X	X			X			X	X				10
Follicular cell, adenoma						X																				1
Follicular cell, carcinoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Probenecid: 400 mg/kg (continued)

Number of Days on Study	3 3 4 4 4 5 5 5 5 5 6 6 6 6 6 6 6 7 7 7 7 7 7 7 3 7 5 9 9 1 6 7 8 8 0 1 5 6 6 7 9 9 0 0 0 0 0 0 0 6 2 7 1 9 3 2 4 0 8 0 1 2 0 6 0 0 5 0 3 4 4 6 7 8
Carcass ID Number	2 2 2 2 2 3 3 2 3 2 2 2 2 2 2 3 2 2 2 2 2 2 2 2 8 9 2 3 5 0 0 6 0 1 3 2 9 9 3 0 7 1 8 4 5 5 4 9 1 5 5 5 5 5 5 4 5 1 5 4 4 4 3 3 3 5 4 4 5 3 4 4 2 3
General Body System	
None	
Genital System	
Epididymis	+ + + + + + + + + + M + + + + + + + + + + M + + +
Preputial gland	+ +
Adenoma	X X X X
Carcinoma	
Bilateral, adenoma	X
Prostate	+ +
Seminal vesicle	+ +
Testes	+ +
Bilateral, interstitial cell, adenoma	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
Interstitial cell, adenoma	X X X X
Hematopoietic System	
Blood	
Bone marrow	+ + + + + + + + + + + + + + + + + A + + + + + + + +
Lymph node	+ + + + + + M + + + + + + + + + + A + + + + + + + +
Lymph node, mesenteric	+ + + + + + M + + + + + + + + + + A + + + + M + + +
Spleen	+ + + + + + + + + + + + + + + + + A + + + + + + + +
Thymus	+ + + + + + M + + + + + + + + + + A + + + + + + + +
Integumentary System	
Mammary gland	M + M M + M + + + M + M M + + M M + + M + M + + M
Skin	+ +
Basal cell carcinoma	
Papilloma squamous	
Subcutaneous tissue, fibroma	X
Subcutaneous tissue, sarcoma	X X
Musculoskeletal System	
Bone	+ +
Skeletal muscle	+ +
Nervous System	
Brain	+ +
Astrocytoma malignant	X
Granular cell tumor benign	X
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	X X
Nose	+ + + + + + + + + + + + + + + + + A + + + + + + +
Trachea	+ +

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Probenecid: 400 mg/kg (continued)

Number of Days on Study	7 1 3	7 2 3	7 2 7	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	2 5 2	2 3 2	2 2 3	2 1 1	2 1 2	2 2 1	2 2 2	2 3 1	2 4 3	2 5 1	2 8 3	2 4 1	2 4 2	2 6 1	2 6 2	2 6 3	2 6 4	2 7 1	2 7 2	2 7 3	2 7 4	2 8 1	2 8 2	2 9 1	3 0 2	**Total Tissues/ Tumors**
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X									X					7
Carcinoma			X																							1
Bilateral, adenoma						X																				2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X		X			X	X	X	X	X	X	X		X	X	X	X	X	37
Interstitial cell, adenoma									X			X								X						7
Hematopoietic System																										
Blood				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	21
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	46
Integumentary System																										
Mammary gland	M	+	+	+	+	M	+	+	+	+	+	M	M	M	+	+	M	M	M	M	+	M	M	+	+	27
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																		X								1
Papilloma squamous		X																								1
Subcutaneous tissue, fibroma		X					X																			3
Subcutaneous tissue, sarcoma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+																									3
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Granular cell tumor benign																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X						X		X	X											6
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Probenecid: 400 mg/kg (continued)

Number of Days on Study	3 3 6	3 7 2	4 5 7	4 9 1	4 9 9	5 1 3	5 6 2	5 7 4	5 8 0	5 8 8	6 0 0	6 1 1	6 5 2	6 6 0	6 6 6	6 7 0	6 9 0	6 9 5	7 0 0	7 0 3	7 0 4	7 0 4	7 0 6	7 0 7	7 0 8
Carcass ID Number	2 8 5	2 9 5	2 2 5	2 3 5	2 5 5	3 0 5	3 0 4	2 6 5	3 0 1	2 1 5	2 3 4	2 2 4	2 9 4	2 9 3	2 3 3	3 0 3	2 7 5	2 1 4	2 8 4	2 4 5	2 5 3	2 5 4	2 4 4	2 9 2	2 1 3
Special Senses System																									
Ear				+						+															
Eye		+	+	+		+	+						+								+	+	+		
Harderian gland							+			+			+										+		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	M	A	+	A	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X		X			X								X				X				
Lymphoma malignant undifferentiated cell type					X																				
Mesothelioma malignant											X		X									X			X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Probenecid: 400 mg/kg (continued)

Number of Days on Study	7 1 3	7 2 3	7 2 7	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	2 5 2	2 3 2	2 2 3	2 1 1	2 1 2	2 2 1	2 2 2	2 3 1	2 4 3	2 5 1	2 8 3	2 4 1	2 4 2	2 6 1	2 6 2	2 6 3	2 6 4	2 7 1	2 7 2	2 7 3	2 7 4	2 8 1	2 8 2	2 9 1	3 0 2	**Total Tissues/ Tumors**
Special Senses System																										
Ear																								+		3
Eye						+	+																			11
Harderian gland																										4
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear										X					X											7
Lymphoma malignant undifferentiated cell type																										1
Mesothelioma malignant															X											5

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Probenecid

	Vehicle Control	100 mg/kg	400 mg/kg
Adrenal Medulla: Benign Pheochromocytoma			
Overall rates[a]	19/49 (39%)	18/50 (36%)	8/50 (16%)
Adjusted rates[b]	49.9%	45.9%	31.9%
Terminal rates[c]	17/36 (47%)	13/34 (38%)	6/22 (27%)
First incidence (days)	707	631	562
Life table tests[d]	P=0.143N	P=0.565	P=0.183N
Logistic regression tests[d]	P=0.022N	P=0.580N	P=0.045N
Cochran-Armitage test[d]	P=0.006N		
Fisher exact test[d]		P=0.469N	P=0.010N
Adrenal Medulla: Benign Pheochromocytoma and Malignant Pheochromocytoma			
Overall rates	20/49 (41%)	19/50 (38%)	8/50 (16%)
Adjusted rates	52.5%	48.5%	31.9%
Terminal rates	18/36 (50%)	14/34 (41%)	6/22 (27%)
First incidence (days)	707	631	562
Life table tests	P=0.106N	P=0.560	P=0.140N
Logistic regression tests	P=0.014N	P=0.585	P=0.030N
Cochran-Armitage test	P=0.003N		
Fisher exact test		P=0.468N	P=0.006N
Lung: Alveolar/Bronchiolar Adenoma			
Overall rates	3/50 (6%)	2/18 (11%)[e]	6/50 (12%)
Adjusted rates	7.7%		22.3%
Terminal rates	2/37 (5%)		4/22 (18%)
First incidence (days)	671		580
Life table tests			P=0.093
Logistic regression tests			P=0.204
Cochran-Armitage test			
Fisher exact test			P=0.243
Mammary Gland: Fibroadenoma			
Overall rates	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted rates	7.8%	5.3%	0.0%
Terminal rates	2/37 (5%)	1/34 (3%)	0/22 (0%)
First incidence (days)	708	650	–[f]
Life table tests	P=0.170N	P=0.539N	P=0.222N
Logistic regression tests	P=0.114N	P=0.516N	P=0.165N
Cochran-Armitage test	P=0.098N		
Fisher exact test		P=0.500N	P=0.121N
Pancreatic Islets: Adenoma			
Overall rates	2/49 (4%)	2/19 (11%)[e]	3/49 (6%)
Adjusted rates	5.6%		10.7%
Terminal rates	2/36 (6%)		1/22 (5%)
First incidence (days)	730 (T)		703
Life table tests			P=0.319
Logistic regression tests			P=0.404
Cochran-Armitage test			
Fisher exact test			P=0.500

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Probenecid
(continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Pancreatic Islets: Adenoma or Carcinoma			
Overall rates	2/49 (4%)	3/19 (16%)[e]	3/49 (6%)
Adjusted rates	5.6%		10.7%
Terminal rates	2/36 (6%)		1/22 (5%)
First incidence (days)	730 (T)		703
Life table tests			P=0.319
Logistic regression tests			P=0.404
Cochran-Armitage test			
Fisher exact test			P=0.500
Pituitary Gland (Pars Distalis): Adenoma			
Overall rates	15/50 (30%)	14/26 (54%)[e]	17/50 (34%)
Adjusted rates	35.3%		49.9%
Terminal rates	10/37 (27%)		7/22 (32%)
First incidence (days)	610		513
Life table tests			P=0.076
Logistic regression tests			P=0.352
Cochran-Armitage test			
Fisher exact test			P=0.415
Preputial Gland: Adenoma			
Overall rates	6/49 (12%)	3/15 (20%)[e]	9/50 (18%)
Adjusted rates	14.1%		26.8%
Terminal rates	3/37 (8%)		3/22 (14%)
First incidence (days)	551		491
Life table tests			P=0.123
Logistic regression tests			P=0.373
Cochran-Armitage test			
Fisher exact test			P=0.303
Preputial Gland: Adenoma or Carcinoma			
Overall rates	6/49 (12%)	5/15 (33%)[e]	10/50 (20%)
Adjusted rates	14.1%		29.9%
Terminal rates	3/37 (8%)		3/22 (14%)
First incidence (days)	551		491
Life table tests			P=0.074
Logistic regression tests			P=0.269
Cochran-Armitage test			
Fisher exact test			P=0.220
Skin (Subcutaneous Tissue): Fibroma			
Overall rates	5/50 (10%)	3/50 (6%)	3/50 (6%)
Adjusted rates	12.2%	8.6%	11.1%
Terminal rates	3/37 (8%)	2/34 (6%)	1/22 (5%)
First incidence (days)	610	723	670
Life table tests	P=0.599N	P=0.404N	P=0.576N
Logistic regression tests	P=0.425N	P=0.371N	P=0.394N
Cochran-Armitage test	P=0.368N		
Fisher exact test		P=0.357N	P=0.357N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Probenecid
(continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma			
Overall rates	7/50 (14%)	4/50 (8%)	3/50 (6%)
Adjusted rates	15.8%	11.4%	11.1%
Terminal rates	3/37 (8%)	3/34 (9%)	1/22 (5%)
First incidence (days)	447	723	670
Life table tests	P=0.350N	P=0.311N	P=0.322N
Logistic regression tests	P=0.157N	P=0.240N	P=0.122N
Cochran-Armitage test	P=0.168N		
Fisher exact test		P=0.262N	P=0.159N
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma			
Overall rates	7/50 (14%)	5/50 (10%)	5/50 (10%)
Adjusted rates	15.8%	13.6%	16.7%
Terminal rates	3/37 (8%)	3/34 (9%)	1/22 (5%)
First incidence (days)	447	664	670
Life table tests	P=0.550	P=0.433N	P=0.598N
Logistic regression tests	P=0.379N	P=0.353N	P=0.333N
Cochran-Armitage test	P=0.391N		
Fisher exact test		P=0.380N	P=0.380N
Testes: Adenoma			
Overall rates	45/49 (92%)	39/44 (89%)	44/50 (88%)
Adjusted rates	100.0%	100.0%	97.8%
Terminal rates	36/36 (100%)	29/29 (100%)	21/22 (95%)
First incidence (days)	551	503	499
Life table tests	P<0.001	P=0.433	P=0.003
Logistic regression tests	P=0.354	P=0.551	P=0.466
Cochran-Armitage test	P=0.382N		
Fisher exact test		P=0.431N	P=0.383N
Thyroid Gland (C-cell): Adenoma			
Overall rates	9/49 (18%)	3/12 (25%)[e]	10/49 (20%)
Adjusted rates	24.3%		35.7%
Terminal rates	9/37 (24%)		6/22 (27%)
First incidence (days)	730 (T)		574
Life table tests			P=0.130
Logistic regression tests			P=0.355
Cochran-Armitage test			
Fisher exact test			P=0.500
Thyroid Gland (C-cell): Adenoma or Carcinoma			
Overall rates	9/49 (18%)	3/12 (25%)[e]	10/49 (20%)
Adjusted rates	24.3%		35.7%
Terminal rates	9/37 (24%)		6/22 (27%)
First incidence (days)	730 (T)		574
Life table tests			P=0.130
Logistic regression tests			P=0.355
Cochran-Armitage test			
Fisher exact test			

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Probenecid
(continued)

	Vehicle Control	100 mg/kg	400 mg/kg
All Organs: Leukemia (Mononuclear)			
Overall rates	6/50 (12%)	10/50 (20%)	7/50 (14%)
Adjusted rates	16.2%	22.9%	20.3%
Terminal rates	6/37 (16%)	3/34 (9%)	2/22 (9%)
First incidence (days)	730 (T)	462	491
Life table tests	P=0.338	P=0.180	P=0.242
Logistic regression tests	P=0.482N	P=0.229	P=0.516
Cochran-Armitage test	P=0.562N		
Fisher exact test		P=0.207	P=0.500
All Organs: Benign Mesothelioma and Malignant Mesothelioma			
Overall rates	5/50 (10%)	2/50 (4%)	5/50 (10%)
Adjusted rates	12.2%	5.1%	15.8%
Terminal rates	2/37 (5%)	1/34 (3%)	1/22 (5%)
First incidence (days)	653	616	600
Life table tests	P=0.267	P=0.261N	P=0.396
Logistic regression tests	P=0.450	P=0.220N	P=0.604
Cochran-Armitage test	P=0.465		
Fisher exact test		P=0.218N	P=0.630N
All Organs: Benign Tumors			
Overall rates	47/50 (94%)	46/50 (92%)	47/50 (94%)
Adjusted rates	100.0%	97.9%	100.0%
Terminal rates	37/37 (100%)	33/34 (97%)	22/22 (100%)
First incidence (days)	551	462	491
Life table tests	P<0.001	P=0.356	P<0.001
Logistic regression tests	P=0.156	P=0.696	P=0.214
Cochran-Armitage test	P=0.564		
Fisher exact test		P=0.500N	P=0.661N
All Organs: Malignant Tumors			
Overall rates	15/50 (30%)	23/50 (46%)	21/50 (42%)
Adjusted rates	35.0%	50.4%	49.7%
Terminal rates	10/37 (27%)	12/34 (35%)	4/22 (18%)
First incidence (days)	447	462	372
Life table tests	P=0.041	P=0.066	P=0.029
Logistic regression tests	P=0.356	P=0.088	P=0.237
Cochran-Armitage test	P=0.240		
Fisher exact test		P=0.074	P=0.149
All Organs: Benign and Malignant Tumors			
Overall rates	48/50 (96%)	48/50 (96%)	48/50 (96%)
Adjusted rates	100.0%	98.0%	100.0%
Terminal rates	37/37 (100%)	33/34 (97%)	22/22 (100%)
First incidence (days)	447	462	372
Life table tests	P<0.001	P=0.293	P=0.001
Logistic regression tests	P=0.446	P=0.652	P=0.505
Cochran-Armitage test	P=0.643		
Fisher exact test		P=0.691N	P=0.691N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Probenecid
(continued)

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly to the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Tissue was examined microscopically only when it was observed to be abnormal at necropsy.
[f] Not applicable; no tumors in animal group

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Probenecid

	Vehicle Control	100 mg/kg	400 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Moribund	10	11	22
Dead	3	4	5
Gavage death		1	1
Survivors			
Terminal sacrifice	34	32	21
Moribund	2	2	1
Died last week of study	1		
Animals examined microscopically	50	50	50
Alimentary System			
Esophagus	(48)	(12)	(48)
Hyperkeratosis			1 (2%)
Necrosis		1 (8%)	
Intestine large, cecum	(48)	(7)	(48)
Inflammation, chronic active			1 (2%)
Lymphoid nodule, hyperplasia			1 (2%)
Intestine large, colon	(47)	(8)	(48)
Parasite	3 (6%)		6 (13%)
Intestine large, rectum	(46)	(9)	(48)
Parasite		1 (11%)	1 (2%)
Intestine small, ileum	(47)	(8)	(47)
Lymphoid nodule, hyperplasia			1 (2%)
Lymphoid tissue, hyperplasia		1 (13%)	
Intestine small, jejunum	(46)	(8)	(47)
Hemorrhage		1 (13%)	
Inflammation, chronic active			1 (2%)
Liver	(50)	(41)	(50)
Basophilic focus	32 (64%)	27 (66%)	34 (68%)
Clear cell focus	1 (2%)	11 (27%)	1 (2%)
Congestion	1 (2%)	1 (2%)	
Cyst		1 (2%)	
Degeneration		1 (2%)	
Degeneration, cystic		1 (2%)	
Eosinophilic focus			1 (2%)
Fatty change, diffuse	8 (16%)	4 (10%)	1 (2%)
Fatty change, focal	27 (54%)	14 (34%)	14 (28%)
Focal cellular change			2 (4%)
Hepatodiaphragmatic nodule	3 (6%)	6 (15%)	3 (6%)
Mixed cell focus	2 (4%)	2 (5%)	1 (2%)
Necrosis	1 (2%)		2 (4%)
Regeneration, focal	1 (2%)		
Artery, inflammation, chronic active	1 (2%)		
Bile duct, hyperplasia	35 (70%)	25 (61%)	37 (74%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Probenecid (continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Alimentary System (continued)			
Mesentery	(9)	(4)	(5)
Artery, necrosis, fibrinoid	2 (22%)		
Fat, inflammation, chronic active			2 (40%)
Fat, necrosis	4 (44%)	1 (25%)	1 (20%)
Fat, pigmentation			1 (20%)
Pancreas	(50)	(20)	(49)
Acinus, atrophy	2 (4%)	1 (5%)	1 (2%)
Acinus, hyperplasia	7 (14%)	2 (10%)	6 (12%)
Artery, mineralization		1 (5%)	
Artery, necrosis, fibrinoid	2 (4%)	1 (5%)	
Pharynx		(1)	
Hyperplasia, pseudoepitheliomatous		1 (100%)	
Salivary glands	(49)	(16)	(49)
Fibrosis		1 (6%)	
Hyperplasia		1 (6%)	
Acinus, inflammation, chronic active	1 (2%)		
Artery, necrosis, fibrinoid	1 (2%)		
Duct, inflammation, acute		1 (6%)	
Duct, inflammation, chronic active	3 (6%)		1 (2%)
Duct, metaplasia		1 (6%)	1 (2%)
Duct, metaplasia, squamous	11 (22%)	5 (31%)	10 (20%)
Stomach, forestomach	(50)	(12)	(50)
Acanthosis	2 (4%)	3 (25%)	6 (12%)
Hyperkeratosis	3 (6%)	3 (25%)	5 (10%)
Hyperplasia, basal cell		1 (8%)	
Inflammation, chronic active	1 (2%)	1 (8%)	1 (2%)
Mineralization		1 (8%)	
Necrosis	2 (4%)	1 (8%)	2 (4%)
Artery, necrosis, fibrinoid	1 (2%)		
Stomach, glandular	(49)	(11)	(49)
Hyperplasia			1 (2%)
Mineralization			1 (2%)
Necrosis			1 (2%)
Artery, necrosis, fibrinoid	1 (2%)		
Cardiovascular System			
Blood vessel	(1)		
Artery, necrosis, fibrinoid	1 (100%)		
Heart	(50)	(8)	(50)
Cardiomyopathy	37 (74%)	8 (100%)	44 (88%)
Thrombus	1 (2%)		
Artery, necrosis, fibrinoid	1 (2%)		

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Probenecid (continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Endocrine System			
Adrenal gland	(49)	(50)	(50)
Accessory adrenal cortical nodule		1 (2%)	
Adrenal gland, cortex	(49)	(50)	(50)
Hemorrhage	1 (2%)	1 (2%)	
Hyperplasia		3 (6%)	
Vacuolization cytoplasmic			1 (2%)
Adrenal gland, medulla	(49)	(50)	(50)
Hyperplasia	9 (18%)	15 (30%)	14 (28%)
Islets, pancreatic	(49)	(19)	(49)
Hyperplasia	4 (8%)	1 (5%)	1 (2%)
Parathyroid gland	(42)	(11)	(42)
Hyperplasia	1 (2%)		
Pituitary gland	(50)	(26)	(50)
Pars distalis, angiectasis	9 (18%)	11 (42%)	9 (18%)
Pars distalis, cyst		1 (4%)	
Pars distalis, hemorrhage	1 (2%)		1 (2%)
Pars distalis, hyperplasia	11 (22%)	6 (23%)	7 (14%)
Pars distalis, necrosis			1 (2%)
Pars distalis, pigmentation		1 (4%)	
Pars intermedia, angiectasis		2 (8%)	
Pars intermedia, hyperplasia			1 (2%)
Thyroid gland	(49)	(12)	(49)
Hemorrhage			1 (2%)
C-cell, hyperplasia	7 (14%)	1 (8%)	10 (20%)
Capsule, necrosis, fibrinoid	1 (2%)		
General Body System			
None			
Genital System			
Epididymis	(49)	(26)	(48)
Fibrosis			1 (2%)
Inflammation, chronic active	1 (2%)		1 (2%)
Spermatocele			2 (4%)
Preputial gland	(49)	(15)	(50)
Cyst	1 (2%)		
Inflammation, chronic active	2 (4%)	1 (7%)	1 (2%)
Necrosis	7 (14%)		7 (14%)
Prostate	(49)	(10)	(50)
Inflammation, chronic active	5 (10%)	2 (20%)	3 (6%)
Artery, necrosis, fibrinoid	1 (2%)		
Epithelium, hyperplasia	2 (4%)		3 (6%)
Seminal vesicle	(49)	(30)	(50)
Concretion		3 (10%)	
Testes	(49)	(44)	(50)
Atrophy			1 (2%)
Congestion			1 (2%)
Interstitial cell, hyperplasia	17 (35%)	20 (45%)	26 (52%)
Seminiferous tubule, atrophy	37 (76%)	25 (57%)	32 (64%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Probenecid (continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Hematopoietic System			
Lymph node	(50)	(27)	(48)
Iliac, infiltration cellular, histiocytic			1 (2%)
Lumbar, angiectasis		1 (4%)	
Lumbar, hematopoietic cell proliferation			1 (2%)
Lumbar, hemorrhage			2 (4%)
Lumbar, infiltration cellular, histiocytic		1 (4%)	2 (4%)
Lumbar, pigmentation		1 (4%)	
Mandibular, angiectasis		1 (4%)	
Mandibular, necrosis			1 (2%)
Mediastinal, angiectasis	1 (2%)	1 (4%)	4 (8%)
Mediastinal, depletion lymphoid			1 (2%)
Mediastinal, infiltration cellular, histiocytic	5 (10%)	2 (7%)	4 (8%)
Mediastinal, pigmentation		4 (15%)	
Pancreatic, infiltration cellular, histiocytic		2 (7%)	1 (2%)
Pancreatic, pigmentation		6 (22%)	
Renal, angiectasis	2 (4%)	1 (4%)	2 (4%)
Renal, depletion lymphoid	1 (2%)		
Renal, hemorrhage			1 (2%)
Renal, infiltration cellular, histiocytic	4 (8%)	2 (7%)	11 (23%)
Renal, pigmentation		4 (15%)	
Lymph node, mesenteric	(50)	(20)	(47)
Angiectasis	1 (2%)	2 (10%)	5 (11%)
Depletion lymphoid			2 (4%)
Hemorrhage	1 (2%)		
Infiltration cellular, mast cell			1 (2%)
Infiltration cellular, histiocytic		4 (20%)	18 (38%)
Pigmentation		9 (45%)	
Renal, angiectasis			1 (2%)
Spleen	(50)	(19)	(49)
Congestion		1 (5%)	
Depletion lymphoid	1 (2%)	1 (5%)	2 (4%)
Fibrosis		1 (5%)	1 (2%)
Hematopoietic cell proliferation	27 (54%)	9 (47%)	38 (78%)
Hemorrhage		1 (5%)	1 (2%)
Infiltration cellular, histiocytic	1 (2%)		3 (6%)
Necrosis	2 (4%)	1 (5%)	
Pigmentation			1 (2%)
Capsule, fibrosis	1 (2%)		
Capsule, inflammation, chronic active	1 (2%)		
Thymus	(46)	(14)	(46)
Atrophy	1 (2%)		1 (2%)
Depletion lymphoid			1 (2%)
Epithelial cell, hyperplasia	2 (4%)		1 (2%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Probenecid (continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Integumentary System			
Mammary gland	(26)	(9)	(27)
Galactocele	7 (27%)	3 (33%)	5 (19%)
Acinus, hyperplasia			1 (4%)
Skin	(49)	(20)	(50)
Abscess			1 (2%)
Cyst epithelial inclusion	2 (4%)	1 (5%)	1 (2%)
Fibrosis			1 (2%)
Hyperkeratosis	4 (8%)	3 (15%)	4 (8%)
Hyperplasia, basal cell		1 (5%)	1 (2%)
Inflammation, acute			1 (2%)
Necrosis	1 (2%)		3 (6%)
Pigmentation		1 (5%)	
Musculoskeletal System			
None			
Nervous System			
Brain	(50)	(8)	(50)
Artery, necrosis, fibrinoid	1 (2%)		
Brain stem, hemorrhage	1 (2%)		
Cerebellum, hemorrhage		1 (13%)	1 (2%)
Cerebellum, necrosis		1 (13%)	
Cerebrum, hemorrhage		1 (13%)	1 (2%)
Respiratory System			
Lung	(50)	(18)	(50)
Atelectasis			1 (2%)
Bronchiectasis	1 (2%)		
Congestion	3 (6%)	4 (22%)	4 (8%)
Edema	1 (2%)	2 (11%)	3 (6%)
Hemorrhage		3 (17%)	6 (12%)
Infiltration cellular, histiocytic	4 (8%)		5 (10%)
Inflammation, acute		1 (6%)	
Inflammation, chronic active	2 (4%)		1 (2%)
Alveolar epithelium, hyperplasia	2 (4%)	3 (17%)	2 (4%)
Artery, necrosis, fibrinoid	1 (2%)		
Bronchiole, metaplasia, squamous	1 (2%)		
Nose	(49)	(9)	(49)
Congestion		1 (11%)	
Inflammation, chronic active	1 (2%)	1 (11%)	7 (14%)
Trachea	(50)	(18)	(50)
Erosion			1 (2%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Probenecid (continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Special Senses System			
Ear	(1)	(3)	(3)
Hemorrhage			1 (33%)
Necrosis			1 (33%)
Eye	(5)	(8)	(11)
Hemorrhage		1 (13%)	
Synechia		1 (13%)	2 (18%)
Lens, cataract	1 (20%)	3 (38%)	3 (27%)
Retina, atrophy			3 (27%)
Retina, hemorrhage	1 (20%)		
Sclera, pigmentation			1 (9%)
Harderian gland	(4)	(7)	(4)
Hyperplasia			1 (25%)
Urinary System			
Kidney	(50)	(50)	(50)
Congestion			2 (4%)
Cyst		1 (2%)	1 (2%)
Hydronephrosis		1 (2%)	
Nephropathy	48 (96%)	48 (96%)	47 (94%)
Artery, inflammation	1 (2%)		
Cortex, mineralization	2 (4%)	9 (18%)	2 (4%)
Papilla, mineralization	32 (64%)	31 (62%)	35 (70%)
Pelvis, mineralization	4 (8%)	12 (24%)	13 (26%)
Pelvis, transitional epithelium, hyperplasia	1 (2%)		
Renal tubule, degeneration		1 (2%)	
Renal tubule, hyperplasia	3 (6%)		
Renal tubule, mineralization			3 (6%)
Renal tubule, pigmentation	46 (92%)	46 (92%)	46 (92%)
Urinary bladder	(48)	(10)	(47)
Calculus gross observation	2 (4%)	2 (20%)	
Calculus micro observation only	3 (6%)	2 (20%)	1 (2%)
Hemorrhage		1 (10%)	
Necrosis		1 (10%)	

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR GAVAGE STUDY OF PROBENECID

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Probenecid

	Vehicle Control	100 mg/kg	400 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Moribund	25	15	20
Dead	1		10
Gavage death			1
Survivors			
Terminal sacrifice	23	35	19
Moribund	1		
Animals examined microscopically	50	50	50
Alimentary System			
Liver	(50)	(30)	(50)
Histiocytic sarcoma		1 (3%)	1 (2%)
Neoplastic nodule		1 (3%)	2 (4%)
Sarcoma, metastatic, uncertain primary site	1 (2%)		
Mesentery	(6)	(2)	(6)
Histiocytic sarcoma			1 (17%)
Sarcoma, metastatic, uncertain primary site	1 (17%)		
Sarcoma stromal, metastatic			1 (17%)
Pancreas	(50)	(14)	(50)
Histiocytic sarcoma			1 (2%)
Salivary glands	(50)	(10)	(48)
Carcinoma, metastatic, thyroid gland	1 (2%)		
Stomach	(50)	(9)	(49)
Stomach, forestomach	(49)	(9)	(49)
Histiocytic sarcoma			1 (2%)
Stomach, glandular	(50)	(9)	(47)
Histiocytic sarcoma			1 (2%)
Cardiovascular System			
Heart	(50)	(9)	(50)
Endocrine System			
Adrenal gland	(50)	(13)	(49)
Adrenal gland, cortex	(50)	(13)	(49)
Adenoma	1 (2%)		1 (2%)
Carcinoma, metastatic	1 (2%)		
Histiocytic sarcoma			1 (2%)
Adrenal gland, medulla	(48)	(13)	(45)
Histiocytic sarcoma			1 (2%)
Pheochromocytoma benign	1 (2%)	1 (8%)	1 (2%)
Bilateral, pheochromocytoma benign	1 (2%)		
Islets, pancreatic	(50)	(11)	(50)
Adenoma		1 (9%)	2 (4%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Probenecid
(continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Endocrine System (continued)			
Pituitary gland	(50)	(50)	(50)
Pars distalis, adenoma	20 (40%)	25 (50%)	15 (30%)
Pars distalis, adenoma, multiple	2 (4%)	1 (2%)	1 (2%)
Pars intermedia, adenoma			1 (2%)
Thyroid gland	(49)	(50)	(47)
Bilateral, c-cell, carcinoma			1 (2%)
C-cell, adenoma	9 (18%)	3 (6%)	1 (2%)
C-cell, carcinoma	3 (6%)	1 (2%)	1 (2%)
Follicular cell, adenoma	1 (2%)	1 (2%)	1 (2%)
General Body System			
None			
Genital System			
Clitoral gland	(36)	(16)	(45)
Adenoma	3 (8%)	7 (44%)	1 (2%)
Carcinoma		1 (6%)	
Ovary	(50)	(16)	(50)
Arrhenoblastoma benign			1 (2%)
Granulosa cell tumor benign	2 (4%)	1 (6%)	1 (2%)
Histiocytic sarcoma		1 (6%)	1 (2%)
Uterus	(50)	(16)	(49)
Adenoma			1 (2%)
Deciduoma NOS	1 (2%)		
Leiomyosarcoma			1 (2%)
Polyp stromal	6 (12%)	10 (63%)	9 (18%)
Sarcoma stromal	1 (2%)		2 (4%)
Bilateral, polyp stromal	1 (2%)		
Hematopoietic System			
Blood	(23)		(18)
Bone marrow	(50)	(8)	(50)
Lymph node	(49)	(21)	(50)
Mandibular, carcinoma, metastatic, thyroid gland	1 (2%)		1 (2%)
Lymph node, mesenteric	(49)	(20)	(50)
Spleen	(50)	(23)	(50)
Sarcoma			1 (2%)
Thymus	(49)	(10)	(46)
Integumentary System			
Mammary gland	(47)	(28)	(36)
Adenocarcinoma	3 (6%)	1 (4%)	
Fibroadenoma	14 (30%)	17 (61%)	5 (14%)
Fibroadenoma, multiple	10 (21%)	6 (21%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Probenecid (continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Integumentary System (continued)			
Skin	(50)	(12)	(49)
Basal cell carcinoma		1 (8%)	
Histiocytic sarcoma			1 (2%)
Neurofibroma	1 (2%)		
Sarcoma	2 (4%)	1 (8%)	
Squamous cell carcinoma	1 (2%)		
Subcutaneous tissue, fibroma	1 (2%)		
Musculoskeletal System			
None			
Nervous System			
Brain	(50)	(10)	(50)
Astrocytoma benign		1 (10%)	
Cerebrum, oligodendroglioma malignant	1 (2%)		
Respiratory System			
Lung	(50)	(26)	(50)
Alveolar/bronchiolar adenoma	2 (4%)	2 (8%)	1 (2%)
Carcinoma, metastatic, thyroid gland	2 (4%)		1 (2%)
Histiocytic sarcoma			1 (2%)
Sarcoma, metastatic, uncertain primary site	1 (2%)		
Trachea	(50)	(46)	(50)
Carcinoma, metastatic, thyroid gland	1 (2%)		
Special Senses System			
None			
Urinary System			
Kidney	(50)	(50)	(50)
Urinary bladder	(50)	(8)	(47)
Systemic Lesions			
Multiple organs[a]	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)	1 (2%)
Leukemia mononuclear	15 (30%)	17 (34%)	17 (34%)
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant undifferentiated cell			1 (2%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Probenecid
(continued)

Tumor Summary			
Total animals with primary neoplasms[b]	48	46	37
Total primary neoplasms	102	100	70
Total animals with benign neoplasms	41	39	29
Total benign neoplasms	75	77	44
Total animals with malignant neoplasms	26	21	24
Total malignant neoplasms	26	23	26
Total animals with secondary neoplasms[c]	3		2
Total secondary neoplasms	9		3
Total animals with malignant neoplasms	1		
Total animals with neoplasms uncertain-benign or malignant	1		
Total uncertain neoplasms	1		

[a] The number in parentheses is the number of animals with any tissue examined microscopically.
[b] Primary tumors: all tumors except metastatic tumors
[c] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Probenecid: Vehicle Control

Number of Days on Study	3 5 4	4 9 5	5 1 0	5 2 9	5 4 4	5 7 9	5 9 3	6 2 0	6 3 5	6 3 6	6 3 6	6 4 4	6 4 9	6 5 1	6 5 2	6 5 2	6 6 3	6 6 3	6 7 5	6 7 7	6 9 2	7 0 4	7 2 0	7 2 2	7 2 2
Carcass ID Number	4 0 5	3 4 5	3 1 5	3 9 5	3 7 5	3 8 5	3 4 4	3 9 4	3 2 5	3 5 5	3 6 5	3 2 4	4 0 3	3 5 4	3 6 4	3 8 4	3 7 4	3 8 2	3 6 3	3 8 3	3 1 4	3 7 3	3 9 3	3 1 3	3 4 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site		X																							
Mesentery		+															+				+				+
Sarcoma, metastatic, uncertain primary site		X																							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland														X											
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma, metastatic														X											
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign									X																
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	M	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X		X		X	X					X	X	X		X			X	X		
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma									X						X				X			X	X		X
C-cell, carcinoma														X											
Follicular cell, adenoma																									

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Probenecid: Vehicle Control (continued)

Number of Days on Study	7 2 2	7 2 9	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	4 0 4	3 5 3	3 1 1	3 1 2	3 2 1	3 2 3	3 3 1	3 3 2	3 3 3	3 3 4	3 3 5	3 4 1	3 5 1	3 6 1	3 7 1	3 7 2	3 8 1	3 9 1	4 0 1	4 0 2	3 2 2	3 4 2	3 5 2	3 6 2	3 9 2	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+		48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+		48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Sarcoma, metastatic, uncertain primary site																										1
Mesentery		+																								6
Sarcoma, metastatic, uncertain primary site																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Carcinoma, metastatic, thyroid gland																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+		49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adenoma																		X								1
Carcinoma, metastatic																										1
Adrenal gland, medulla	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Pheochromocytoma benign																										1
Bilateral, pheochromocytoma benign																					X					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Parathyroid gland	+	+	+	+	M	M	+	+	+	+	M	+	M	+	+	+	M	+	+	+	+	+	+	M	M	38
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Pars distalis, adenoma		X			X	X	X	X		X		X	X		X										X	20
Pars distalis, adenoma, multiple	X																			X						2
Thyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
C-cell, adenoma		X											X												X	9
C-cell, carcinoma								X											X							3
Follicular cell, adenoma															X											1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Probenecid: Vehicle Control (continued)

Number of Days on Study	3 5 4	4 9 5	5 1 0	5 2 9	5 4 4	5 7 9	5 9 3	6 2 0	6 3 5	6 3 6	6 3 6	6 4 4	6 4 9	6 5 1	6 5 2	6 5 2	6 6 3	6 6 3	6 6 5	6 7 7	6 9 2	7 0 4	7 2 0	7 2 2	7 2 2
Carcass ID Number	4 0 5	3 4 5	3 1 5	3 9 5	3 7 5	3 8 5	3 4 4	3 9 4	3 2 5	3 5 5	3 6 5	3 2 4	3 0 3	4 5 4	3 6 4	3 8 4	3 7 4	3 8 2	6 6 3	6 8 3	3 1 4	3 7 3	3 9 3	3 1 3	3 4 3
General Body System																									
Tissue NOS																									
Genital System																									
Clitoral gland	M	+	+	M	+	+	M	+	M	M	M	M	+	+	M	+	+	+	+	+	+	M	+	+
Adenoma													X					X						
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																						X		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Deciduoma NOS	X																							
Polyp stromal											X		X						X			X		
Sarcoma stromal					X																			
Bilateral, polyp stromal			X																					
Hematopoietic System																									
Blood																		+		+				+
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mandibular, carcinoma, metastatic, thyroid gland														X										
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma															X				X					
Fibroadenoma							X			X	X					X			X			X		
Fibroadenoma, multiple												X			X								X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurofibroma						X																		
Sarcoma																	X							
Squamous cell carcinoma																								
Subcutaneous tissue, fibroma																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																				+				
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cerebrum, oligodendroglioma malignant											X													

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Probenecid: Vehicle Control (continued)

Number of Days on Study	7 2 2	7 2 9	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	4 0 4	3 5 3	3 1 1	3 1 2	3 2 1	3 2 3	3 3 1	3 3 2	3 3 3	3 3 4	3 3 5	3 4 1	3 5 1	3 6 1	3 7 1	3 7 2	3 8 1	3 9 1	4 0 1	4 0 2	3 2 2	3 4 2	3 5 2	3 6 2	3 9 2	**Total Tissues/ Tumors**
General Body System																										
Tissue NOS					+																					1
Genital System																										
Clitoral gland	M	+	+	+	M	+	+	M	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	36
Adenoma																							X			3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign																X										2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Deciduoma NOS																										1
Polyp stromal						X												X								6
Sarcoma stromal																										1
Bilateral, polyp stromal																										1
Hematopoietic System																										
Blood	+		+	+	+	+		+	+	+	+	+	+	+	+		+	+		+	+	+		+	+	23
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mandibular, carcinoma, metastatic, thyroid gland																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenocarcinoma															X											3
Fibroadenoma	X				X				X		X							X			X				X	14
Fibroadenoma, multiple			X					X		X					X	X						X				10
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurofibroma																										1
Sarcoma							X																			2
Squamous cell carcinoma																							X			1
Subcutaneous tissue, fibroma																				X						1
Musculoskeletal System																										
Bone	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cerebrum, oligodendroglioma malignant																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Probenecid: Vehicle Control (continued)

Number of Days on Study	3 5 4	4 9 5	5 1 0	5 2 9	5 4 4	5 7 9	5 9 3	6 2 0	6 3 5	6 3 6	6 3 6	6 4 4	6 4 9	6 5 1	6 5 2	6 5 2	6 6 3	6 6 3	6 7 5	6 7 7	6 9 2	7 0 4	7 2 0	7 2 2	7 2 2
Carcass ID Number	4 0 5	3 4 5	3 1 5	3 9 5	3 7 5	3 8 5	3 4 4	3 9 4	3 2 5	3 5 5	3 6 5	3 2 4	4 0 3	3 5 4	3 6 4	3 8 4	3 7 4	3 8 2	3 6 3	3 8 3	3 1 4	3 7 3	3 9 3	3 1 3	3 4 3
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, thyroid gland														X											
Sarcoma, metastatic, uncertain primary site		X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland														X											
Special Senses System																									
Ear	+		+	+	+		+	+																	
Eye	+		+	+	+		+	+			+							+		+					
Harderian gland				+				+												+					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X		X		X	X				X							X	X	X		X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Probenecid: Vehicle Control (continued)

Number of Days on Study	7 2 2	7 2 9	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	4 0 4	3 5 3	3 1 1	3 1 2	3 2 1	3 2 3	3 3 1	3 3 2	3 3 3	3 3 4	3 3 5	3 4 1	3 5 1	3 6 1	3 7 1	3 7 2	3 8 1	3 9 1	4 0 1	4 0 2	3 2 2	3 4 2	3 5 2	3 6 2	3 9 2	**Total Tissues/ Tumors**
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma															X		X									2
Carcinoma, metastatic, thyroid gland								X																		2
Sarcoma, metastatic, uncertain primary site																										1
Nose	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																										1
Special Senses System																										
Ear																										6
Eye							+												+							11
Harderian gland							+				+						+									6
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear									X			X		X				X			X					15

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Probenecid: 100 mg/kg

Number of Days on Study	0 8 5	0 9 7	5 3 7	5 5 1	5 7 2	5 9 2	5 9 3	6 0 3	6 1 7	6 9 1	6 9 9	7 0 8	7 2 1	7 2 2	7 2 2	7 2 9	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4
Carcass ID Number	4 7 5	4 6 5	4 3 5	4 4 5	4 6 1	4 7 4	4 1 5	4 4 4	5 0 5	4 7 3	4 6 4	4 2 5	4 8 5	4 2 3	4 2 4	4 4 1	4 3 4	5 0 4	4 1 1	4 1 2	4 1 3	4 1 4	4 2 1	4 2 2	4 3 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+																
Intestine large, cecum	+	+	+	+	+	+	+	+	+																
Intestine large, colon	+	+	+	+	+	+	+	+	+																
Intestine large, rectum	M	+	+	+	+	+	+	+	+																
Intestine small	+	+	+	+	+	+	+	+	+			+						+							
Intestine small, duodenum	+	+	+	+	+	+	+	+	+																
Intestine small, ileum	+	+	+	+	+	+	+	+	+									+							
Intestine small, jejunum	+	+	+	+	+	+	+	+	+			+						+							
Liver	+	+	+	+	+	+	+	+	+	+		+	+	+		+	+			+			+	+	+
Histiocytic sarcoma																									
Neoplastic nodule																				X					
Mesentery																								+	
Pancreas	+	+	+	+	+	+	+	+	+	+		+	+				+								
Salivary glands	+	+	+	+	+	+	+	+	+										+						
Stomach	+	+	+	+	+	+	+	+	+																
Stomach, forestomach	+	+	+	+	+	+	+	+	+																
Stomach, glandular	+	+	+	+	+	+	+	+	+																
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+																
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+			+					+							+	
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+			+					+							+	
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+			+					+							+	
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+			+													
Adenoma																									
Parathyroid gland	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+		+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X		X	X			X		X	X			X	X	X				X	X
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma													X											X	
C-cell, carcinoma																X									
Follicular cell, adenoma																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Probenecid: 100 mg/kg (continued)

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	4 3 2	4 3 3	4 4 2	4 4 3	4 5 1	4 5 2	4 5 3	4 5 4	4 5 5	4 6 2	4 6 3	4 7 1	4 7 2	4 8 1	4 8 2	4 8 3	4 8 4	4 9 1	4 9 2	4 9 3	4 9 4	4 9 5	5 0 1	5 0 2	5 0 3	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large																										9
Intestine large, cecum																										9
Intestine large, colon																										9
Intestine large, rectum																										8
Intestine small																										11
Intestine small, duodenum																										9
Intestine small, ileum																										10
Intestine small, jejunum																										11
Liver				+			+			+	+	+					+		+	+			+	+	+	30
Histiocytic sarcoma																								X		1
Neoplastic nodule																										1
Mesentery						+																				2
Pancreas																									+	14
Salivary glands																										10
Stomach																										9
Stomach, forestomach																										9
Stomach, glandular																										9
Cardiovascular System																										
Heart																										9
Endocrine System																										
Adrenal gland																					+					13
Adrenal gland, cortex																					+					13
Adrenal gland, medulla																					+					13
Pheochromocytoma benign																					X					1
Islets, pancreatic																									+	11
Adenoma																									X	1
Parathyroid gland	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X			X	X	X	X	X	X		X		X						X		X		X	25
Pars distalis, adenoma, multiple																								X		1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																							X			3
C-cell, carcinoma																										1
Follicular cell, adenoma															X											1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Probenecid: 100 mg/kg (continued)

Number of Days on Study	0 8 5	0 9 7	5 3 7	5 5 1	5 7 2	5 9 2	5 9 3	6 0 3	6 1 7	6 9 1	6 9 9	7 0 8	7 2 1	7 2 2	7 2 2	7 2 9	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4
Carcass ID Number	4 7 5	4 6 5	4 3 5	4 4 5	4 6 1	4 7 4	4 1 5	4 4 4	4 0 5	4 7 3	4 6 4	4 2 5	4 8 5	4 2 3	4 2 4	4 4 1	4 3 4	5 0 4	4 1 1	4 1 2	4 1 3	4 1 4	4 2 1	4 2 2	4 3 1
General Body System																									
None																									
Genital System																									
Clitoral gland	+	M	M	M	+	M	+	+	+	+	+		+					+					+		
Adenoma							X		X														X		
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+					+				+							
Granulosa cell tumor benign																									
Histiocytic sarcoma																									
Uterus	+	+	+	+	+	+	+	+	+	+		+													
Polyp stromal				X			X	X		X		X													
Hematopoietic System																									
Bone marrow	+	+	+	+	M	+	+	+	+																
Lymph node	+	+	+	+	+	+	+	+	+	+		+	+	+	+		+	+					+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+		+	+	+	+		+	+					+		+
Spleen	+	+	+	+	+	+	+	+	+	+		+					+						+	+	
Thymus	+	+	+	+	+	+	+	+	+								+								
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+							+
Adenocarcinoma																		X							
Fibroadenoma				X	X	X	X		X	X	X	X	X		X										
Fibroadenoma, multiple			X											X				X							X
Skin	+	+	+	+	+	+	+	+	+																
Basal cell carcinoma																									
Sarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	M	+	+	+	+																
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+				+												
Astrocytoma benign													X												

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Probenecid: 100 mg/kg (continued)

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	4 3 2	4 3 3	4 4 2	4 4 3	4 5 1	4 5 2	4 5 3	4 5 4	4 5 5	4 6 2	4 6 3	4 7 1	4 7 2	4 8 1	4 8 2	4 8 3	4 8 4	4 9 1	4 9 2	4 9 3	4 9 4	4 9 5	5 0 1	5 0 2	5 0 3	**Total Tissues/ Tumors**
General Body System																										
None																										
Genital System																										
Clitoral gland			+						+						+					+			+	+		16
Adenoma			X						X						X									X		7
Carcinoma																				X						1
Ovary							+					+			+			+						+		16
Granulosa cell tumor benign												X														1
Histiocytic sarcoma																								X		1
Uterus	+							+	+								+				+					16
Polyp stromal	X							X	X								X				X					10
Hematopoietic System																										
Bone marrow																										8
Lymph node						+														+						21
Lymph node, mesenteric						+														+						20
Spleen				+		+			+								+		+	+	+	+	+			23
Thymus																										10
Integumentary System																										
Mammary gland		+			+				+	+	+				+	+		+		+	+			+		28
Adenocarcinoma																										1
Fibroadenoma					X				X	X					X	X		X			X					17
Fibroadenoma, multiple											X													X		6
Skin		+								+		+														12
Basal cell carcinoma												X														1
Sarcoma										X																1
Musculoskeletal System																										
Bone																										8
Nervous System																										
Brain																										10
Astrocytoma benign																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Probenecid: 100 mg/kg (continued)

Number of Days on Study	0 8 5	0 9 7	5 3 7	5 5 1	5 7 2	5 9 2	5 9 3	6 0 3	6 1 7	6 9 1	6 9 9	7 0 8	7 2 1	7 2 2	7 2 2	7 2 9	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4
Carcass ID Number	4 7 5	4 6 5	4 3 5	4 4 5	4 6 1	4 7 4	4 1 5	4 4 4	5 0 5	4 7 3	4 6 4	4 2 5	4 8 5	4 2 3	4 2 4	4 4 1	4 3 4	5 0 4	4 1 1	4 1 2	4 1 3	4 1 4	4 2 1	4 2 2	4 3 1
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+				+	+						+	+		+		
Alveolar/bronchiolar adenoma													X												
Nose	+	+	+	+	+	+	+	+	+																
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+	+	+	+
Special Senses System																									
Ear										+		+	+												
Eye						+				+		+	+				+	+		+					+
Harderian gland						+				+							+								
Lacrimal gland																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	M	+	+	+	+	+	+																
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leukemia mononuclear		X			X				X	X		X				X	X			X				X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Probenecid: 100 mg/kg (continued)

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	4 3 2	4 3 3	4 4 2	4 4 3	4 5 1	4 5 2	4 5 3	4 5 4	4 5 5	4 5 2	4 6 3	4 6 1	4 7 2	4 7 1	4 8 2	4 8 3	4 8 4	4 9 1	4 9 2	4 9 3	4 9 4	4 9 5	5 0 1	5 0 2	5 0 3	**Total Tissues/ Tumors**
Respiratory System																										
Lung			+	+				+			+		+	+		+	+		+	+	+	+				26
Alveolar/bronchiolar adenoma											X															2
Nose																										9
Trachea	+	+	+	+	+	+	+	+	+	+	+		+	+		+	+	+	+	+	+	+	+	+	+	46
Special Senses System																										
Ear							+																			4
Eye					+		+		+	+	+									+						13
Harderian gland											+									+						5
Lacrimal gland																				+						1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder																										8
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																								X		1
Leukemia mononuclear				X			X		X								X		X	X			X	X		17

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Probenecid: 400 mg/kg

Number of Days on Study	0 9 4	1 3 5	2 0 3	2 1 6	2 6 0	2 6 6	2 7 0	2 8 8	4 9 5	5 1 2	5 2 6	5 5 7	5 6 1	5 9 2	5 9 2	6 0 3	6 0 4	6 0 5	6 2 4	6 3 7	6 3 9	6 4 9	6 5 2	6 5 8	6 7 0
Carcass ID Number	5 6 5	5 1 5	6 0 5	5 4 5	5 5 5	5 8 5	5 8 4	5 5 4	5 4 4	5 7 5	5 3 5	5 3 4	5 8 3	6 3 4	6 7 4	5 1 4	5 9 5	7 4 3	4 1 3	1 2 5	5 7 2	5 6 3	6 0 4	5 9 4
Alimentary System																									
Esophagus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Intestine large	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Intestine large, cecum	A	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Intestine large, rectum	A	+	+	A	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Intestine small	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Intestine small, duodenum	A	+	+	+	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Intestine small, ileum	A	+	+	A	+	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+
Intestine small, jejunum	A	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Neoplastic nodule																									
Mesentery			+													+							+		+
Histiocytic sarcoma																									X
Sarcoma stromal, metastatic																						X			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Salivary glands	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Stomach	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Stomach, glandular	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Histiocytic sarcoma																									X
Cardiovascular System																									
Blood vessel									+																
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			
Histiocytic sarcoma																									X
Adrenal gland, medulla	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Histiocytic sarcoma																									X
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	M	M	+	M	M	+	+	+	M	+	+	M	+	M	+	+	+	+	+	M	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma												X							X	X				X
Pars distalis, adenoma, multiple																									
Pars intermedia, adenoma																									
Thyroid gland	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Bilateral, c-cell, carcinoma																									
C-cell, adenoma																									
C-cell, carcinoma																									
Follicular cell, adenoma																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Probenecid: 400 mg/kg (continued)

Number of Days on Study	6 7 7	6 9 5	6 9 8	7 0 5	7 2 1	7 2 2	7 3 2	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	5 3 3	5 1 2	5 5 3	5 6 2	5 6 1	5 2 4	5 7 1	5 1 1	5 2 3	5 2 1	5 2 2	5 3 1	5 3 2	5 4 1	5 4 2	5 5 1	5 5 2	5 8 1	5 8 2	5 9 1	5 9 2	5 9 3	6 0 1	6 0 2	6 0 3	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Neoplastic nodule					X										X											2
Mesentery							+			+																6
Histiocytic sarcoma																										1
Sarcoma stromal, metastatic																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										1
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+		49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+		49
Adenoma																										1
Histiocytic sarcoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+		45
Histiocytic sarcoma																										1
Pheochromocytoma benign									X																	1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adenoma				X					X																	2
Parathyroid gland	+	+	+	+	+	M	+	M	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	M		34
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Pars distalis, adenoma			X	X		X	X	X		X	X			X						X	X			X		15
Pars distalis, adenoma, multiple									X																	1
Pars intermedia, adenoma														X												1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Bilateral, c-cell, carcinoma						X																				1
C-cell, adenoma																				X						1
C-cell, carcinoma			X																							1
Follicular cell, adenoma																							X			1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Probenecid: 400 mg/kg (continued)

Number of Days on Study	0 9 4	1 3 5	2 0 3	2 1 6	2 6 0	2 6 6	2 7 0	2 8 8	4 9 5	5 1 2	5 2 6	5 5 7	5 6 1	5 9 2	5 9 2	6 0 3	6 0 4	6 0 5	6 2 4	6 3 7	6 3 9	6 4 9	6 5 2	6 5 8	6 7 0
Carcass ID Number	5 6 5	5 1 5	6 0 5	5 4 5	5 5 5	5 8 5	5 8 4	5 5 4	5 4 4	5 7 5	5 3 5	5 3 4	5 8 3	5 6 4	5 7 4	5 1 4	5 9 5	5 7 3	5 4 3	5 1 3	5 2 5	5 7 2	5 6 3	6 0 4	5 9 4
General Body System																									
None																									
Genital System																									
Clitoral gland	M	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+
Adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Arrhenoblastoma benign																									
Granulosa cell tumor benign														X											
Histiocytic sarcoma																									X
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leiomyosarcoma																									
Polyp stromal									X						X				X						X
Sarcoma stromal																	X						X		
Hematopoietic System																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mandibular, carcinoma, metastatic, thyroid gland																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																									
Thymus	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	+	M	M	M	M	M	+	+	M	+	+	+	+	+	M	+	+	+	+	M	M	+	+
Fibroadenoma										X		X							X	X					
Skin	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord												+													
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, thyroid gland																									
Histiocytic sarcoma																									X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Probenecid: 400 mg/kg (continued)

Number of Days on Study	6 7 7	6 9 5	6 9 8	7 0 5	7 2 1	7 2 2	7 3 2	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	5 3 3	5 1 2	5 5 3	5 6 2	5 6 1	5 2 4	5 7 1	5 1 1	5 2 3	5 2 1	5 2 2	5 2 1	5 3 3	5 3 2	5 4 1	5 4 2	5 5 1	5 5 2	5 8 1	5 8 2	5 9 1	5 9 2	5 9 3	6 0 1	6 0 2	6 0 3	**Total Tissues/ Tumors**
General Body System																											
None																											
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma							X																				1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Arrhenoblastoma benign																					X						1
Granulosa cell tumor benign																											1
Histiocytic sarcoma																											1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Adenoma																								X			1
Leiomyosarcoma					X																						1
Polyp stromal													X	X							X			X	X		9
Sarcoma stromal																											2
Hematopoietic System																											
Blood							+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		18
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mandibular, carcinoma, metastatic, thyroid gland						X																					1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																			X								1
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	M	+	+	36
Fibroadenoma																	X										5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																											1
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X																									1
Carcinoma, metastatic, thyroid gland						X																					1
Histiocytic sarcoma																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Probenecid: 400 mg/kg (continued)

Number of Days on Study	0 9 4	1 3 5	2 0 3	2 1 6	2 6 0	2 6 6	2 7 0	2 8 8	4 9 5	5 1 2	5 2 6	5 5 7	5 6 1	5 9 2	5 9 2	6 0 3	6 0 4	6 0 5	6 2 4	6 3 7	6 3 9	6 4 9	6 5 2	6 5 8	6 7 0
Carcass ID Number	5 6 5	5 1 5	6 0 5	5 4 5	5 5 5	5 8 5	5 8 4	5 5 4	5 4 4	5 7 5	5 3 5	5 3 4	5 8 3	5 6 4	5 7 4	5 1 4	5 9 5	5 7 3	5 4 3	5 1 3	5 2 5	5 7 2	5 6 3	6 0 4	5 9 4
Special Senses System																									
Ear					+								+												
Eye													+						+						
Harderian gland													+						+						+
Lacrimal gland																									+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	A	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Leukemia mononuclear									X				X	X								X		X	
Lymphoma malignant histiocytic																									
Lymphoma malignant undifferentiated cell type																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Probenecid: 400 mg/kg (continued)

Number of Days on Study	6 7 7	6 9 5	6 9 8	7 0 5	7 2 1	7 2 2	7 3 2	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	5 3 3	5 1 2	5 5 3	5 6 2	5 6 1	5 2 4	5 7 1	5 1 1	5 2 3	5 2 1	5 2 2	5 3 1	5 3 2	5 4 1	5 4 2	5 5 1	5 5 2	5 8 1	5 8 2	5 9 1	5 9 2	5 9 3	6 0 1	6 0 2	6 0 3	**Total Tissues/ Tumors**
Special Senses System																										
Ear																										2
Eye		+	+	+															+							6
Harderian gland		+	+	+															+							7
Lacrimal gland		+																								2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear	X		X	X	X			X	X	X	X			X		X	X							X		17
Lymphoma malignant histiocytic													X													1
Lymphoma malignant undifferentiated cell type		X																								1

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Probenecid

	Vehicle Control	100 mg/kg	400 mg/kg
Clitoral Gland: Adenoma			
Overall rates	3/36 (8%)	7/16 (44%)[e]	1/45 (2%)
Adjusted rates	10.2%		5.3%
Terminal rates	1/20 (5%)		1/19 (5%)
First incidence (days)	649		729 (T)
Life table tests			P=0.368N
Logistic regression tests			P=0.277N
Cochran-Armitage test			
Fisher exact test			P=0.229N
Clitoral Gland: Adenoma or Carcinoma			
Overall rates	3/36 (8%)	8/16 (50%)[e]	1/45 (2%)
Adjusted rates	10.2%		5.3%
Terminal rates	1/20 (5%)		1/19 (5%)
First incidence (days)	649		729 (T)
Life table tests			P=0.368N
Logistic regression tests			P=0.277N
Cochran-Armitage test			
Fisher exact test			P=0.229N
Mammary Gland: Fibroadenoma			
Overall rates	24/50 (48%)	23/50 (46%)	5/50 (10%)
Adjusted rates	65.7%	48.8%	15.6%
Terminal rates	12/24 (50%)	11/35 (31%)	1/19 (5%)
First incidence (days)	593	537	512
Life table tests	P=0.002N	P=0.149N	P=0.002N
Logistic regression tests	P<0.001N	P=0.479N	P<0.001N
Cochran-Armitage test	P<0.001N		
Fisher exact test		P=0.500N	P<0.001N
Mammary Gland: Adenocarcinoma			
Overall rates	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rates	9.7%	2.9%	0.0%
Terminal rates	1/24 (4%)	1/35 (3%)	0/19 (0%)
First incidence (days)	652	729 (T)	–[f]
Life table tests	P=0.147N	P=0.214N	P=0.171N
Logistic regression tests	P=0.129N	P=0.295N	P=0.149N
Cochran-Armitage test	P=0.107N		
Fisher exact test		P=0.309N	P=0.121N
Mammary Gland: Fibroadenoma or Adenocarcinoma			
Overall rates	24/50 (48%)	23/50 (46%)	5/50 (10%)
Adjusted rates	65.7%	48.8%	15.6%
Terminal rates	12/24 (50%)	11/35 (31%)	1/19 (5%)
First incidence (days)	593	537	512
Life table tests	P=0.002N	P=0.149N	P<0.002N
Logistic regression tests	P<0.001N	P=0.479N	P<0.001N
Cochran-Armitage test	P<0.001N		
Fisher exact test		P=0.500N	P<0.001N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Probenecid
(continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Pituitary Gland (Pars Distalis): Adenoma			
Overall rates	22/50 (44%)	26/50 (52%)	16/50 (32%)
Adjusted rates	60.7%	63.2%	60.0%
Terminal rates	11/24 (46%)	20/35 (57%)	9/19 (47%)
First incidence (days)	544	592	557
Life table tests	P=0.490N	P=0.356N	P=0.466N
Logistic regression tests	P=0.294N	P=0.339	P=0.385N
Cochran-Armitage test	P=0.070N		
Fisher exact test		P=0.274	P=0.151N
Thyroid Gland (C-cell): Adenoma			
Overall rates	9/49 (18%)	3/50 (6%)	1/47 (2%)
Adjusted rates	28.3%	8.2%	5.3%
Terminal rates	3/23 (13%)	2/35 (6%)	1/19 (5%)
First incidence (days)	635	721	729 (T)
Life table tests	P=0.032N	P=0.021N	P=0.031N
Logistic regression tests	P=0.023N	P=0.040N	P=0.021N
Cochran-Armitage test	P=0.014N		
Fisher exact test		P=0.056N	P=0.009N
Thyroid Gland (C-cell): Carcinoma			
Overall rates	3/49 (6%)	1/50 (2%)	2/47 (4%)
Adjusted rates	11.2%	2.9%	9.1%
Terminal rates	2/23 (9%)	1/35 (3%)	0/19 (0%)
First incidence (days)	651	729 (T)	698
Life table tests	P=0.615	P=0.195N	P=0.606N
Logistic regression tests	P=0.645	P=0.261N	P=0.595N
Cochran-Armitage test	P=0.571N		
Fisher exact test		P=0.301N	P=0.520N
Thyroid Gland (C-cell): Adenoma or Carcinoma			
Overall rates	12/49 (24%)	4/50 (8%)	3/47 (6%)
Adjusted rates	37.2%	11.0%	13.9%
Terminal rates	5/23 (22%)	3/35 (9%)	1/19 (5%)
First incidence (days)	635	721	698
Life table tests	P=0.069N	P=0.006N	P=0.049N
Logistic regression tests	P=0.046N	P=0.015N	P=0.031N
Cochran-Armitage test	P=0.025N		
Fisher exact test		P=0.024N	P=0.014N
Uterus: Stromal Polyp			
Overall rates	7/50 (14%)	10/50 (20%)	9/50 (18%)
Adjusted rates	20.4%	23.9%	34.8%
Terminal rates	2/24 (8%)	5/35 (14%)	5/19 (26%)
First incidence (days)	510	551	495
Life table tests	P=0.194	P=0.497	P=0.232
Logistic regression tests	P=0.360	P=0.297	P=0.304
Cochran-Armitage test	P=0.441		
Fisher exact test		P=0.298	P=0.393

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Probenecid
(continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Uterus: Stromal Polyp or Stromal Sarcoma			
Overall rates	8/50 (16%)	10/50 (20%)	11/50 (22%)
Adjusted rates	22.2%	23.9%	39.0%
Terminal rates	2/24 (8%)	5/35 (14%)	5/19 (26%)
First incidence (days)	510	551	495
Life table tests	P=0.107	P=0.595	P=0.162
Logistic regression tests	P=0.254	P=0.397	P=0.244
Cochran-Armitage test	P=0.306		
Fisher exact test		P=0.398	P=0.306
All Organs: Leukemia (Mononuclear)			
Overall rates	15/50 (30%)	17/50 (34%)	17/50 (34%)
Adjusted rates	40.1%	41.6%	58.4%
Terminal rates	5/24 (21%)	12/35 (34%)	8/19 (42%)
First incidence (days)	510	97	495
Life table tests	P=0.106	P=0.418N	P=0.187
Logistic regression tests	P=0.298	P=0.413	P=0.252
Cochran-Armitage test	P=0.426		
Fisher exact test		P=0.415	P=0.415
All Organs: Benign Tumors			
Overall rates	41/50 (82%)	39/50 (78%)	29/50 (58%)
Adjusted rates	93.0%	81.3%	84.6%
Terminal rates	21/24 (88%)	26/35 (74%)	14/19 (74%)
First incidence (days)	510	537	495
Life table tests	P=0.481N	P=0.030N	P=0.332N
Logistic regression tests	P=0.071N	P=0.394N	P=0.099N
Cochran-Armitage test	P=0.003N		
Fisher exact test		P=0.402N	P=0.008N
All Organs: Malignant Tumors			
Overall rates	27/50 (54%)	21/50 (42%)	24/50 (48%)
Adjusted rates	63.3%	51.7%	72.2%
Terminal rates	10/24 (42%)	16/35 (46%)	10/19 (53%)
First incidence (days)	495	97	495
Life table tests	P=0.167	P=0.033N	P=0.383
Logistic regression tests	P=0.471	P=0.161N	P=0.567
Cochran-Armitage test	P=0.443N		
Fisher exact test		P=0.158N	P=0.345N
All Organs: Benign or Malignant Tumors			
Overall rates	49/50 (98%)	46/50 (92%)	37/50 (74%)
Adjusted rates	98.0%	93.9%	94.8%
Terminal rates	23/24 (96%)	32/35 (91%)	17/19 (89%)
First incidence (days)	354	97	495
Life table tests	P=0.446	P=0.012N	P=0.444N
Logistic regression tests	P=0.010N	P=0.201N	P=0.028N
Cochran-Armitage test	P<0.001N		
Fisher exact test		P=0.181N	P<0.001N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Probenecid
(continued)

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly to the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Tissue was examined microscopically only when it was observed to be abnormal at necropsy.
[f] Not applicable; no tumors in animal group

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Probenecid

	Vehicle Control	100 mg/kg	400 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Moribund	25	15	20
Dead	1		10
Gavage death			1
Survivors			
Terminal sacrifice	23	35	19
Moribund	1		
Animals examined microscopically	50	50	50
Alimentary System			
Esophagus	(48)	(49)	(48)
Inflammation, chronic active			1 (2%)
Intestine large, cecum	(50)	(9)	(44)
Parasite			1 (2%)
Intestine large, colon	(49)	(9)	(48)
Parasite	2 (4%)		9 (19%)
Intestine large, rectum	(48)	(8)	(45)
Parasite	1 (2%)	1 (13%)	
Intestine small, ileum	(49)	(10)	(44)
Lymphoid nodule, hyperplasia	2 (4%)		1 (2%)
Lymphoid tissue, hyperplasia		1 (10%)	
Intestine small, jejunum	(48)	(11)	(44)
Lymphoid nodule, hyperplasia	1 (2%)	1 (9%)	1 (2%)
Liver	(50)	(30)	(50)
Angiectasis	2 (4%)	1 (3%)	
Basophilic focus	35 (70%)	20 (67%)	27 (54%)
Clear cell focus		1 (3%)	1 (2%)
Congestion			1 (2%)
Cyst	1 (2%)		
Fatty change, diffuse	8 (16%)	2 (7%)	1 (2%)
Fatty change, focal	9 (18%)	7 (23%)	3 (6%)
Focal cellular change	1 (2%)		
Hepatodiaphragmatic nodule	4 (8%)	7 (23%)	5 (10%)
Mixed cell focus	5 (10%)	2 (7%)	5 (10%)
Necrosis	1 (2%)		2 (4%)
Pigmentation	2 (4%)	1 (3%)	
Regeneration, focal	1 (2%)		2 (4%)
Bile duct, hyperplasia	12 (24%)	7 (23%)	7 (14%)
Mesentery	(6)	(2)	(6)
Artery, pigmentation	1 (17%)		
Artery, thrombus	1 (17%)		
Fat, hemorrhage			1 (17%)
Fat, inflammation, chronic active	1 (17%)		
Fat, mineralization	1 (17%)		1 (17%)
Fat, necrosis	4 (67%)	2 (100%)	4 (67%)
Fat, pigmentation	1 (17%)		
Pancreas	(50)	(14)	(50)
Acinus, atrophy	1 (2%)		1 (2%)
Acinus, hyperplasia	2 (4%)		1 (2%)
Artery, pigmentation	1 (2%)		

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Probenecid (continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Alimentary System (continued)			
Salivary glands	(50)	(10)	(48)
Acinus, hypertrophy	2 (4%)		
Acinus, inflammation, chronic active	1 (2%)		1 (2%)
Acinus, necrosis	2 (4%)		
Duct, inflammation, acute		1 (10%)	
Duct, inflammation, chronic active	5 (10%)		1 (2%)
Duct, metaplasia, squamous	18 (36%)	2 (20%)	13 (27%)
Duct, mineralization			1 (2%)
Stomach, forestomach	(49)	(9)	(49)
Acanthosis	2 (4%)		1 (2%)
Hemorrhage			1 (2%)
Hyperkeratosis	2 (4%)	1 (11%)	
Inflammation, chronic active			1 (2%)
Necrosis	2 (4%)		
Stomach, glandular	(50)	(9)	(47)
Hyperplasia		1 (11%)	
Mineralization	1 (2%)		
Necrosis			1 (2%)
Cardiovascular System			
Blood vessel			(1)
Artery, inflammation, chronic active			1 (100%)
Heart	(50)	(9)	(50)
Cardiomyopathy	32 (64%)	3 (33%)	31 (62%)
Mineralization		1 (11%)	1 (2%)
Endocrine System			
Adrenal gland, cortex	(50)	(13)	(49)
Congestion			1 (2%)
Hemorrhage			1 (2%)
Vacuolization cytoplasmic	1 (2%)		2 (4%)
Adrenal gland, medulla	(48)	(13)	(45)
Hyperplasia	5 (10%)	1 (8%)	6 (13%)
Islets, pancreatic	(50)	(11)	(50)
Hyperplasia	1 (2%)		1 (2%)
Pituitary gland	(50)	(50)	(50)
Pars distalis, angiectasis	24 (48%)	24 (48%)	15 (30%)
Pars distalis, cyst	7 (14%)	3 (6%)	4 (8%)
Pars distalis, hyperplasia	15 (30%)	13 (26%)	11 (22%)
Pars intermedia, angiectasis			1 (2%)
Pars intermedia, hyperplasia	1 (2%)		1 (2%)
Pars nervosa, cyst		1 (2%)	
Thyroid gland	(49)	(50)	(47)
Mineralization			1 (2%)
C-cell, hyperplasia	8 (16%)	13 (26%)	4 (9%)
Follicular cell, hyperplasia			2 (4%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Probenecid (continued)

	Vehicle Control	100 mg/kg	400 mg/kg
General Body System			
Tissue NOS	(1)		
Abscess	1 (100%)		
Mineralization	1 (100%)		
Genital System			
Clitoral gland	(36)	(16)	(45)
Hyperplasia		1 (6%)	
Inflammation, acute		3 (19%)	
Inflammation, chronic active			1 (2%)
Necrosis		1 (6%)	1 (2%)
Ovary	(50)	(16)	(50)
Cyst	2 (4%)	1 (6%)	4 (8%)
Pigmentation			1 (2%)
Uterus	(50)	(16)	(49)
Cyst	1 (2%)		
Decidual reaction			1 (2%)
Hemorrhage			1 (2%)
Bilateral, abscess			1 (2%)
Endometrium, hyperplasia, adenomatous			1 (2%)
Hematopoietic System			
Bone marrow	(50)	(8)	(50)
Hypoplasia	1 (2%)		
Lymph node	(49)	(21)	(50)
Lumbar, infiltration cellular, plasma cell		1 (5%)	
Mandibular, hematopoietic cell proliferation			1 (2%)
Mandibular, infiltration cellular, plasma cell		1 (5%)	
Mediastinal, angiectasis	2 (4%)		
Mediastinal, infiltration cellular, plasma cell	1 (2%)	1 (5%)	
Mediastinal, infiltration cellular, histiocytic	3 (6%)		3 (6%)
Pancreatic, depletion lymphoid	1 (2%)		
Pancreatic, hematopoietic cell proliferation	1 (2%)		
Pancreatic, infiltration cellular, histiocytic	2 (4%)	1 (5%)	2 (4%)
Renal, angiectasis	3 (6%)		
Renal, infiltration cellular, histiocytic	4 (8%)	2 (10%)	2 (4%)
Lymph node, mesenteric	(49)	(20)	(50)
Angiectasis	2 (4%)	2 (10%)	1 (2%)
Depletion lymphoid	1 (2%)	1 (5%)	1 (2%)
Infiltration cellular, mast cell			1 (2%)
Infiltration cellular, histiocytic	1 (2%)	7 (35%)	7 (14%)
Spleen	(50)	(23)	(50)
Angiectasis		1 (4%)	
Depletion lymphoid	3 (6%)	1 (4%)	5 (10%)
Fibrosis	1 (2%)		
Hematopoietic cell proliferation	38 (76%)	6 (26%)	23 (46%)
Hemorrhage	2 (4%)	1 (4%)	1 (2%)
Infiltration cellular, histiocytic	9 (18%)	2 (9%)	15 (30%)
Necrosis	2 (4%)	1 (4%)	1 (2%)
Pigmentation		4 (17%)	

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Probenecid (continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Hematopoietic System (continued)			
Thymus	(49)	(10)	(46)
Cyst			1 (2%)
Depletion lymphoid	2 (4%)	1 (10%)	1 (2%)
Hemorrhage			2 (4%)
Necrosis			1 (2%)
Integumentary System			
Mammary gland	(47)	(28)	(36)
Galactocele	36 (77%)	13 (46%)	6 (17%)
Acinus, hyperplasia	1 (2%)	1 (4%)	1 (3%)
Skin	(50)	(12)	(49)
Acanthosis		1 (8%)	
Cyst epithelial inclusion			1 (2%)
Hyperkeratosis		1 (8%)	1 (2%)
Necrosis			1 (2%)
Musculoskeletal System			
Skeletal muscle	(1)		
Artery, pigmentation	1 (100%)		
Artery, thrombus	1 (100%)		
Nervous System			
Brain	(50)	(10)	(50)
Hemorrhage			1 (2%)
Inflammation, acute		1 (10%)	
Brain stem, hemorrhage	1 (2%)		
Cerebrum, hemorrhage			1 (2%)
Cerebrum, necrosis	2 (4%)		
Medulla, hemorrhage	1 (2%)		
Respiratory System			
Lung	(50)	(26)	(50)
Atelectasis			1 (2%)
Congestion	6 (12%)	10 (38%)	5 (10%)
Edema			8 (16%)
Embolus tumor	1 (2%)		
Fibrosis			1 (2%)
Hemorrhage	2 (4%)	2 (8%)	5 (10%)
Infiltration cellular, histiocytic	3 (6%)		6 (12%)
Inflammation, chronic active		1 (4%)	3 (6%)
Mineralization			1 (2%)
Alveolar epithelium, hyperplasia	2 (4%)	2 (8%)	3 (6%)
Mediastinum, atypical cells	1 (2%)		
Nose	(49)	(9)	(50)
Inflammation, chronic active	1 (2%)		2 (4%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Probenecid (continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Special Senses System			
Eye	(11)	(13)	(6)
Hemorrhage	1 (9%)		
Synechia		2 (15%)	1 (17%)
Lens, cataract	3 (27%)	4 (31%)	3 (50%)
Retina, atrophy		2 (15%)	1 (17%)
Harderian gland	(6)	(5)	(7)
Hyperplasia	2 (33%)		
Inflammation, chronic active	1 (17%)		
Pigmentation	2 (33%)	1 (20%)	1 (14%)
Urinary System			
Kidney	(50)	(50)	(50)
Atrophy	1 (2%)		
Cyst			1 (2%)
Hydronephrosis	1 (2%)		
Nephropathy	41 (82%)	33 (66%)	30 (60%)
Pigmentation		1 (2%)	
Cortex, inflammation, acute			1 (2%)
Cortex, mineralization	4 (8%)	3 (6%)	10 (20%)
Papilla, mineralization	18 (36%)	10 (20%)	24 (48%)
Papilla, necrosis			1 (2%)
Pelvis, mineralization	43 (86%)	30 (60%)	30 (60%)
Renal tubule, pigmentation	48 (96%)	47 (94%)	46 (92%)
Urinary bladder	(50)	(8)	(47)
Hemorrhage	2 (4%)		1 (2%)
Inflammation, acute	1 (2%)		
Mineralization		1 (13%)	
Necrosis			1 (2%)
Transitional epithelium, hyperplasia			1 (2%)

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR GAVAGE STUDY OF PROBENECID

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Probenecid

	Vehicle Control	100 mg/kg	400 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Dead	7	6	13
Moribund	5	19	13
Gavage death		2	
Survivors			
Terminal sacrifice	38	23	24
Animals examined microscopically	50	50	50
Alimentary System			
Intestine large	(49)	(49)	(47)
Anus, squamous cell carcinoma			1 (2%)
Intestine large, cecum	(48)	(46)	(43)
Sarcoma		1 (2%)	
Intestine small, duodenum	(48)	(45)	(42)
Intestine small, ileum	(48)	(44)	(43)
Intestine small, jejunum	(48)	(43)	(39)
Liver	(50)	(50)	(50)
Carcinoma, metastatic, uncertain primary site			1 (2%)
Hemangiosarcoma		2 (4%)	
Hemangiosarcoma, multiple		1 (2%)	1 (2%)
Hepatocellular carcinoma	7 (14%)	12 (24%)	11 (22%)
Hepatocellular adenoma	12 (24%)	2 (4%)	7 (14%)
Hepatocellular adenoma, multiple			3 (6%)
Histiocytic sarcoma		1 (2%)	2 (4%)
Sarcoma, metastatic, uncertain primary site			1 (2%)
Mesentery	(1)	(2)	(1)
Pancreas	(47)	(50)	(50)
Carcinoma, metastatic, uncertain primary site			1 (2%)
Acinus, adenoma			1 (2%)
Stomach, forestomach	(49)	(50)	(48)
Papilloma squamous		1 (2%)	
Cardiovascular System			
Heart	(49)	(50)	(50)
Sarcoma, metastatic, uncertain primary site			1 (2%)
Endocrine System			
Adrenal gland, medulla	(48)	(44)	(46)
Pheochromocytoma benign	1 (2%)	1 (2%)	1 (2%)
Thyroid gland	(48)	(50)	(47)
Follicular cell, adenoma	1 (2%)		
General Body System			
None			

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Probenecid (continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Genital System			
Epididymis	(49)	(50)	(50)
Prostate	(48)	(46)	(50)
Seminal vesicle	(49)	(50)	(50)
Testes	(49)	(50)	(50)
Interstitial cell, adenoma	1 (2%)		
Hematopoietic System			
Bone marrow	(49)	(50)	(50)
Hemangioma			1 (2%)
Histiocytic sarcoma		1 (2%)	
Lymph node	(44)	(45)	(42)
Lumbar, histiocytic sarcoma		1 (2%)	
Mandibular, histiocytic sarcoma		1 (2%)	
Mediastinal, histiocytic sarcoma		1 (2%)	
Renal, histiocytic sarcoma		1 (2%)	
Renal, sarcoma, metastatic, uncertain primary site			1 (2%)
Lymph node, mesenteric	(44)	(42)	(38)
Carcinoma, metastatic, uncertain primary site			1 (3%)
Histiocytic sarcoma		1 (2%)	1 (3%)
Spleen	(49)	(50)	(48)
Hemangiosarcoma		1 (2%)	
Histiocytic sarcoma		1 (2%)	1 (2%)
Sarcoma			1 (2%)
Thymus	(47)	(36)	(36)
Integumentary System			
Skin	(47)	(49)	(48)
Papilloma squamous		1 (2%)	
Subcutaneous tissue, fibroma			3 (6%)
Subcutaneous tissue, fibrosarcoma	1 (2%)	4 (8%)	3 (6%)
Subcutaneous tissue, hemangiosarcoma		1 (2%)	1 (2%)
Subcutaneous tissue, neurofibroma		1 (2%)	1 (2%)
Subcutaneous tissue, neurofibrosarcoma		1 (2%)	
Subcutaneous tissue, sarcoma		1 (2%)	
Musculoskeletal System			
Skeletal muscle			(1)
Carcinoma, metastatic, uncertain primary site			1 (100%)
Nervous System			
Brain	(49)	(50)	(50)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Probenecid (continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Respiratory System			
Lung	(49)	(50)	(50)
Alveolar/bronchiolar adenoma	3 (6%)	4 (8%)	4 (8%)
Alveolar/bronchiolar carcinoma	2 (4%)		2 (4%)
Carcinoma, metastatic, harderian gland	1 (2%)		
Carcinoma, metastatic, uncertain primary site			2 (4%)
Hemangiosarcoma, metastatic, skin			1 (2%)
Hepatocellular carcinoma, metastatic, liver	1 (2%)	3 (6%)	7 (14%)
Histiocytic sarcoma			2 (4%)
Sarcoma, metastatic, uncertain primary site			1 (2%)
Mediastinum, fibrosarcoma, early invasion		1 (2%)	
Special Senses System			
Harderian gland	(4)	(1)	
Adenoma	2 (50%)	1 (100%)	
Carcinoma	2 (50%)		
Urinary System			
Kidney	(49)	(50)	(50)
Carcinoma, metastatic, uncertain primary site			2 (4%)
Histiocytic sarcoma		1 (2%)	
Urinary bladder	(48)	(49)	(47)
Histiocytic sarcoma		1 (2%)	
Systemic Lesions			
Multiple organs[a]	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)	2 (4%)
Lymphoma malignant lymphocytic		1 (2%)	2 (4%)
Lymphoma malignant mixed	1 (2%)	1 (2%)	1 (2%)
Lymphoma malignant undifferentiated cell	2 (4%)	1 (2%)	2 (4%)
Tumor Summary			
Total animals with primary neoplasms[b]	25	26	36
Total primary neoplasms	35	40	48
Total animals with benign neoplasms	18	10	19
Total benign neoplasms	20	11	21
Total animals with malignant neoplasms	15	24	24
Total malignant neoplasms	15	29	27
Total animals with secondary neoplasms[c]	2	3	8
Total secondary neoplasms	2	3	20
Total animals with malignant neoplasms			2

[a] Number of animals with any tissue examined microscopically
[b] Primary tumors: all tumors except metastatic tumors
[c] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Probenecid: Vehicle Control

Number of Days on Study	0 0 3	3 1 0	3 9 0	4 1 0	5 2 2	5 4 1	5 7 6	5 8 2	6 0 6	6 1 4	6 8 0	6 8 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2
Carcass ID Number	0 2 1	0 4 5	0 3 5	1 0 5	0 5 5	0 3 4	1 0 4	0 9 5	0 2 4	0 7 5	0 5 4	0 6 5	0 1 2	0 1 3	0 1 4	0 2 2	0 2 3	0 2 5	0 3 1	0 3 2	0 3 3	0 4 1	0 4 2	0 4 3	0 5 1
Alimentary System																									
Esophagus	+	+	M	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	M	A	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Intestine small, jejunum	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma					X	X				X		X						X							
Hepatocellular adenoma						X	X	X		X		X													
Mesentery																		+							
Pancreas	+	+	+	+	M	+	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	M	+	M	M	M	M	+	+	+	+	+	M	+	+	+	+	+	+	M	M	M	+	+
Pituitary gland	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M	M
Thyroid gland	+	+	+	+	+	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									X
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland			+		+		+			+	+														
Prostate	+	+	+	+	+	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Probenecid: Vehicle Control (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	0 5 2	0 5 3	0 6 1	0 6 2	0 7 1	0 7 2	0 7 3	0 7 4	0 8 1	0 8 2	0 8 3	0 8 4	0 8 5	0 9 3	0 1 1	0 1 5	0 4 4	0 6 3	0 6 4	0 9 1	0 9 2	0 9 4	1 0 1	1 0 2	1 0 3	**Total Tissues/ Tumors**
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	44
Gallbladder	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma		X																					X		7
Hepatocellular adenoma										X		X			X	X						X	X	X	12
Mesentery																									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	47
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign				X																					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid gland	+	+	M	M	M	+	M	+	+	M	+	M	+	+	+	+	+	M	M	+	+	M	+	+	31
Pituitary gland	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	M	M	+	38
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell, adenoma																									1
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland				+						+			+	+	+	+	+								12
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell, adenoma																			X						1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Probenecid: Vehicle Control (continued)

Number of Days on Study	0 0 3	3 1 0	3 9 0	4 1 0	5 2 2	5 4 1	5 7 6	5 8 2	6 0 6	6 1 4	6 8 0	6 8 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2
Carcass ID Number	0 2 1	0 4 5	0 3 5	1 0 5	0 5 5	0 3 4	1 0 4	0 9 5	0 2 4	0 7 5	0 5 4	0 6 5	0 1 2	0 1 3	0 2 4	0 2 2	0 2 3	0 2 5	0 3 1	0 3 2	0 3 3	0 4 1	0 4 2	0 4 3	0 5 1
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma			X																						
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X									X			
Alveolar/bronchiolar carcinoma											X														
Carcinoma, metastatic, harderian gland																									
Hepatocellular carcinoma, metastatic, liver												X													
Nose	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	M	+	M	+	+
Trachea	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									+
Harderian gland																									+
Adenoma																									
Carcinoma																									X
Urinary System																									
Kidney	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Lymphoma malignant undifferentiated cell type													X												

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Probenecid: Vehicle Control (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	0 5 2	0 5 3	0 6 1	0 6 2	0 7 1	0 7 2	0 7 3	0 7 4	0 8 1	0 8 2	0 8 3	0 8 4	0 8 5	0 9 3	0 1 1	0 1 5	0 4 4	0 6 3	0 6 4	0 9 1	0 9 2	0 9 4	1 0 1	1 0 2	1 0 3	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	44
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	44
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	47
Integumentary System																										
Mammary gland	M	M	M	M	M	+	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	+	M	+	4
Skin	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																				X						3
Alveolar/bronchiolar carcinoma																						X				2
Carcinoma, metastatic, harderian gland																	X									1
Hepatocellular carcinoma, metastatic, liver																										1
Nose	+	M	+	+	+	+	M	+	+	+	+	+	M	+	+	M	+	+	+	+	M	+	+	M	+	40
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye																	+					+				3
Harderian gland										+							+					+				4
Adenoma										X												X				2
Carcinoma																	X									2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed			X																							1
Lymphoma malignant undifferentiated cell type															X											2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Probenecid: 100 mg/kg

Number of Days on Study	0 0 1 2 2 3 3 4 4 4 4 4 4 4 5 5 5 6 6 6 6 6 6 7 0 0 4 0 3 0 9 1 2 3 4 5 6 9 1 6 8 3 4 4 4 4 5 8 0 3 3 3 8 9 5 0 6 6 1 3 2 3 2 5 1 9 5 5 5 5 6 9 3 7
Carcass ID Number	1 1 1 1 1 1 1 1 1 1 1 2 1 1 1 1 1 1 1 2 1 1 1 1 3 4 2 2 7 5 4 8 5 2 7 0 4 9 9 3 9 2 6 8 0 7 9 3 4 1 1 5 4 5 5 5 5 4 3 4 5 4 5 4 5 3 2 5 4 4 3 2 4 3
Alimentary System	
Esophagus	+ +
Gallbladder	A A M A + M + + A + + + + A M + + + A + + + + +
Intestine large	+ + + + + + + + + + + + + A + + + + + + + + + +
Intestine large, cecum	+ M + + + + + + A + + + + + A + + + + + + + + +
Sarcoma	
Intestine large, colon	+ + + + + + + + + + + + + A + + + + + + + + + +
Intestine large, rectum	+ M + + + + + + M + + + M A + + + + + + + + + +
Intestine small	+ + + A + + + + A + + + + A + + + + + + + + + +
Intestine small, duodenum	A M + A + + + + A + + + + A + + + + + + + + + +
Intestine small, ileum	M + + A + + + + A + + + + A + + + + + + + + + +
Intestine small, jejunum	A M M A + + + + A + + + + A + + + + + + + + + +
Liver	+ +
Hemangiosarcoma	
Hemangiosarcoma, multiple	X
Hepatocellular carcinoma	X X X X X X X
Hepatocellular adenoma	X
Histiocytic sarcoma	X
Mesentery	
Pancreas	+ +
Salivary glands	+ +
Stomach	+ +
Stomach, forestomach	+ +
Papilloma squamous	
Stomach, glandular	+ +
Cardiovascular System	
Heart	+ +
Endocrine System	
Adrenal gland	+ +
Adrenal gland, cortex	+ +
Adrenal gland, medulla	M + M + + +
Pheochromocytoma benign	
Islets, pancreatic	+ +
Parathyroid gland	+ M M + + + + + + + + + + + + + + M + + + + + +
Pituitary gland	+ + + + + M + M + + + + + + M + + + + + + M + +
Thyroid gland	+ +
General Body System	
Tissue NOS	
Genital System	
Epididymis	+ +
Preputial gland	+ + A + + +
Prostate	+ + + + M + + + M + + + + + + + + + + + + + + +
Seminal vesicle	+ +
Testes	+ +

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Probenecid: 100 mg/kg (continued)

Number of Days on Study	7 1 7	7 2 5	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 4	7 3 5	7 3 1	7 3 1	7 3 1	7 3 2	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	
Carcass ID Number	1 6 4	1 1 5	1 1 1	1 1 2	1 1 3	1 1 4	1 2 1	1 3 2	1 3 3	1 4 2	1 5 1	1 5 2	1 5 3	1 6 1	1 6 2	1 6 3	1 7 1	1 7 2	1 8 1	1 8 2	1 8 3	1 9 1	2 0 3	2 0 1	2 0 2	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Sarcoma						X																				1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma	X										X															2
Hemangiosarcoma, multiple																										1
Hepatocellular carcinoma		X										X							X					X	X	12
Hepatocellular adenoma		X																								2
Histiocytic sarcoma																										1
Mesentery										+															+	2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous										X																1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	M	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	44
Pheochromocytoma benign												X														1
Islets, pancreatic	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	M	M	+	M	M	M	+	M	+	M	+	M	+	+	+	M	M	+	M	+	+	+	M	+	+	35
Pituitary gland	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
Tissue NOS						+																				1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+			+	+			+				+			+				+		+				+	15
Prostate	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Probenecid: 100 mg/kg (continued)

Number of Days on Study	0 0 1 2 2 3 3 4 4 4 4 4 4 4 5 5 5 6 6 6 6 6 6 7 0 0 4 0 3 0 9 1 2 3 4 5 6 9 1 6 8 3 4 4 4 4 5 8 0 3 3 3 8 9 5 0 6 6 1 3 2 3 2 5 1 9 5 5 5 5 6 9 3 7
Carcass ID Number	1 1 1 1 1 1 1 1 1 1 1 2 1 1 1 1 1 1 1 2 1 1 1 1 3 4 2 2 7 5 4 8 5 2 7 0 4 9 9 3 9 2 6 8 0 7 9 3 4 1 1 5 4 5 5 5 5 4 3 4 5 4 5 4 5 3 2 5 4 4 3 2 4 3
Hematopoietic System	
Blood	
Bone marrow	+ +
Histiocytic sarcoma	X
Lymph node	+ + M M + + + + M + + + + + + + + + M + + M + + +
Lumbar, histiocytic sarcoma	X
Mandibular, histiocytic sarcoma	X
Mediastinal, histiocytic sarcoma	X
Renal, histiocytic sarcoma	X
Lymph node, mesenteric	+ + M M M + + + M + + + + + + + M + M + + M M + +
Histiocytic sarcoma	X
Spleen	+ +
Hemangiosarcoma	
Histiocytic sarcoma	X
Thymus	A + M + M M + + M + M + + + M M M + A + + + M + +
Integumentary System	
Mammary gland	M M M M M + M M M + M M M M + + M M + M M + M M M
Skin	+ +
Papilloma squamous	
Subcutaneous tissue, fibrosarcoma	X X
Subcutaneous tissue, hemangiosarcoma	
Subcutaneous tissue, neurofibroma	X
Subcutaneous tissue, neurofibrosarcoma	X
Subcutaneous tissue, sarcoma	
Musculoskeletal System	
Bone	+ +
Nervous System	
Brain	+ +
Spinal cord	
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	X
Hepatocellular carcinoma, metastatic, liver	X X
Mediastinum, fibrosarcoma, early invasion	X
Nose	+ + M + + + + + M + + + + + + + + + + + + + + M +
Trachea	+ +
Special Senses System	
Harderian gland	
Adenoma	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Probenecid: 100 mg/kg (continued)

Number of Days on Study	7 1 7	7 2 5	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	
Carcass ID Number	1 6 4	1 1 5	1 1 1	1 1 2	1 1 3	1 1 4	1 2 1	1 3 2	1 3 3	1 4 2	1 5 1	1 5 2	1 5 3	1 6 1	1 6 2	1 6 3	1 7 1	1 7 2	1 8 1	1 8 2	1 8 3	1 9 1	2 0 3	2 0 1	2 0 2	**Total Tissues/ Tumors**
Hematopoietic System																										
Blood		+	+			+	+		+		+				+	+	+		+	+	+	+	+			14
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lumbar, histiocytic sarcoma																										1
Mandibular, histiocytic sarcoma																										1
Mediastinal, histiocytic sarcoma																										1
Renal, histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma	X																									1
Histiocytic sarcoma																										1
Thymus	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	36
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	+	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	8
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous											X															1
Subcutaneous tissue, fibrosarcoma										X					X											4
Subcutaneous tissue, hemangiosarcoma	X																									1
Subcutaneous tissue, neurofibroma																										1
Subcutaneous tissue, neurofibrosarcoma																										1
Subcutaneous tissue, sarcoma			X																							1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord															+											1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X																		X					X		4
Hepatocellular carcinoma, metastatic, liver												X														3
Mediastinum, fibrosarcoma, early invasion																										1
Nose	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	45
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland	+																									1
Adenoma	X																									1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Probenecid: 100 mg/kg (continued)

Number of Days on Study	0 0 1 2 2 3 3 4 4 4 4 4 4 4 5 5 5 6 6 6 6 6 6 7 0 0 4 0 3 0 9 1 2 3 4 5 6 9 1 6 8 3 4 4 4 4 5 8 0 3 3 3 8 9 5 0 6 6 1 3 2 3 2 5 1 9 5 5 5 5 6 9 3 7
Carcass ID Number	1 1 1 1 1 1 1 1 1 1 1 2 1 1 1 1 1 1 1 2 1 1 1 1 3 4 2 2 7 5 4 8 5 2 7 0 4 9 9 3 9 2 6 8 0 7 9 3 4 1 1 5 4 5 5 5 5 4 3 4 5 4 5 4 5 3 2 5 4 4 3 2 4 3
Urinary System	
Kidney	+ +
Histiocytic sarcoma	X
Urinary bladder	+ +
Histiocytic sarcoma	X
Systemic Lesions	
Multiple organs	+ +
Histiocytic sarcoma	X
Lymphoma malignant lymphocytic	X
Lymphoma malignant mixed	
Lymphoma malignant undifferentiated cell type	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Probenecid: 100 mg/kg (continued)

Number of Days on Study	7 1 7	7 2 5	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2		
Carcass ID Number	1 6 4	1 1 5	1 1 1	1 1 2	1 1 3	1 1 4	1 1 1	1 2 2	1 3 3	1 3 3	1 4 2	1 5 1	1 5 2	1 5 3	1 6 1	1 6 2	1 6 3	1 7 1	1 7 2	1 8 1	1 8 2	1 8 3	1 9 1	2 0 3	2 0 1	2 0 2	**Total Tissues/ Tumors**
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Histiocytic sarcoma																											1
Urinary bladder	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Histiocytic sarcoma																											1
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Histiocytic sarcoma																											1
Lymphoma malignant lymphocytic																		X									1
Lymphoma malignant mixed																											1
Lymphoma malignant undifferentiated cell type																					X						1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Probenecid: 400 mg/kg

Number of Days on Study	0 2 0	0 3 1	3 0 4	3 0 6	3 5 5	4 0 8	4 3 8	5 0 9	5 1 5	5 6 8	5 6 8	5 8 9	6 1 1	6 1 1	6 2 0	6 2 6	6 3 4	6 3 5	6 4 0	6 4 6	6 6 7	6 8 6	7 1 7	7 2 2	7 2 5
Carcass ID Number	3 0 1	3 0 2	2 5 5	2 7 5	2 6 5	2 4 5	2 3 5	2 7 4	2 5 4	2 9 4	2 9 5	2 6 4	2 8 5	3 0 4	3 3 4	2 7 3	2 4 4	2 8 4	2 8 3	2 1 5	2 2 5	2 7 2	2 5 2	2 2 4	2 3 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Gallbladder	M	A	+	+	M	A	+	+	+	+	M	M	+	+	+	+	A	+	+	+	+	A	+	+	M
Intestine large	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Anus, squamous cell carcinoma							X																		
Intestine large, cecum	+	A	+	A	A	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	A	+	+	+
Intestine large, colon	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	A	A	+	+	M	+	+	M	+	+	+	+	+	A	+	+	+	+	A	+	+	+
Intestine small	+	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	A	A	A	+	A	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	A	+	+	M	+	A	+	+	+
Intestine small, jejunum	+	A	+	A	A	+	+	A	+	+	M	M	M	+	+	+	A	+	+	+	+	A	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uncertain primary site													X												
Hemangiosarcoma, multiple																	X								
Hepatocellular carcinoma							X			X	X	X		X		X			X		X				X
Hepatocellular adenoma																X							X		
Hepatocellular adenoma, multiple									X						X										
Histiocytic sarcoma					X																				
Sarcoma, metastatic, uncertain primary site																					X				
Mesentery																						+			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uncertain primary site													X												
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	A	A	+	M	A	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site																					X				
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Parathyroid gland	M	+	M	M	M	M	+	+	+	+	+	+	M	M	+	+	M	M	+	+	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	M	+	M	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Probenecid: 400 mg/kg (continued)

Number of Days on Study	7 2 7	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 9 3	2 1 1	2 1 2	2 1 3	2 1 4	2 2 1	2 2 2	2 2 3	2 3 1	2 3 2	2 4 1	2 4 2	2 4 3	2 5 1	2 5 3	2 6 1	2 6 2	2 6 3	2 7 1	2 8 1	2 8 2	2 9 1	2 9 2	3 0 3	3 0 5	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Anus, squamous cell carcinoma																									1
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	A	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine small	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	39
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, uncertain primary site																									1
Hemangiosarcoma, multiple																									1
Hepatocellular carcinoma		X																			X				11
Hepatocellular adenoma		X											X				X		X					X	7
Hepatocellular adenoma, multiple																X									3
Histiocytic sarcoma															X										2
Sarcoma, metastatic, uncertain primary site																									1
Mesentery																									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, uncertain primary site																									1
Acinus, adenoma						X																			1
Salivary glands	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, uncertain primary site																									1
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Pheochromocytoma benign												X													1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	M	M	+	+	+	M	M	M	+	M	+	M	M	+	+	+	+	M	M	+	+	M	M	+	28
Pituitary gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	44
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Probenecid: 400 mg/kg (continued)

Number of Days on Study	0 2 0	0 3 1	3 0 4	3 0 6	3 5 5	4 0 8	4 3 8	5 0 9	5 1 5	5 6 8	5 6 8	5 8 9	6 1 1	6 1 1	6 2 0	6 2 6	6 3 4	6 3 5	6 4 0	6 4 6	6 6 7	6 8 6	7 1 7	7 2 2	7 2 5
Carcass ID Number	3 0 1	3 0 2	2 5 5	2 7 5	2 6 5	2 4 5	2 3 5	2 7 4	2 5 4	2 9 4	2 9 5	2 6 4	2 8 5	3 0 4	2 3 4	2 7 3	2 4 4	2 8 4	2 8 3	2 1 5	2 2 5	2 7 2	2 5 2	2 2 4	2 3 3
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+		+		+	+		+	+		+							+					+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Lymph node	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	M	M	+	+	M	+	+	+	+	M
Renal, sarcoma, metastatic, uncertain primary site																					X				
Lymph node, mesenteric	+	+	+	M	+	+	+	M	M	+	+	M	+	+	+	M	M	+	+	M	M	+	+	+	M
Carcinoma, metastatic, uncertain primary site													X												
Histiocytic sarcoma					X																				
Spleen	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Sarcoma																									
Thymus	M	+	M	M	M	+	M	M	+	+	+	+	+	+	+	M	M	M	+	M	+	M	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	+
Skin	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Subcutaneous tissue, fibroma																				X					
Subcutaneous tissue, fibrosarcoma									X														X		
Subcutaneous tissue, hemangiosarcoma																				X					
Subcutaneous tissue, neurofibroma																		X							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle													+												
Carcinoma, metastatic, uncertain primary site													X												
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord										+								+							

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Probenecid: 400 mg/kg (continued)

Number of Days on Study	7 2 7	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 9 3	2 1 1	2 1 2	2 1 3	2 1 4	2 2 1	2 2 2	2 2 3	2 3 1	2 3 2	2 4 1	2 4 2	2 4 3	2 5 1	2 5 3	2 6 1	2 6 2	2 6 3	2 7 1	2 8 1	2 8 2	2 9 1	2 9 2	3 0 3	3 0 5	**Total Tissues/ Tumors**
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland							+	+							+		+	+	+		+	+	+	+		21
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma														X												1
Lymph node	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	42
Renal, sarcoma, metastatic, uncertain primary site																										1
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	38
Carcinoma, metastatic, uncertain primary site																										1
Histiocytic sarcoma																										1
Spleen	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Sarcoma														X												1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	M	36
Integumentary System																										
Mammary gland	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Subcutaneous tissue, fibroma	X				X																					3
Subcutaneous tissue, fibrosarcoma					X																					3
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, neurofibroma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Carcinoma, metastatic, uncertain primary site																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Probenecid: 400 mg/kg (continued)

Number of Days on Study	0 2 0	0 3 1	3 0 4	3 0 6	3 5 5	4 0 8	4 3 8	5 0 9	5 1 5	5 1 6	5 6 8	5 8 8	6 1 9	6 1 1	6 2 0	6 2 6	6 3 4	6 3 5	6 4 0	6 4 6	6 6 7	6 8 6	7 1 7	7 2 2	7 2 5
Carcass ID Number	3 0 1	3 0 2	2 5 5	2 7 5	2 6 5	2 4 5	2 3 5	2 7 4	2 5 4	2 9 4	2 9 5	2 6 4	2 8 5	3 0 4	2 3 4	2 7 3	2 4 4	2 8 4	2 8 3	2 1 5	2 2 5	2 7 2	2 5 2	2 2 4	2 3 3
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma															X			X					X		
Alveolar/bronchiolar carcinoma										X															
Carcinoma, metastatic, uncertain primary site													X								X				
Hemangiosarcoma, metastatic, skin																				X					
Hepatocellular carcinoma, metastatic, liver										X		X	X	X		X					X				
Histiocytic sarcoma					X																				
Sarcoma, metastatic, uncertain primary site																					X				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	M	M	+	M	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uncertain primary site													X								X				
Urinary bladder	+	+	+	+	A	+	+	+	M	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Lymphoma malignant lymphocytic				X																		X			
Lymphoma malignant mixed																									
Lymphoma malignant undifferentiated cell type																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Probenecid: 400 mg/kg (continued)

Number of Days on Study	7 2 7	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 9 3	2 1 1	2 1 2	2 1 3	2 1 4	2 2 1	2 2 2	2 2 3	2 3 1	2 3 2	2 4 1	2 4 2	2 4 3	2 5 1	2 5 3	2 6 1	2 6 2	2 6 3	2 7 1	2 8 1	2 8 2	2 9 1	2 9 2	3 0 3	3 0 5	**Total Tissues/ Tumors**
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X																		4
Alveolar/bronchiolar carcinoma									X																	2
Carcinoma, metastatic, uncertain primary site																										2
Hemangiosarcoma, metastatic, skin																										1
Hepatocellular carcinoma, metastatic, liver																					X					7
Histiocytic sarcoma															X											2
Sarcoma, metastatic, uncertain primary site																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	43
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, uncertain primary site																										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma															X											2
Lymphoma malignant lymphocytic																										2
Lymphoma malignant mixed																					X					1
Lymphoma malignant undifferentiated cell type			X				X																			2

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Probenecid

	Vehicle Control	100 mg/kg	400 mg/kg
Harderian Gland: Adenoma or Carcinoma			
Overall rates[a]	4/50 (8%)	1/50 (2%)	0/50 (0%)
Adjusted rates[b]	10.5%	4.0%	0.0%
Terminal rates[c]	4/38 (11%)	0/23 (0%)	0/24 (0%)
First incidence (days)	731 (T)	717	–[e]
Life table tests[d]	P=0.108N	P=0.352N	P=0.135N
Logistic regression tests[d]	P=0.089N	P=0.309N	P=0.135N
Cochran-Armitage test[d]	P=0.059N		
Fisher exact test[d]		P=0.181N	P=0.059N
Liver: Hepatocellular Adenoma			
Overall rates	12/50 (24%)	2/50 (4%)	10/50 (20%)
Adjusted rates	27.6%	7.6%	33.4%
Terminal rates	7/38 (18%)	0/23 (0%)	6/24 (25%)
First incidence (days)	541	659	515
Life table tests	P=0.268	P=0.041N	P=0.442
Logistic regression tests	P=0.427	P=0.008N	P=0.470N
Cochran-Armitage test	P=0.474		
Fisher exact test		P=0.004N	P=0.405N
Liver: Hepatocellular Carcinoma			
Overall rates	7/50 (14%)	12/50 (24%)	11/50 (22%)
Adjusted rates	16.3%	36.8%	29.3%
Terminal rates	3/38 (8%)	4/23 (17%)	2/24 (8%)
First incidence (days)	522	492	438
Life table tests	P=0.175	P=0.038	P=0.109
Logistic regression tests	P=0.286	P=0.118	P=0.234
Cochran-Armitage test	P=0.294		
Fisher exact test		P=0.154	P=0.218
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rates	15/50 (30%)	12/50 (24%)	19/50 (38%)
Adjusted rates	33.8%	36.8%	50.1%
Terminal rates	9/38 (24%)	4/23 (17%)	7/24 (29%)
First incidence (days)	522	492	438
Life table tests	P=0.058	P=0.404	P=0.070
Logistic regression tests	P=0.132	P=0.427N	P=0.237
Cochran-Armitage test	P=0.153		
Fisher exact test		P=0.326N	P=0.263
Lung: Alveolar/Bronchiolar Adenoma			
Overall rates	3/49 (6%)	4/50 (8%)	4/50 (8%)
Adjusted rates	7.9%	15.1%	12.9%
Terminal rates	3/38 (8%)	2/23 (9%)	1/24 (4%)
First incidence (days)	731 (T)	645	620
Life table tests	P=0.332	P=0.269	P=0.319
Logistic regression tests	P=0.441	P=0.347	P=0.444
Cochran-Armitage test	P=0.497		
Fisher exact test		P=0.511	P=0.511

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Probenecid
(continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall rates	5/49 (10%)	4/50 (8%)	6/50 (12%)
Adjusted rates	12.8%	15.1%	18.7%
Terminal rates	4/38 (11%)	2/23 (9%)	2/24 (8%)
First incidence (days)	680	645	568
Life table tests	P=0.244	P=0.502	P=0.281
Logistic regression tests	P=0.362	P=0.616	P=0.447
Cochran-Armitage test	P=0.416		
Fisher exact test		P=0.487N	P=0.514
Skin (Subcutaneous Tissue): Fibroma			
Overall rates	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rates	0.0%	0.0%	11.0%
Terminal rates	0/38 (0%)	0/23 (0%)	1/24 (4%)
First incidence (days)	-	-	646
Life table tests	P=0.018	-	P=0.066
Logistic regression tests	P=0.026	-	P=0.097
Cochran-Armitage test	P=0.030		
Fisher exact test		-	P=0.121
Skin (Subcutaneous Tissue): Fibrosarcoma			
Overall rates	1/50 (2%)	4/50 (8%)	3/50 (6%)
Adjusted rates	2.1%	13.0%	9.8%
Terminal rates	0/38 (0%)	2/23 (9%)	1/24 (4%)
First incidence (days)	390	390	515
Life table tests	P=0.320	P=0.114	P=0.231
Logistic regression tests	P=0.417	P=0.246	P=0.340
Cochran-Armitage test	P=0.402		
Fisher exact test		P=0.181	P=0.309
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma			
Overall rates	1/50 (2%)	4/50 (8%)	5/50 (10%)
Adjusted rates	2.1%	13.0%	16.2%
Terminal rates	0/38 (0%)	2/23 (9%)	1/24 (4%)
First incidence (days)	390	390	515
Life table tests	P=0.087	P=0.114	P=0.059
Logistic regression tests	P=0.135	P=0.246	P=0.113
Cochran-Armitage test	P=0.131		
Fisher exact test		P=0.181	P=0.102
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma			
Overall rates	1/50 (2%)	5/50 (10%)	3/50 (6%)
Adjusted rates	2.1%	17.1%	9.8%
Terminal rates	0/38 (0%)	3/23 (13%)	1/24 (4%)
First incidence (days)	390	390	515
Life table tests	P=0.358	P=0.051	P=0.231
Logistic regression tests	P=0.472	P=0.134	P=0.340
Cochran-Armitage test	P=0.460		
Fisher exact test		P=0.102	P=0.309

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Probenecid
(continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma			
Overall rates	1/50 (2%)	5/50 (10%)	5/50 (10%)
Adjusted rates	2.1%	17.1%	16.2%
Terminal rates	0/38 (0%)	3/23 (13%)	1/24 (4%)
First incidence (days)	390	390	515
Life table tests	P=0.110	P=0.051	P=0.059
Logistic regression tests	P=0.174	P=0.134	P=0.113
Cochran-Armitage test	P=0.171		
Fisher exact test		P=0.102	P=0.102
All Organs: Hemangiosarcoma			
Overall rates	0/50 (0%)	3/50 (6%)	2/50 (4%)
Adjusted rates	0.0%	11.0%	6.1%
Terminal rates	0/38 (0%)	1/23 (4%)	0/24 (0%)
First incidence (days)	–	645	634
Life table tests	P=0.302	P=0.066	P=0.195
Logistic regression tests	P=0.362	P=0.084	P=0.240
Cochran-Armitage test	P=0.377		
Fisher exact test		P=0.121	P=0.247
All Organs: Hemangioma or Hemangiosarcoma			
Overall rates	0/50 (0%)	3/50 (6%)	3/50 (6%)
Adjusted rates	0.0%	11.0%	10.0%
Terminal rates	0/38 (0%)	1/23 (4%)	1/24 (4%)
First incidence (days)	–	645	634
Life table tests	P=0.135	P=0.066	P=0.077
Logistic regression tests	P=0.180	P=0.084	P=0.111
Cochran-Armitage test	P=0.195		
Fisher exact test		P=0.121	P=0.121
All Organs: Malignant Lymphoma (Lymphocytic, Mixed, or Undifferentiated Cell Type)			
Overall rates	3/50 (6%)	3/50 (6%)	5/50 (10%)
Adjusted rates	7.9%	12.0%	17.3%
Terminal rates	3/38 (8%)	2/23 (9%)	3/24 (13%)
First incidence (days)	731 (T)	659	306
Life table tests	P=0.151	P=0.430	P=0.175
Logistic regression tests	P=0.255	P=0.516	P=0.331
Cochran-Armitage test	P=0.280		
Fisher exact test		P=0.661N	P=0.357
All Organs: Benign Tumors			
Overall rates	18/50 (36%)	10/50 (20%)	19/50 (38%)
Adjusted rates	41.6%	34.8%	58.2%
Terminal rates	13/38 (34%)	5/23 (22%)	11/24 (46%)
First incidence (days)	541	635	515
Life table tests	P=0.062	P=0.407N	P=0.099
Logistic regression tests	P=0.176	P=0.162N	P=0.344
Cochran-Armitage test	P=0.262		
Fisher exact test		P=0.059N	P=0.500

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Probenecid
(continued)

	Vehicle Control	100 mg/kg	400 mg/kg
All Organs: Malignant Tumors			
Overall rates	15/50 (30%)	24/50 (48%)	25/50 (50%)
Adjusted rates	33.8%	65.7%	59.1%
Terminal rates	9/38 (24%)	11/23 (48%)	8/24 (33%)
First incidence (days)	390	390	306
Life table tests	P=0.019	P=0.003	P=0.006
Logistic regression tests	P=0.054	P=0.022	P=0.036
Cochran-Armitage test	P=0.062		
Fisher exact test		P=0.050	P=0.033
All Organs: Benign and Malignant Tumors			
Overall rates	25/50 (50%)	26/50 (52%)	37/50 (74%)
Adjusted rates	54.2%	67.9%	82.2%
Terminal rates	17/38 (45%)	11/23 (48%)	16/24 (67%)
First incidence (days)	390	390	306
Life table tests	P=0.001	P=0.053	P<0.001
Logistic regression tests	P=0.003	P=0.305	P=0.006
Cochran-Armitage test	P=0.006		
Fisher exact test		P=0.500	P=0.011

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly to the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no tumors in animal group

TABLE C4
Historical Incidence of Skin Tumors in Male B6C3F$_1$ Mice Receiving Corn Oil by Gavage[a]

Study	Incidence in Controls		
	Fibroma	Fibrosarcoma	Fibroma or Fibrosarcoma
Historical Incidence at EG&G Mason Research Institute			
Bromoform[b]	3/50	2/50	5/50
Phenylbutazone[b]	1/50	3/50	4/50
Probenecid[b]	0/50	1/50	1/50
Diglycidyl resorcinol ether	4/50	4/50	8/50
1,2-Dichloropropane	3/50	4/50	7/50
Chlorodibromomethane	0/50	2/50	2/50
N-Butyl chloride	3/50	8/50	11/50
Bromodichloromethane	0/49	7/49	7/49
Bis(2-chloroisopropyl) ether	0/50	1/50	1/50
N-Butyl chloride	1/50	14/50	14/50
Total	15/499 (3.0%)	46/499 (9.2%)	60/499 (12.0%)
Standard deviation	3.2%	8.1%	8.6%
Range	0%–8%	2%–28%	2%–28%
Overall Historical Incidence			
Total	44/2,340 (1.9%)	125/2,340 (5.3%)	168/2,340 (7.2%)
Standard deviation	2.2%	6.3%	7.1%
Range	0%–8%	0%–28%	0%–29%

[a] Data from 2-year studies tabulated by the Toxicology Data Management System through 22 December 1989 and the Carcinogenesis Bioassay Data System through 6 March 1990.
[b] The incidences shown for the three studies are limited to skin tumors occurring at subcutaneous sites.

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Probenecid

	Vehicle Control	100 mg/kg	400 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Dead	7	6	13
Moribund	5	19	13
Gavage death		2	
Survivors			
Terminal sacrifice	38	23	24
Animals examined microscopically	50	50	50
Alimentary System			
Gallbladder	(46)	(40)	(40)
Hemorrhage	1 (2%)		
Intestine large	(49)	(49)	(47)
Anus, inflammation, chronic active		1 (2%)	
Anus, necrosis		1 (2%)	
Intestine large, colon	(49)	(49)	(47)
Lymphoid nodule, hyperplasia		2 (4%)	
Intestine large, rectum	(48)	(45)	(40)
Inflammation, acute			1 (3%)
Necrosis			1 (3%)
Intestine small, duodenum	(48)	(45)	(42)
Necrosis		1 (2%)	
Intestine small, ileum	(48)	(44)	(43)
Epithelium, hyperplasia	1 (2%)		
Lymphoid nodule, hyperplasia	1 (2%)	2 (5%)	
Intestine small, jejunum	(48)	(43)	(39)
Lymphoid nodule, hyperplasia		1 (2%)	
Liver	(50)	(50)	(50)
Angiectasis			1 (2%)
Clear cell focus			2 (4%)
Cyst		1 (2%)	1 (2%)
Fatty change, focal	2 (4%)	1 (2%)	2 (4%)
Hematopoietic cell proliferation		1 (2%)	1 (2%)
Hemorrhage			1 (2%)
Mineralization			3 (6%)
Necrosis	4 (8%)	8 (16%)	14 (28%)
Necrosis, coagulative		1 (2%)	
Pigmentation			2 (4%)
Mesentery	(1)	(2)	(1)
Fat, inflammation, chronic active	1 (100%)		
Fat, mineralization	1 (100%)		
Fat, necrosis		2 (100%)	
Pancreas	(47)	(50)	(50)
Acinus, atrophy	1 (2%)		
Acinus, hypertrophy		2 (4%)	
Stomach	(49)	(50)	(48)
Submucosa, inflammation, chronic active	1 (2%)		

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Probenecid (continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Alimentary System (continued)			
Stomach, forestomach	(49)	(50)	(48)
Acanthosis	2 (4%)	3 (6%)	7 (15%)
Acanthosis, focal	1 (2%)		1 (2%)
Hyperkeratosis	7 (14%)	5 (10%)	10 (21%)
Inflammation, acute		1 (2%)	
Inflammation, chronic active			2 (4%)
Necrosis		3 (6%)	4 (8%)
Stomach, glandular	(47)	(50)	(45)
Hyperplasia	2 (4%)	1 (2%)	1 (2%)
Inflammation, chronic active	3 (6%)		
Mineralization	1 (2%)		
Necrosis		2 (4%)	1 (2%)
Pigmentation		1 (2%)	
Cardiovascular System			
Heart	(49)	(50)	(50)
Cardiomyopathy	1 (2%)		
Inflammation, acute		2 (4%)	
Inflammation, chronic active	1 (2%)	1 (2%)	
Mineralization			2 (4%)
Thrombus		1 (2%)	
Endocrine System			
Adrenal gland	(48)	(50)	(49)
Accessory adrenal cortical nodule	1 (2%)	1 (2%)	1 (2%)
Capsule, hyperplasia	23 (48%)	22 (44%)	30 (61%)
Capsule, hyperplasia, focal	1 (2%)	2 (4%)	
Adrenal gland, cortex	(48)	(50)	(49)
Hemorrhage		1 (2%)	
Hyperplasia	22 (46%)	23 (46%)	28 (57%)
Hypertrophy			1 (2%)
Adrenal gland, medulla	(48)	(44)	(46)
Hyperplasia	7 (15%)	10 (23%)	6 (13%)
Islets, pancreatic	(47)	(49)	(49)
Hyperplasia	1 (2%)		2 (4%)
Parathyroid gland	(31)	(35)	(28)
Cyst			1 (4%)
Hyperplasia			1 (4%)
Pituitary gland	(38)	(44)	(44)
Pars distalis, cyst		1 (2%)	
Pars distalis, hyperplasia		1 (2%)	1 (2%)
Pars distalis, hyperplasia, adenomatous	1 (3%)		
Thyroid gland	(48)	(50)	(47)
Cyst			1 (2%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Probenecid (continued)

	Vehicle Control	100 mg/kg	400 mg/kg
General Body System			
None			
Genital System			
Preputial gland	(12)	(15)	(21)
Dilatation	5 (42%)	3 (20%)	8 (38%)
Inflammation, acute	1 (8%)		2 (10%)
Inflammation, chronic		1 (7%)	
Inflammation, chronic active	4 (33%)	4 (27%)	5 (24%)
Necrosis	4 (33%)	4 (27%)	4 (19%)
Prostate	(48)	(46)	(50)
Inflammation, acute	2 (4%)	2 (4%)	4 (8%)
Inflammation, chronic active		2 (4%)	
Necrosis		1 (2%)	
Epithelium, hyperplasia		2 (4%)	
Seminal vesicle	(49)	(50)	(50)
Hemorrhage	1 (2%)		
Inflammation, acute	1 (2%)		2 (4%)
Inflammation, chronic active		1 (2%)	
Testes	(49)	(50)	(50)
Atrophy	1 (2%)		
Spermatocele	1 (2%)		
Interstitial cell, hyperplasia			1 (2%)
Seminiferous tubule, atrophy	1 (2%)	2 (4%)	2 (4%)
Seminiferous tubule, mineralization	1 (2%)	2 (4%)	2 (4%)
Hematopoietic System			
Bone marrow	(49)	(50)	(50)
Angiectasis			1 (2%)
Lymph node	(44)	(45)	(42)
Axillary, infiltration cellular, plasma cell	1 (2%)	2 (4%)	1 (2%)
Axillary, infiltration cellular, lymphocytic	1 (2%)		
Inguinal, infiltration cellular, lymphocytic	1 (2%)		
Lumbar, hematopoietic cell proliferation		3 (7%)	
Lumbar, hyperplasia, plasma cell		1 (2%)	
Lumbar, infiltration cellular, plasma cell	2 (5%)	7 (16%)	2 (5%)
Lumbar, infiltration cellular, lymphocytic	1 (2%)		
Lumbar, infiltration cellular, histiocytic		1 (2%)	
Lumbar, inflammation, acute			1 (2%)
Mandibular, necrosis			1 (2%)
Mediastinal, angiectasis			1 (2%)
Mediastinal, hematopoietic cell proliferation			1 (2%)
Mediastinal, infiltration cellular, histiocytic	1 (2%)		
Pancreatic, hematopoietic cell proliferation		1 (2%)	
Renal, hematopoietic cell proliferation		1 (2%)	
Renal, infiltration cellular, plasma cell	1 (2%)	2 (4%)	3 (7%)
Renal, infiltration cellular, histiocytic		2 (4%)	

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Probenecid (continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Hematopoietic System (continued)			
Lymph node, mesenteric	(44)	(42)	(38)
Angiectasis	20 (45%)	19 (45%)	14 (37%)
Hematopoietic cell proliferation	4 (9%)	6 (14%)	9 (24%)
Necrosis			1 (3%)
Spleen	(49)	(50)	(48)
Angiectasis			2 (4%)
Atrophy			1 (2%)
Depletion lymphoid		2 (4%)	1 (2%)
Fibrosis	1 (2%)		
Hematopoietic cell proliferation	19 (39%)	25 (50%)	29 (60%)
Hyperplasia, lymphoid	1 (2%)		
Necrosis			1 (2%)
Lymphoid follicle, hyperplasia	1 (2%)		
Thymus	(47)	(36)	(36)
Atrophy	1 (2%)	1 (3%)	1 (3%)
Depletion lymphoid		4 (11%)	2 (6%)
Integumentary System			
Skin	(47)	(49)	(48)
Hemorrhage		1 (2%)	
Hyperplasia, basal cell	1 (2%)		
Inflammation, acute		1 (2%)	
Inflammation, chronic active		1 (2%)	
Necrosis	1 (2%)	2 (4%)	
Inguinal, fungus	1 (2%)		
Inguinal, inflammation, chronic active	1 (2%)		
Inguinal, necrosis	1 (2%)		
Prepuce, acanthosis		1 (2%)	
Prepuce, hemorrhage		1 (2%)	1 (2%)
Prepuce, inflammation, acute			1 (2%)
Prepuce, inflammation, chronic active	2 (4%)	1 (2%)	
Prepuce, necrosis	2 (4%)	3 (6%)	2 (4%)
Subcutaneous tissue, mineralization			1 (2%)
Subcutaneous tissue, necrosis			1 (2%)
Musculoskeletal System			
Bone	(49)	(50)	(50)
Joint, hyperostosis	1 (2%)		
Tarsal, hyperostosis	35 (71%)	33 (66%)	36 (72%)
Nervous System			
None			

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Probenecid (continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Respiratory System			
Lung	(49)	(50)	(50)
Bacterium			1 (2%)
Congestion		2 (4%)	2 (4%)
Hemorrhage	6 (12%)	2 (4%)	4 (8%)
Infiltration cellular, histiocytic	2 (4%)	1 (2%)	2 (4%)
Inflammation, acute	2 (4%)	2 (4%)	2 (4%)
Necrosis			1 (2%)
Pigmentation			1 (2%)
Alveolar epithelium, hyperplasia	3 (6%)	2 (4%)	
Nose	(40)	(45)	(43)
Edema	1 (3%)		
Special Senses System			
None			
Urinary System			
Kidney	(49)	(50)	(50)
Atrophy		1 (2%)	
Bacterium	1 (2%)		
Casts protein		3 (6%)	4 (8%)
Congestion		1 (2%)	1 (2%)
Glomerulosclerosis			4 (8%)
Hydronephrosis		1 (2%)	1 (2%)
Inflammation, acute		4 (8%)	1 (2%)
Inflammation, chronic			1 (2%)
Inflammation, chronic active		1 (2%)	1 (2%)
Cortex, mineralization	16 (33%)	4 (8%)	9 (18%)
Papilla, mineralization	2 (4%)		3 (6%)
Papilla, necrosis	1 (2%)	2 (4%)	1 (2%)
Renal tubule, casts protein		1 (2%)	1 (2%)
Renal tubule, regeneration	1 (2%)		4 (8%)
Urinary bladder	(48)	(49)	(47)
Calculus micro observation only	1 (2%)	2 (4%)	2 (4%)
Inflammation, acute		2 (4%)	3 (6%)
Inflammation, chronic active		2 (4%)	
Mineralization	1 (2%)		
Necrosis		3 (6%)	1 (2%)
Transitional epithelium, hyperplasia		2 (4%)	

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR GAVAGE STUDY OF PROBENECID

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Probenecid

	Vehicle Control	100 mg/kg	400 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Moribund	9	9	9
Dead	8	7	9
Accident		1	
Survivors			
Terminal sacrifice	32	31	32
Moribund		1	
Other	1	1	
Animals examined microscopically	49	49	50
Alimentary System			
Gallbladder	(44)	(41)	(45)
Intestine large, cecum	(47)	(14)	(47)
Sarcoma			1 (2%)
Intestine large, colon	(48)	(15)	(49)
Histiocytic sarcoma		1 (7%)	
Intestine small, ileum	(47)	(16)	(46)
Intestine small, jejunum	(46)	(14)	(44)
Histiocytic sarcoma		1 (7%)	
Liver	(48)	(49)	(49)
Hemangiosarcoma			1 (2%)
Hemangiosarcoma, metastatic			1 (2%)
Hepatocellular carcinoma	2 (4%)	2 (4%)	3 (6%)
Hepatocellular adenoma	3 (6%)	2 (4%)	10 (20%)
Hepatocellular adenoma, multiple			4 (8%)
Histiocytic sarcoma		1 (2%)	1 (2%)
Pancreas	(48)	(19)	(47)
Histiocytic sarcoma		1 (5%)	
Salivary glands	(45)	(15)	(49)
Stomach	(47)	(49)	(49)
Stomach, forestomach	(47)	(49)	(49)
Papilloma squamous	3 (6%)	2 (4%)	2 (4%)
Squamous cell carcinoma		1 (2%)	
Cardiovascular System			
Heart	(48)	(15)	(49)
Endocrine System			
Adrenal gland	(48)	(14)	(49)
Hepatocellular carcinoma, metastatic, liver	1 (2%)		
Histiocytic sarcoma		1 (7%)	
Capsule, adenoma			1 (2%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Probenecid (continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Endocrine System (continued)			
Islets, pancreatic	(48)	(15)	(46)
Adenoma	1 (2%)		
Pituitary gland	(41)	(13)	(38)
Pars distalis, adenoma	1 (2%)		4 (11%)
Pars distalis, adenoma, multiple	1 (2%)		
Pars intermedia, adenoma		1 (8%)	
Thyroid gland	(48)	(48)	(48)
Follicular cell, adenoma		2 (4%)	2 (4%)
General Body System			
Tissue NOS	(1)	(1)	
Sarcoma	1 (100%)		
Genital System			
Ovary	(47)	(48)	(50)
Cystadenoma			1 (2%)
Histiocytic sarcoma		1 (2%)	
Luteoma		1 (2%)	
Uterus	(48)	(30)	(50)
Histiocytic sarcoma		1 (3%)	2 (4%)
Polyp stromal		1 (3%)	
Sarcoma			1 (2%)
Endometrium, histiocytic sarcoma		1 (3%)	
Hematopoietic System			
Bone marrow	(48)	(14)	(49)
Lymph node	(43)	(26)	(45)
Lymph node, mesenteric	(41)	(20)	(44)
Histiocytic sarcoma		1 (5%)	1 (2%)
Spleen	(48)	(25)	(49)
Hemangiosarcoma		1 (4%)	
Hemangiosarcoma, metastatic			1 (2%)
Thymus	(42)	(12)	(42)
Integumentary System			
Skin	(46)	(16)	(48)
Subcutaneous tissue, fibrosarcoma			1 (2%)
Subcutaneous tissue, hemangiosarcoma			1 (2%)
Subcutaneous tissue, sarcoma		1 (6%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Probenecid (continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Musculoskeletal System			
None			
Nervous System			
Brain	(47)	(15)	(49)
Respiratory System			
Lung	(49)	(23)	(49)
Alveolar/bronchiolar adenoma	1 (2%)	4 (17%)	5 (10%)
Alveolar/bronchiolar carcinoma	2 (4%)		1 (2%)
Carcinoma, metastatic, harderian gland		1 (4%)	
Fibrosarcoma, metastatic, skin			1 (2%)
Hepatocellular carcinoma, metastatic, liver	1 (2%)		
Histiocytic sarcoma		1 (4%)	
Special Senses System			
Harderian gland		(1)	(2)
Adenoma			1 (50%)
Carcinoma		1 (100%)	
Urinary System			
Kidney	(48)	(19)	(49)
Histiocytic sarcoma		1 (5%)	
Urinary bladder	(44)	(13)	(47)
Systemic Lesions			
Multiple organs[a]	(49)	(49)	(50)
Histiocytic sarcoma		2 (4%)	3 (6%)
Lymphoma malignant lymphocytic	2 (4%)	1 (2%)	2 (4%)
Lymphoma malignant mixed	2 (4%)	2 (4%)	3 (6%)
Lymphoma malignant undifferentiated cell	7 (14%)	6 (12%)	2 (4%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Probenecid (continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Tumor Summary			
Total animals with primary neoplasms[b]	23	21	31
Total primary neoplasms	26	30	49
Total animals with benign neoplasms	10	10	22
Total benign neoplasms	10	13	30
Total animals with malignant neoplasms	15	16	17
Total malignant neoplasms	16	17	19
Total animals with secondary neoplasms[c]	1	1	2
Total secondary neoplasms	2	1	3

[a] Number of animals with any tissue examined microscopically
[b] Primary tumors: all tumors except metastatic tumors
[c] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Probenecid: Vehicle Control

Number of Days on Study	0 1 3	0 2 9	5 3 9	5 8 0	5 9 6	6 0 3	6 1 2	6 1 2	6 4 8	6 5 5	6 6 0	6 8 7	6 8 7	7 0 4	7 0 9	7 0 9	7 2 1	7 2 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2
Carcass ID Number	3 3 1	3 1 1	4 0 5	4 0 4	3 5 5	3 6 5	3 2 5	3 3 5	3 3 4	3 8 5	3 4 5	3 2 4	3 6 4	3 4 4	3 1 5	3 6 3	3 6 2	1 2 4	2 2 1	2 2 2	2 3 3	3 3 2	4 3 3	5 2 3
Alimentary System																									
Esophagus	M		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	
Gallbladder	M		+	A	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, cecum	A		+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, colon	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, rectum	A		+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	
Intestine small	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, duodenum	A		+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, ileum	A		+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, jejunum	A		+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Liver	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hepatocellular carcinoma												X			X									
Hepatocellular adenoma							X		X															
Mesentery			+					+	+															
Pancreas	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Salivary glands	A		+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	
Stomach	A		+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, forestomach	A		+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Papilloma squamous																									
Stomach, glandular	A		+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Cardiovascular System																									
Heart	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Endocrine System																									
Adrenal gland	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hepatocellular carcinoma, metastatic, liver															X										
Adrenal gland, cortex	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adrenal gland, medulla	A		+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	
Islets, pancreatic	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma																			X						
Parathyroid gland	M		M	M	+	M	+	+	+	+	+	M	+	+	M	M	+	M	+	+	+	M	+	+	+
Pituitary gland	A		+	+	+	M	+	+	+	+	+	M	+	+	M	M	M	M	+	+	+	+	+	M	+
Pars distalis, adenoma																									
Pars distalis, adenoma, multiple																									
Thyroid gland	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
General Body System																									
Tissue NOS																									
Sarcoma																									

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Probenecid: Vehicle Control (continued)

Number of Days on Study	7 3 2	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	3 5 4	3 4 1	3 5 1	3 5 2	3 6 1	3 7 1	3 7 2	3 7 3	3 7 4	3 7 5	3 8 1	3 8 2	3 8 3	3 9 1	3 9 2	3 9 3	3 9 4	3 9 5	4 0 1	4 0 2	3 1 2	3 1 3	3 4 3	3 8 4	4 0 3	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma																										2
Hepatocellular adenoma								X																		3
Mesentery																										3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Papilloma squamous					X						X			X												3
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	46
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma, metastatic, liver																										1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	45
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										1
Parathyroid gland	M	M	+	+	M	M	+	M	+	+	M	M	M	+	+	+	M	+	+	M	+	+	M	+	+	29
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Pars distalis, adenoma																								X		1
Pars distalis, adenoma, multiple																				X						1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
General Body System																										
Tissue NOS									+																	1
Sarcoma									X																	1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Probenecid: Vehicle Control (continued)

Number of Days on Study	0 1 3	0 2 9	5 3 9	5 8 0	5 9 6	6 0 3	6 1 2	6 1 2	6 4 8	6 5 5	6 6 0	6 8 7	6 8 7	7 0 4	7 0 9	7 0 9	7 2 1	7 2 4	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2
Carcass ID Number	3 3 1	3 1 1	4 0 5	4 0 4	3 5 5	3 6 5	3 2 5	3 3 5	3 3 4	3 8 5	3 4 5	3 2 4	3 6 4	3 4 4	3 1 5	3 6 3	3 6 2	3 1 4	3 2 1	3 2 2	3 2 3	3 3 2	3 3 3	4 2 2	5 3 3
Genital System																										
Ovary	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																										
Blood																			+	+	+	+	+	+	+	+
Bone marrow	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	M		M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+
Lymph node, mesenteric	M		M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+
Spleen	M		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	A		M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+
Integumentary System																										
Mammary gland	M		+	+	+	+	+	+	+	M	+	M	M	+	M	+	+	+	M	M	M	M	+	+	+	M
Skin	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Musculoskeletal System																										
Bone	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	A		+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																										
Lung	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																		X								
Alveolar/bronchiolar carcinoma																	X									
Hepatocellular carcinoma, metastatic, liver															X											
Nose	A		+	M	+	+	+	+	+	M	+	+	M	+	M	+	+	+	M	+	+	+	+	+	+	+
Trachea	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
None																										
Urinary System																										
Kidney	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A		+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic								X												X						
Lymphoma malignant mixed																X					X					
Lymphoma malignant undifferentiated cell type										X		X						X							X	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Probenecid: Vehicle Control (continued)

Number of Days on Study	7 3 2	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	3 5 4	3 4 1	3 5 1	3 5 2	3 6 1	3 7 1	3 7 2	3 7 3	3 7 4	3 7 5	3 8 1	3 8 2	3 8 3	3 9 1	3 9 2	3 9 3	3 9 4	3 9 5	4 0 1	4 0 2	3 1 2	3 1 3	3 4 3	3 8 4	4 0 3	**Total Tissues/ Tumors**
Genital System																										
Ovary	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hematopoietic System																										
Blood	+	+	+	+	+	+	+	+	+	+	+		+	+		+	+	+	+	+	+	+	+	+	+	30
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Lymph node, mesenteric	+	+	+	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	42
Integumentary System																										
Mammary gland	M	M	M	M	+	M	M	M	M	M	M	+	M	M	+	+	M	+	M	M	M	+	+	+	M	22
Skin	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																					X					2
Hepatocellular carcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	41
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	44
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										2
Lymphoma malignant mixed																										2
Lymphoma malignant undifferentiated cell type								X									X						X		7

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Probenecid: 100 mg/kg

Number of Days on Study	0 2 9	1 0 8	3 3 7	3 4 7	4 8 8	5 3 6	5 4 7	5 5 0	5 7 0	5 9 5	6 0 6	6 2 7	6 4 4	6 4 6	6 7 4	6 8 6	6 9 4	7 1 7	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	4 7 1	5 0 5	4 4 5	4 5 5	4 5 4	4 7 5	4 6 5	4 7 4	4 6 4	4 3 5	4 3 4	4 8 5	4 8 4	5 0 4	4 8 3	4 9 5	5 0 3	4 1 5	4 1 1	4 1 2	4 1 3	4 1 4	4 2 1	4 2 2	4 2 3
Alimentary System																									
Esophagus		+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder		+	A	A	+	+	+	+	+	A	M	+	+	A	+	M	+	+	+	+	+	+	+	+	+
Intestine large		+	+	+	+	+	+	+	+	+	+	+		+		+									
Intestine large, cecum		+	+	+	+	+	+	+	+	+	M	+		+		+									
Intestine large, colon		+	+	+	+	+	+	+	+	+	+	+		+		+									
Histiocytic sarcoma																X									
Intestine large, rectum		+	+	+	M	M	A	+	+	M	+	+		+		M									
Intestine small		+	+	+	+	+	A	+	+	+	+	+		+		+									
Intestine small, duodenum		+	+	+	A	+	A	+	+	+	+	+		A		+									
Intestine small, ileum		+	+	+	+	+	A	+	+	+	+	+		+		+									
Intestine small, jejunum		+	+	+	A	+	A	+	+	+	+	+		A		+									
Histiocytic sarcoma																X									
Liver		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma										X															
Hepatocellular adenoma										X															
Histiocytic sarcoma																X									
Mesentery					+				+				+												
Pancreas		+	+	+	+	+	+	+	+	+	+	+		+		+			+		+				
Histiocytic sarcoma																X									
Salivary glands		+	+	+	+	+	+	+	+	+	+	+		+		+									
Stomach		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Squamous cell carcinoma																									
Stomach, glandular		+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart		+	+	+	+	+	+	+	+	+	+	+		+		+									
Endocrine System																									
Adrenal gland		+	+	+	M	+	+	+	+	+	+	+		+		+									
Histiocytic sarcoma																X									
Adrenal gland, cortex		+	+	+	M	+	+	+	+	+	+	+		+		+									
Adrenal gland, medulla		+	+	+	M	+	+	+	+	+	+	+		+		+									
Islets, pancreatic		+	+	+	+	+	A	+	+	+	+	+		+		+					+				
Parathyroid gland		+	M	M	+	+	M	M	+	M	M	M		+	+	+			+	+	+		+		+
Pituitary gland		+	+	+	+	M	+	M	M	+	+	+		+		+							+		
Pars intermedia, adenoma																							X		
Thyroid gland		+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																X									
General Body System																									
Tissue NOS														+											

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Probenecid: 100 mg/kg (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	4 2 4	4 2 5	4 3 1	4 3 2	4 3 3	4 4 4	4 5 3	4 4 1	4 4 2	4 4 3	4 5 1	4 5 2	4 6 1	4 6 2	4 6 3	4 7 2	4 7 3	4 8 1	4 8 2	4 9 1	4 9 2	4 9 3	4 9 4	5 0 1	5 0 2	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Gallbladder	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	41
Intestine large																						+	+			15
Intestine large, cecum																						+	+			14
Intestine large, colon																						+	+			15
Histiocytic sarcoma																										1
Intestine large, rectum																						+	+			10
Intestine small		+																				+	+		+	16
Intestine small, duodenum		+																				+	+		+	14
Intestine small, ileum		+																				+	+		+	16
Intestine small, jejunum		+																				+	+		+	14
Histiocytic sarcoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma			X																							2
Hepatocellular adenoma																	X									2
Histiocytic sarcoma																										1
Mesentery																		+			+					5
Pancreas		+																+				+	+			19
Histiocytic sarcoma																										1
Salivary glands																						+	+			15
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous			X	X																						2
Squamous cell carcinoma															X											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cardiovascular System																										
Heart																						+	+			15
Endocrine System																										
Adrenal gland																						+	+			14
Histiocytic sarcoma																										1
Adrenal gland, cortex																						+	+			14
Adrenal gland, medulla																						+	+			14
Islets, pancreatic																						+	+			15
Parathyroid gland	+	+	+	+		+	+		+		+	+		+	+		+			+	+	+	M	+	+	29
Pituitary gland				M								+											+			13
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell, adenoma																						X				2
General Body System																										
Tissue NOS																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Probenecid: 100 mg/kg (continued)

Number of Days on Study	0 2 9	1 0 8	3 3 7	3 4 7	4 8 8	5 3 6	5 4 7	5 5 0	5 7 0	5 9 5	6 0 6	6 2 7	6 4 4	6 4 6	6 7 4	6 8 6	6 9 4	7 1 7	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	4 7 1	5 0 5	4 4 5	4 5 5	4 5 4	4 7 5	4 6 5	4 7 4	4 6 4	4 6 5	4 3 4	4 3 5	4 8 5	4 8 4	5 0 4	4 8 3	4 9 5	5 0 3	4 1 5	4 1 1	4 1 2	4 1 3	4 1 4	4 2 1	4 2 2	4 2 3
Genital System																										
Ovary		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																	X									
Luteoma																										
Oviduct						+																				
Uterus		+	+	+	+	+	+	+	+	+	+	+			+	+	+	+	+	+		+		+	+	
Histiocytic sarcoma																	X									
Polyp stromal										X																
Endometrium, histiocytic sarcoma																									X	
Vagina											+															
Hematopoietic System																										
Blood																				+		+		+	+	+
Bone marrow		+	+	+	+	+	+	+	+	+	+	+		+												
Lymph node		+	+	+	+	+	+	+	+	+	+	+		+	+	+	+					+	+	+	+	
Lymph node, mesenteric		+	+	+	+	+	+	+	+	+	+	+		+		+	+					+	+			
Histiocytic sarcoma																	X									
Spleen		+	+	+	+	+	+	+	+	+	+	+		+		+	+					+	+			+
Hemangiosarcoma												X														
Thymus		+	+	+	+	+	+	M	+	+	+	+		+									+			
Integumentary System																										
Mammary gland		M	+	M	+	+	+	+	+	+	+	+		+		+										
Skin		+	+	+	+	+	+	+	+	+	+	+		+		+		+								
Subcutaneous tissue, sarcoma																		X								
Musculoskeletal System																										
Bone		+	+	+	+	+	+	+	+	+	+	+		+												
Nervous System																										
Brain		+	+	+	+	+	+	+	+	+	+	+		+		+										
Respiratory System																										
Lung		+	+	+	+	+	+	+	+	+	+	+		+		+	+		+							+
Alveolar/bronchiolar adenoma										X									X							X
Carcinoma, metastatic, harderian gland																		X								
Histiocytic sarcoma																	X									
Nose		+	+	+	+	+	+	+	+	M	+	+		+												
Trachea		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Eye																		+								
Harderian gland																		+								
Carcinoma																		X								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Probenecid: 100 mg/kg (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	4 2 4	4 2 5	4 3 1	4 3 2	4 3 3	4 4 4	4 5 3	4 4 1	4 4 2	4 4 3	4 5 1	4 5 2	4 6 1	4 6 2	4 6 3	4 7 2	4 7 3	4 8 1	4 8 2	4 9 1	4 9 2	4 9 3	4 9 4	5 0 1	5 0 2	**Total Tissues/ Tumors**
Genital System																										
Ovary	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma														X												1
Luteoma																										1
Oviduct																										1
Uterus			+								+		+	+		+		+		+			+	+	+	30
Histiocytic sarcoma																										1
Polyp stromal																										1
Endometrium, histiocytic sarcoma																										1
Vagina																										1
Hematopoietic System																										
Blood	+	+			+	+	+	+	+		+	+	+	+	+	+	+	+	+		+	+	+	+	+	26
Bone marrow																						+	+			14
Lymph node		+		+				+									+				+	+	+			26
Lymph node, mesenteric		+																			+	+	+			20
Histiocytic sarcoma																										1
Spleen		+	+	+									+				+					+	+		+	25
Hemangiosarcoma																										1
Thymus																										12
Integumentary System																										
Mammary gland				+																		+	+			14
Skin																						+	+			16
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone																						+	+			14
Nervous System																										
Brain																						+	+			15
Respiratory System																										
Lung				+								+		+		+						+	+		+	23
Alveolar/bronchiolar adenoma				X																						4
Carcinoma, metastatic, harderian gland																										1
Histiocytic sarcoma																										1
Nose																						+	+			13
Trachea		+		+	+	+			+	+	+	+		+	+	+	+	+			+	+	+	+	+	+	43
Special Senses System																										
Eye																										1
Harderian gland																										1
Carcinoma																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Probenecid: 100 mg/kg (continued)

Number of Days on Study	0 2 9	1 0 8	3 3 7	3 4 7	4 8 8	5 3 6	5 4 7	5 5 0	5 7 0	5 9 5	6 0 6	6 2 7	6 4 4	6 4 6	6 7 4	6 8 6	6 9 4	7 1 7	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	4 7 1	5 0 5	4 4 5	4 5 5	4 5 4	4 7 5	4 6 5	4 7 4	4 6 4	4 3 5	4 3 4	4 8 5	4 8 4	5 0 4	4 8 3	4 9 5	5 0 3	4 1 5	4 1 1	4 1 2	4 1 3	4 1 4	4 2 1	4 2 2	4 2 3
Urinary System																									
Kidney		+	+	+	+	+	+	+	+	+	+	+		+		+	+				+				
Histiocytic sarcoma																X									
Urinary bladder		+	+	+	+	+	+	+	+	M	+	+		+											
Systemic Lesions																									
Multiple organs		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																X								X	
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																					X		X		
Lymphoma malignant undifferentiated cell type														X								X			

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Probenecid: 100 mg/kg (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	4 2 4	4 2 5	4 3 1	4 3 2	4 3 3	4 4 4	4 5 3	4 4 1	4 4 2	4 4 3	4 5 1	4 5 2	4 6 1	4 6 2	4 6 3	4 7 2	4 7 3	4 8 1	4 8 2	4 9 1	4 9 2	4 9 3	4 9 4	5 0 1	5 0 2	**Total Tissues/ Tumors**
Urinary System																										
Kidney	+	+																				+	+			19
Histiocytic sarcoma																										1
Urinary bladder																						+	+			13
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										2
Lymphoma malignant lymphocytic				X																						1
Lymphoma malignant mixed																										2
Lymphoma malignant undifferentiated cell type		X	X															X					X			6

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Probenecid: 400 mg/kg

Number of Days on Study	3 0 3	3 4 3	3 4 3	4 0 8	4 2 2	4 7 5	4 8 6	5 1 4	5 2 7	5 6 7	5 8 3	5 8 5	5 8 6	6 0 5	6 4 3	6 7 2	7 1 6	7 1 7	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	5 7 5	6 0 4	6 0 5	5 2 5	5 7 4	5 2 4	5 2 3	5 9 5	5 8 5	5 5 5	6 0 3	5 3 5	5 4 5	5 9 4	5 4 4	5 6 5	5 3 4	5 5 4	5 1 1	1 1 2	1 1 3	5 1 4	5 1 5	5 2 1	5 2 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	+	+	+	+	+	+	+	+	M	A	+	M	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+
Sarcoma																									
Intestine large, colon	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	A	+	+	M	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+
Intestine small	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	+	+	A	+	+	+	+	A	A	+	A	A	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	+	A	+	+	+	+	+	A	+	A	A	+	+	+	+	+	+	M	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hemangiosarcoma, metastatic																						X			
Hepatocellular carcinoma																	X								
Hepatocellular adenoma													X					X			X		X		
Hepatocellular adenoma, multiple																									
Histiocytic sarcoma											X														
Mesentery				+		+	+	+			+		+		+		+								
Pancreas	+	M	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																			X						
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	A	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																									
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	M	+	+	+	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	M	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	M	+	M	+	M	M	M	M	M	M	+	M	M	M	+	+	+	M	+	+	+	+
Pituitary gland	M	M	M	+	+	+	+	M	+	M	M	+	+	M	M	M	+	+	+	+	+	M	+	+	+
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Probenecid: 400 mg/kg (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	5 3 1	5 3 2	5 3 3	5 4 1	5 4 2	5 4 3	5 5 1	5 5 2	5 5 3	5 6 1	5 6 2	5 6 3	5 6 4	5 8 4	5 7 1	5 7 2	5 7 3	5 8 1	5 8 2	5 8 3	5 9 1	5 9 2	5 9 3	6 0 1	6 0 2	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Sarcoma												X														1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma														X												1
Hemangiosarcoma, metastatic																										1
Hepatocellular carcinoma									X													X				3
Hepatocellular adenoma				X			X		X		X		X						X							10
Hepatocellular adenoma, multiple	X														X		X							X		4
Histiocytic sarcoma																										1
Mesentery									+																	9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous																				X						2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Capsule, adenoma		X																								1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	46
Parathyroid gland	+	+	+	M	M	M	+	+	M	+	M	M	+	+	M	+	+	M	+	M	+	+	+	+	+	28
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	38
Pars distalis, adenoma																	X			X	X	X				4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell, adenoma		X							X																	2
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Probenecid: 400 mg/kg (continued)

Number of Days on Study	3 3 3 4 4 4 4 5 5 5 5 5 5 6 6 6 7 7 7 7 7 7 7 7 0 4 4 0 2 7 8 1 2 6 8 8 8 0 4 7 1 1 3 3 3 3 3 3 3 3 3 3 8 2 5 6 4 7 7 3 5 6 5 3 2 6 7 0 0 0 0 0 0 0
Carcass ID Number	5 6 6 5 5 5 5 5 5 5 6 5 5 5 5 5 5 5 5 5 5 5 5 5 7 0 0 2 7 2 2 9 8 5 0 3 4 9 4 6 3 5 1 1 1 1 1 2 2 5 4 5 5 4 4 3 5 5 5 3 5 5 4 4 5 4 4 1 2 3 4 5 1 2
Genital System	
Clitoral gland	
Ovary	+ +
Cystadenoma	X
Uterus	+ +
Histiocytic sarcoma	X
Sarcoma	
Vagina	+
Hematopoietic System	
Blood	+ + + + +
Bone marrow	+ + + + + + + + + + + + + + M + + + + + + + + + +
Lymph node	+ + A + + + + + + + + + + + M + + + + + + M + + +
Lymph node, mesenteric	+ + A + + + + + + + + + + + M + + + + + + M + + +
Histiocytic sarcoma	
Spleen	+ + + + + + + + + + + + + + M + + + + + + + + + +
Hemangiosarcoma, metastatic	X
Thymus	+ M + + M + M M + + M + M + M M + + + + + + + + +
Integumentary System	
Mammary gland	+ M M M + + M + + + + + + + + M + M + M + + M M M +
Skin	+ + + + + + + + M + + + + + + + + + + + + + + + +
Subcutaneous tissue, fibrosarcoma	X
Subcutaneous tissue, hemangiosarcoma	X
Musculoskeletal System	
Bone	+ + + + + + + + + + + + + + M + + + + + + + + + +
Nervous System	
Brain	+ + + + + + + + + + + + + + M + + + + + + + + + +
Respiratory System	
Lung	+ + + + + + + + + + + + + + M + + + + + + + + + +
Alveolar/bronchiolar adenoma	X
Alveolar/bronchiolar carcinoma	X
Fibrosarcoma, metastatic, skin	X
Nose	+ + + + + + + + + + + + + + M + + + + + + + + + +
Trachea	+ + + + + + + + + + + + + + M + + + + + + + + + +
Special Senses System	
Eye	+
Harderian gland	+
Adenoma	
Urinary System	
Kidney	+ + + + + + + + + + + + + + M + + + + + + + + + +
Urinary bladder	+ + A + + M + + + + + + + + + A + + + + + + + + +

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Probenecid: 400 mg/kg (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	5 3 1	5 3 2	5 3 3	5 4 1	5 4 2	5 4 3	5 5 1	5 5 2	5 5 3	5 6 1	5 6 2	5 6 3	5 6 4	5 8 4	5 7 1	5 7 2	5 7 3	5 8 1	5 8 2	5 8 3	5 9 1	5 9 2	5 9 3	6 0 1	6 0 2	**Total Tissues/ Tumors**
Genital System																										
Clitoral gland													+													1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																			X							2
Sarcoma								X																		1
Vagina																										1
Hematopoietic System																										
Blood	+	+	+	+	+	+		+	+	+	+		+	+		+	+							+	+	22
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	45
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	44
Histiocytic sarcoma																	X									1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma, metastatic																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Integumentary System																										
Mammary gland	+	M	M	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	+	M	M	M	+	32
Skin	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, hemangiosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma							X											X						X	X	5
Alveolar/bronchiolar carcinoma																										1
Fibrosarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	46
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye																					+					2
Harderian gland																					+					2
Adenoma																					X					1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Probenecid: 400 mg/kg (continued)

Number of Days on Study	3 0 3	3 4 3	3 4 3	4 0 8	4 2 2	4 7 5	4 8 6	5 1 4	5 2 7	5 6 7	5 8 3	5 8 5	5 8 6	6 0 5	6 4 3	6 7 2	7 1 6	7 1 7	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	5 7 5	6 0 4	6 0 5	5 2 5	5 7 4	5 2 4	5 2 3	5 9 5	5 8 5	5 5 5	6 0 3	5 3 5	5 4 5	5 9 4	5 4 4	5 6 5	5 3 4	5 5 4	5 1 1	5 1 2	5 1 3	5 1 4	5 1 5	5 2 1	5 2 2
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X													
Lymphoma malignant lymphocytic																	X							
Lymphoma malignant mixed																			X					
Lymphoma malignant undifferentiated cell type																								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Probenecid: 400 mg/kg (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	531	532	533	541	542	543	551	552	553	561	562	563	564	584	587	591	592	593	581	582	583	591	592	593	599	600	602	**Total Tissues/ Tumors**
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																	X		X									3
Lymphoma malignant lymphocytic																X												2
Lymphoma malignant mixed				X					X																			3
Lymphoma malignant undifferentiated cell type																									X	X		2

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Probenecid

	Vehicle Control	100 mg/kg	400 mg/kg
Liver: Hepatocellular Adenoma			
Overall rates[a]	3/48 (6%)	2/49 (4%)	14/49 (29%)
Adjusted rates[b]	7.6%	5.5%	41.0%
Terminal rates[c]	1/32 (3%)	1/32 (3%)	12/32 (38%)
First incidence (days)	612	595	586
Life table tests[d]	P<0.001	P=0.535N	P=0.003
Logistic regression tests[d]	P<0.001	P=0.447N	P=0.002
Cochran-Armitage test[d]	P<0.001		
Fisher exact test[d]		P=0.490N	P=0.004
Liver: Hepatocellular Carcinoma			
Overall rates	2/48 (4%)	2/49 (4%)	3/49 (6%)
Adjusted rates	5.3%	5.5%	9.0%
Terminal rates	0/32 (0%)	1/32 (3%)	2/32 (6%)
First incidence (days)	687	595	716
Life table tests	P=0.405	P=0.661	P=0.483
Logistic regression tests	P=0.395	P=0.683N	P=0.448
Cochran-Armitage test	P=0.432		
Fisher exact test		P=0.684N	P=0.510
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rates	5/48 (10%)	3/49 (6%)	16/49 (33%)
Adjusted rates	12.5%	8.5%	45.6%
Terminal rates	1/32 (3%)	2/32 (6%)	13/32 (41%)
First incidence (days)	612	595	586
Life table tests	P<0.001	P=0.402N	P=0.007
Logistic regression tests	P<0.001	P=0.329N	P=0.003
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.346N	P=0.007
Lung: Alveolar/Bronchiolar Adenoma			
Overall rates	1/49 (2%)	4/23 (17%)[e]	5/49 (10%)
Adjusted rates	3.0%		15.1%
Terminal rates	0/32 (0%)		4/32 (13%)
First incidence (days)	722		716
Life table tests			P=0.105
Logistic regression tests			P=0.081
Cochran-Armitage test			
Fisher exact test			P=0.102
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall rates	3/49 (6%)	4/23 (17%)[e]	6/49 (12%)
Adjusted rates	8.8%		18.1%
Terminal rates	1/32 (3%)		5/32 (16%)
First incidence (days)	721		716
Life table tests			P=0.242
Logistic regression tests			P=0.195
Cochran-Armitage test			
Fisher exact test			P=0.243

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Probenecid
(continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Pituitary Gland (Pars Distalis): Adenoma			
Overall rates	2/41 (5%)	0/13 (0%)[e]	4/38 (11%)
Adjusted rates	6.5%		13.8%
Terminal rates	2/31 (6%)		4/29 (14%)
First incidence (days)	730 (T)		730 (T)
Life table tests			P=0.304
Logistic regression tests			P=0.304
Cochran-Armitage test			
Fisher exact test			P=0.302
Stomach (Forestomach): Squamous Papilloma			
Overall rates	3/49 (6%)	2/49 (4%)	2/50 (4%)
Adjusted rates	9.4%	6.3%	6.3%
Terminal rates	3/32 (9%)	2/32 (6%)	2/32 (6%)
First incidence (days)	730 (T)	730 (T)	730 (T)
Life table tests	P=0.485N	P=0.500N	P=0.500N
Logistic regression tests	P=0.485N	P=0.500N	P=0.500N
Cochran-Armitage test	P=0.475N		
Fisher exact test		P=0.500N	P=0.490N
Stomach (Forestomach): Squamous Papilloma or Squamous Cell Carcinoma			
Overall rates	3/49 (6%)	3/49 (6%)	2/50 (4%)
Adjusted rates	9.4%	9.4%	6.3%
Terminal rates	3/32 (9%)	3/32 (9%)	2/32 (6%)
First incidence (days)	730 (T)	730 (T)	730 (T)
Life table tests	P=0.429N	P=0.665	P=0.500N
Logistic regression tests	P=0.429N	P=0.665	P=0.500N
Cochran-Armitage test	P=0.419N		
Fisher exact test		P=0.661N	P=0.490N
All Organs: Malignant Lymphoma (Lymphocytic, Mixed, or Undifferentiated Cell Type)			
Overall rates	11/49 (22%)	9/49 (18%)	7/50 (14%)
Adjusted rates	28.8%	27.0%	21.1%
Terminal rates	6/32 (19%)	8/32 (25%)	6/32 (19%)
First incidence (days)	612	646	716
Life table tests	P=0.229N	P=0.434N	P=0.248N
Logistic regression tests	P=0.272N	P=0.472N	P=0.291N
Cochran-Armitage test	P=0.194N		
Fisher exact test		P=0.401N	P=0.204N
All Organs: Benign Tumors			
Overall rates	10/49 (20%)	10/49 (20%)	22/50 (44%)
Adjusted rates	27.7%	28.9%	62.8%
Terminal rates	7/32 (22%)	8/32 (25%)	19/32 (59%)
First incidence (days)	612	595	586
Life table tests	P=0.002	P=0.572	P=0.008
Logistic regression tests	P<0.001	P=0.532	P=0.002
Cochran-Armitage test	P=0.003		
Fisher exact test		P=0.599N	P=0.010

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Probenecid
(continued)

	Vehicle Control	100 mg/kg	400 mg/kg
All Organs: Malignant Tumors			
Overall rates	15/49 (31%)	16/49 (33%)	17/50 (34%)
Adjusted rates	38.1%	41.9%	48.4%
Terminal rates	8/32 (25%)	10/32 (31%)	14/32 (44%)
First incidence (days)	612	595	583
Life table tests	P=0.368	P=0.454	P=0.386
Logistic regression tests	P=0.278	P=0.419	P=0.270
Cochran-Armitage test	P=0.429		
Fisher exact test		P=0.500	P=0.442
All Organs: Benign and Malignant Tumors			
Overall rates	23/49 (47%)	21/49 (43%)	31/50 (62%)
Adjusted rates	55.7%	55.1%	86.0%
Terminal rates	14/32 (44%)	15/32 (47%)	27/32 (84%)
First incidence (days)	612	595	583
Life table tests	P=0.036	P=0.481N	P=0.072
Logistic regression tests	P=0.006	P=0.540N	P=0.012
Cochran-Armitage test	P=0.047		
Fisher exact test		P=0.420N	P=0.096

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly to the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Tissue was examined microscopically only when it was observed to be abnormal at necropsy.

TABLE D4
Historical Incidence of Liver Tumors in Female B6C3F$_1$ Mice Receiving Corn Oil by Gavage[a]

Study	Incidence in Controls		
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
Bromoform	3/49	1/49	4/49
Phenylbutazone	4/50	1/50	5/50
Probenecid	3/49	2/49	5/49
Diglycidyl resorcinol ether	3/48	0/48	3/48
1,2-Dichloropropane	1/50	1/50	2/50
Chlorodibromomethane	2/50	4/50	6/50
N-Butyl chloride	8/50	1/50	9/50
Bromodichloromethane	1/50	2/50	3/50
BCPE	5/50	2/50	7/50
N-Butyl chloride	1/50	2/50	3/50
Total	31/496 (6.3%)	16/496 (3.2%)	47/496 (9.5%)
Standard deviation	4.4	2.2	4.3
Range	2%–16%	0%–8%	4%–18%
Overall Historical Incidence			
Total	114/2336 (4.9%)	64/2336 (2.7%)	176/2336 (7.5%)
Standard deviation	3.9	2.3	4.8
Range	0%–20%	0%–10%	0%–30%

[a] Data from 2-year studies tabulated by the Toxicology Data Management System through 22 December 1989 and the Carcinogenesis Bioassay Data System through 6 March 1990.

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Probenecid

	Vehicle Control	100 mg/kg	400 mg/kg
Disposition Summary			
Animals initially in study	50	50	50
Early deaths			
Moribund	9	9	9
Dead	8	7	9
Accident		1	
Survivors			
Terminal sacrifice	32	31	32
Moribund		1	
Other	1	1	
Animals examined microscopically	49	49	50
Alimentary System			
Intestine large, colon	(48)	(15)	(49)
Lymphoid nodule, hyperplasia		1 (7%)	
Intestine small, ileum	(47)	(16)	(46)
Necrosis	1 (2%)		
Lymphoid nodule, hyperplasia			1 (2%)
Intestine small, jejunum	(46)	(14)	(44)
Necrosis	1 (2%)		
Lymphoid nodule, hemorrhage	1 (2%)		
Lymphoid nodule, hyperplasia			1 (2%)
Liver	(48)	(49)	(49)
Angiectasis			2 (4%)
Basophilic focus	2 (4%)		2 (4%)
Clear cell focus	1 (2%)		
Congestion		1 (2%)	
Cyst			2 (4%)
Eosinophilic focus			2 (4%)
Fatty change			1 (2%)
Fatty change, diffuse	1 (2%)	1 (2%)	
Fatty change, focal	2 (4%)	8 (16%)	2 (4%)
Hematopoietic cell proliferation	1 (2%)	7 (14%)	7 (14%)
Mineralization	2 (4%)		
Necrosis	10 (21%)	4 (8%)	4 (8%)
Necrosis, coagulative		1 (2%)	1 (2%)
Bile duct, hyperplasia, cystic		1 (2%)	
Mesentery	(3)	(5)	(9)
Hemorrhage		1 (20%)	
Inflammation, acute	1 (33%)	3 (60%)	8 (89%)
Inflammation, chronic active	1 (33%)		
Fat, inflammation, chronic active	1 (33%)	1 (20%)	
Fat, necrosis	1 (33%)	1 (20%)	1 (11%)
Pancreas	(48)	(19)	(47)
Acinus, atrophy			1 (2%)
Acinus, hyperplasia	2 (4%)		
Salivary glands	(45)	(15)	(49)
Mineralization	1 (2%)		

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Probenecid (continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Alimentary System (continued)			
Stomach, forestomach	(47)	(49)	(49)
Acanthosis	11 (23%)	11 (22%)	7 (14%)
Hyperkeratosis	14 (30%)	12 (24%)	9 (18%)
Inflammation, acute	2 (4%)		1 (2%)
Inflammation, chronic active		1 (2%)	2 (4%)
Mineralization	1 (2%)		
Necrosis	2 (4%)	6 (12%)	1 (2%)
Stomach, glandular	(46)	(48)	(48)
Dilatation	1 (2%)		
Hyperplasia	5 (11%)	14 (29%)	1 (2%)
Inflammation, acute		1 (2%)	
Inflammation, chronic active	1 (2%)	2 (4%)	1 (2%)
Necrosis			1 (2%)
Pigmentation	1 (2%)		
Cardiovascular System			
Heart	(48)	(15)	(49)
Cardiomyopathy	1 (2%)		
Endocrine System			
Adrenal gland	(48)	(14)	(49)
Accessory adrenal cortical nodule	1 (2%)		
Hematopoietic cell proliferation	2 (4%)	1 (7%)	5 (10%)
Capsule, hyperplasia	38 (79%)	7 (50%)	43 (88%)
Adrenal gland, cortex	(48)	(14)	(49)
Cyst	1 (2%)		
Hyperplasia	37 (77%)	7 (50%)	39 (80%)
Hypertrophy	1 (2%)		1 (2%)
Adrenal gland, medulla	(45)	(14)	(44)
Degeneration	1 (2%)		
Pituitary gland	(41)	(13)	(38)
Angiectasis	1 (2%)		
Pars distalis, angiectasis	3 (7%)		5 (13%)
Pars distalis, cyst			1 (3%)
Pars distalis, hyperplasia	13 (32%)	2 (15%)	8 (21%)
Pars distalis, hyperplasia, focal	1 (2%)		1 (3%)
Pars intermedia, hyperplasia			1 (3%)
Thyroid gland	(48)	(48)	(48)
Infiltration cellular, lymphocytic			1 (2%)
Follicle, cyst	1 (2%)		1 (2%)
Follicular cell, hyperplasia		1 (2%)	1 (2%)
General Body System			
None			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Probenecid (continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Genital System			
Ovary	(47)	(48)	(50)
Abscess	1 (2%)	3 (6%)	11 (22%)
Angiectasis			2 (4%)
Cyst	4 (9%)	4 (8%)	9 (18%)
Degeneration, cystic	12 (26%)	9 (19%)	7 (14%)
Hemorrhage	2 (4%)	1 (2%)	2 (4%)
Hyperplasia	1 (2%)	1 (2%)	
Inflammation, acute			1 (2%)
Mineralization	2 (4%)	1 (2%)	
Pigmentation	3 (6%)	1 (2%)	
Bilateral, abscess		4 (8%)	
Uterus	(48)	(30)	(50)
Angiectasis			1 (2%)
Cyst		1 (3%)	
Hemorrhage	1 (2%)		1 (2%)
Hyperplasia	1 (2%)		
Inflammation, acute	1 (2%)	2 (7%)	2 (4%)
Mineralization			1 (2%)
Necrosis		1 (3%)	1 (2%)
Endometrium, hyperplasia	36 (75%)	14 (47%)	33 (66%)
Vagina		(1)	(1)
Inflammation, chronic active			1 (100%)
Hematopoietic System			
Bone marrow	(48)	(14)	(49)
Myelofibrosis	13 (27%)		5 (10%)
Lymph node	(43)	(26)	(45)
Hematopoietic cell proliferation			1 (2%)
Lumbar, angiectasis		1 (4%)	
Lumbar, hematopoietic cell proliferation		3 (12%)	6 (13%)
Lumbar, infiltration cellular, plasma cell	1 (2%)	8 (31%)	5 (11%)
Lumbar, infiltration cellular, histiocytic		1 (4%)	
Mandibular, hematopoietic cell proliferation			2 (4%)
Mandibular, infiltration cellular, plasma cell	1 (2%)		
Mediastinal, hematopoietic cell proliferation			1 (2%)
Mediastinal, infiltration cellular, plasma cell		2 (8%)	1 (2%)
Pancreatic, angiectasis			1 (2%)
Pancreatic, hematopoietic cell proliferation		1 (4%)	2 (4%)
Renal, hematopoietic cell proliferation		2 (8%)	4 (9%)
Renal, hemorrhage		1 (4%)	
Renal, infiltration cellular, plasma cell	1 (2%)	8 (31%)	3 (7%)
Renal, infiltration cellular, histiocytic		1 (4%)	
Lymph node, mesenteric	(41)	(20)	(44)
Angiectasis	4 (10%)		4 (9%)
Depletion lymphoid			1 (2%)
Hematopoietic cell proliferation	3 (7%)	2 (10%)	7 (16%)
Hemorrhage		1 (5%)	
Infiltration cellular, plasma cell	1 (2%)	3 (15%)	2 (5%)
Infiltration cellular, histiocytic		1 (5%)	
Necrosis			1 (2%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Probenecid (continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Hematopoietic System (continued)			
Spleen	(48)	(25)	(49)
Angiectasis			1 (2%)
Atrophy			1 (2%)
Hematopoietic cell proliferation	24 (50%)	15 (60%)	32 (65%)
Hemorrhage		1 (4%)	
Necrosis	1 (2%)		
Thrombus		1 (4%)	
Lymphoid follicle, hyperplasia	2 (4%)		3 (6%)
Thymus	(42)	(12)	(42)
Angiectasis	1 (2%)		
Depletion lymphoid			1 (2%)
Integumentary System			
Skin	(46)	(16)	(48)
Bacterium			1 (2%)
Cyst epithelial inclusion			1 (2%)
Musculoskeletal System			
None			
Nervous System			
None			
Respiratory System			
Lung	(49)	(23)	(49)
Bacterium			2 (4%)
Congestion	1 (2%)		
Hemorrhage	4 (8%)	1 (4%)	1 (2%)
Infiltration cellular, histiocytic	2 (4%)	1 (4%)	1 (2%)
Inflammation, acute			4 (8%)
Inflammation, chronic active		2 (9%)	
Pleura, abscess		2 (9%)	
Pleura, inflammation, acute			2 (4%)
Special Senses System			
Harderian gland		(1)	(2)
Mineralization		1 (100%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Probenecid (continued)

	Vehicle Control	100 mg/kg	400 mg/kg
Urinary System			
Kidney	(48)	(19)	(49)
Cyst	1 (2%)		
Degeneration	1 (2%)		
Hydronephrosis	1 (2%)		
Inflammation, acute			1 (2%)
Inflammation, chronic active		1 (5%)	
Cortex, mineralization	1 (2%)	1 (5%)	1 (2%)
Papilla, mineralization	1 (2%)		2 (4%)
Renal tubule, pigmentation	1 (2%)		
Renal tubule, regeneration	1 (2%)		
Urinary bladder	(44)	(13)	(47)
Edema	1 (2%)		
Infiltration cellular, polymorphonuclear	1 (2%)		

APPENDIX E
ORGAN WEIGHTS
AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE E1
Organ Weights for Rats in the 13-Week Gavage Studies of Probenecid[a]

Organ	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg	800 mg/kg
Male						
Necropsy body wt (g)	358 ± 9	345 ± 7	343 ± 8	349 ± 6	337 ± 8	305 ± 7**
Brain	1.96 ± 0.03	1.94 ± 0.01	1.98 ± 0.02	1.95 ± 0.03	1.98 ± 0.05	1.83 ± 0.02*
Heart	1.05 ± 0.03	0.96 ± 0.03*	1.00 ± 0.04	0.96 ± 0.03*	1.01 ± 0.04	0.85 ± 0.02**[b]
R. Kidney	1.21 ± 0.04	1.26 ± 0.04	1.23 ± 0.03	1.25 ± 0.04	1.20 ± 0.04	1.14 ± 0.03[c]
Liver	12.98 ± 0.50	14.15 ± 0.37	14.28 ± 0.45	15.73 ± 0.61**	14.39 ± 0.87	13.69 ± 0.38[c]
Lungs	1.78 ± 0.10	2.01 ± 0.06	2.00 ± 0.15	1.81 ± 0.11	1.62 ± 0.07	1.58 ± 0.04[b]
R. Testis	1.52 ± 0.03	1.52 ± 0.02	1.51 ± 0.02	1.54 ± 0.03	1.59 ± 0.08	1.62 ± 0.02**[c]
Thymus	0.34 ± 0.04	0.45 ± 0.04*	0.34 ± 0.02	0.32 ± 0.02	0.33 ± 0.04	0.31 ± 0.04[c]
Female						
Necropsy body wt (g)	200 ± 3	210 ± 5	207 ± 4	200 ± 4	184 ± 2**	188 ± 2**
Brain	1.77 ± 0.02	1.65 ± 0.10	1.80 ± 0.02	1.83 ± 0.02	1.78 ± 0.04	1.76 ± 0.01
Heart	0.65 ± 0.01	0.67 ± 0.02	0.66 ± 0.02	0.66 ± 0.02	0.64 ± 0.02	0.61 ± 0.01[c]
R. Kidney	0.67 ± 0.03	0.80 ± 0.02**	0.76 ± 0.01	0.73 ± 0.02	0.71 ± 0.01	0.75 ± 0.01
Liver	6.52 ± 0.12	7.27 ± 0.27*	7.58 ± 0.18**	7.08 ± 0.22**	7.50 ± 0.10**	8.09 ± 0.17**
Lungs	1.13 ± 0.05	1.34 ± 0.06	1.35 ± 0.08	1.40 ± 0.09	1.14 ± 0.05	1.13 ± 0.02
Thymus	0.25 ± 0.02	0.32 ± 0.03*	0.28 ± 0.02	0.29 ± 0.02	0.24 ± 0.02	0.29 ± 0.03

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Organ weights are given in grams (mean ± standard error); n=10 for all groups except where noted.
[b] n=8
[c] n=9

TABLE E2
Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Gavage Studies of Probenecid[a]

Organ	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg	800 mg/kg
Male						
Necropsy body wt (g)	358 ± 9	345 ± 7	343 ± 8	349 ± 6	337 ± 8	305 ± 7**
Brain	5.49 ± 0.12	5.63 ± 0.12	5.78 ± 0.11	5.59 ± 0.08	5.92 ± 0.21**	6.05 ± 0.15**
Heart	2.95 ± 0.09	2.77 ± 0.05	2.92 ± 0.10	2.75 ± 0.07	3.00 ± 0.11	2.81 ± 0.06[b]
R. Kidney	3.39 ± 0.12	3.64 ± 0.08	3.58 ± 0.04	3.59 ± 0.07	3.57 ± 0.09	3.76 ± 0.05**[c]
Liver	36.2 ± 0.85	41.0 ± 0.56**	41.6 ± 0.85**	45.0 ± 1.46**	42.8 ± 0.24**	45.0 ± 0.87**[c]
Lungs	4.99 ± 0.33	5.81 ± 0.14	5.84 ± 0.43	5.16 ± 0.29	4.85 ± 0.23	5.28 ± 0.18[b]
R. Testis	4.26 ± 0.07	4.42 ± 0.09	4.40 ± 0.07	4.41 ± 0.07	4.74 ± 0.24**	5.33 ± 0.12**[c]
Thymus	0.94 ± 0.10	1.31 ± 0.10*	0.98 ± 0.05	0.92 ± 0.05	0.98 ± 0.12	1.00 ± 0.11[c]
Female						
Necropsy body wt (g)	200 ± 3	210 ± 5	207 ± 4	200 ± 4	184 ± 2**	188 ± 2**
Brain	8.85 ± 0.16	7.89 ± 0.48	8.71 ± 0.14	9.20 ± 0.13	9.69 ± 0.26*	9.35 ± 0.11*
Heart	3.25 ± 0.05	3.19 ± 0.06	3.17 ± 0.06	3.28 ± 0.04	3.50 ± 0.10	3.21 ± 0.06[c]
R. Kidney	3.33 ± 0.15	3.80 ± 0.06*	3.65 ± 0.06	3.64 ± 0.07	3.86 ± 0.07**	4.00 ± 0.04**
Liver	32.6 ± 0.67	34.7 ± 1.09	36.6 ± 0.98**	35.5 ± 1.17*	40.8 ± 0.43**	43.1 ± 0.90**
Lungs	5.64 ± 0.22	6.40 ± 0.25	6.49 ± 0.32	7.04 ± 0.48*	6.20 ± 0.27	6.03 ± 0.13
Thymus	1.24 ± 0.11	1.56 ± 0.14	1.33 ± 0.09	1.45 ± 0.12	1.29 ± 0.10	1.52 ± 0.14

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Organ-weight-to-body weight ratios are given in mg organ weight/g body weight (mean ± standard error); n=10 for all groups except where noted.
[b] n=8
[c] n=9

TABLE E3
Organ Weights for Mice in the 13-Week Gavage Studies of Probenecid[a]

Organ	Vehicle Control	100 mg/kg	200 mg/kg	400 mg/kg	800 mg/kg	1,600 mg/kg[b]
Male						
Necropsy body wt (g)	31.4 ± 0.7	33.4 ± 0.6	31.4 ± 0.6	31.9 ± 0.7	31.8 ± 0.5	29.6 ± 0.4
Brain	0.469 ± 0.007	0.470 ± 0.006	0.456 ± 0.005	0.462 ± 0.008	0.479 ± 0.007	0.471 ± 0.006
Heart	0.166 ± 0.004[c]	0.172 ± 0.007	0.158 ± 0.006	0.157 ± 0.011[c]	0.170 ± 0.007[c]	0.148 ± 0.002
R. Kidney	0.266 ± 0.010	0.329 ± 0.007**	0.303 ± 0.009	0.304 ± 0.011[c]	0.306 ± 0.008[c]	0.298 ± 0.011
Liver	1.509 ± 0.056	1.662 ± 0.044	1.654 ± 0.037[c]	1.695 ± 0.101[c]	1.933 ± 0.042**[c]	2.063 ± 0.035**
Lungs	0.228 ± 0.027[c]	0.228 ± 0.010	0.204 ± 0.011[c]	0.226 ± 0.012[c]	0.253 ± 0.022[c]	0,197 ± 0.013
R. Testis	0.119 ± 0.004	0.119 ± 0.003	0.130 ± 0.014[d]	0.122 ± 0.004[d]	0.126 ± 0.003[c]	0.118 ± 0.005
Thymus	0.040 ± 0.002	0.041 ± 0.004	0.046 ± 0.005[c]	0.044 ± 0.005[c]	0.055 ± 0.006[c]	0.051 ± 0.006
Female						
Necropsy body wt (g)	25.6 ± 0.6	25.0 ± 0.5	25.2 ± 0.5	25.3 ± 0.6	23.4 ± 0.4**	23.7 ± 0.6*
Brain	0.512 ± 0.016	0.495 ± 0.011	0.470 ± 0.008	0.507 ± 0.009	0.469 ± 0.006*	0.476 ± 0.007
Heart	0.138 ± 0.007	0.132 ± 0.005[c]	0.123 ± 0.009[e]	0.123 ± 0.003[c]	0.124 ± 0.003	0.120 ± 0.005
R. Kidney	0.198 ± 0.012	0.207 ± 0.005	0.207 ± 0.005[d]	0.204 ± 0.004[c]	0.198 ± 0.006	0.205 ± 0.009
Liver	1.190 ± 0.042	1.245 ± 0.023	1.253 ± 0.024[c]	1.196 ± 0.026	1.281 ± 0.031*	1.629 ± 0.071**
Lungs	0.245 ± 0.019	0.225 ± 0.014[c]	0.222 ± 0.012[d]	0.213 ± 0.011[c]	0.225 ± 0.010	0.224 ± 0.023
Thymus	0.063 ± 0.007	0.046 ± 0.004[d]	0.047 ± 0.003[c]	0.049 ± 0.003[d]	0.054 ± 0.004	0.053 ± 0.004

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Organ weights are given in grams (mean ± standard error); n=10 for all groups except where noted.
[b] For organ weights, n=5 for males and n=7 for females.
[c] n=9
[d] n=8
[e] n=7

TABLE E4
Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Gavage Studies of Probenecid[a]

Organ	Vehicle Control	100 mg/kg	200 mg/kg	400 mg/kg	800 mg/kg	1,600 mg/kg[b]
Male						
Necropsy body wt (g)	31.4 ± 0.7	33.4± 0.6	31.4 ± 0.6	31.9 ± 0.7	31.8 ± 0.5	29.6 ± 0.4
Brain	14.8 ± 0.43	14.1 ± 0.21	14.6 ± 0.31	14.4 ± 0.28	15.0 ± 0.38	15.9 ± 0.24*
Heart	5.3 ± 0.17[c]	5.2 ± 0.21	5.0 ± 0.13	4.9 ± 0.30[c]	5.3 ± 0.23[c]	5.0 ± 0.05
R. Kidney	8.5 ± 0.40	9.9 ± 0.19*	9.7 ± 0.30*	9.4 ± 0.25[c]	9.6 ± 0.23[c]	10.1 ± 0.27**
Liver	48.1 ± 1.95	49.7 ± 1.09	53.1 ± 1.40**[c]	52.6 ± 2.71*[c]	60.6 ± 1.19**[c]	69.7 ± 0.63**
Lungs	7.3 ± 0.78[c]	6.8 ± 0.31	6.5 ± 0.40[c]	7.1 ± 0.37[c]	7.9 ± 0.71[c]	6.7 ± 0.39
R. Testis	3.8 ± 0.18	3.6 ± 0.10	4.2 ± 0.42[d]	3.8 ± 0.14[d]	4.0 ± 0.13[c]	4.0 ± 0.14
Thymus	1.3 ± 0.09	1.2 ± 0.10	1.5 ± 0.18[c]	1.4 ± 0.17[c]	1.7 ± 0.21[c]	1.7 ± 0.21
Female						
Necropsy body wt (g)	25.6 ± 0.6	25.0 ± 0.5	25.2 ± 0.5	25.3 ± 0.6	23.4 ± 0.4**	23.7 ± 0.6*
Brain	20.1 ± 0.67	19.8 ± 0.46	18.7 ± 0.57	20.0 ± 0.64	20.1 ± 0.37	20.2 ± 0.44
Heart	5.4 ± 0.22	5.3 ± 0.19[c]	4.9 ± 0.37[e]	4.9 ± 0.13[c]	5.3 ± 0.11	5.1 ± 0.12
R. Kidney	7.8 ± 0.42	8.3 ± 0.16	8.2 ± 0.26[d]	8.0 ± 0.17[c]	8.5 ± 0.15	8.7 ± 0.29
Liver	46.5 ± 1.14	49.8 ± 0.67*	49.8 ± 0.77*[c]	47.4 ± 1.02	54.7 ± 0.68**	68.8 ± 1.82**
Lungs	9.6 ± 0.74	9.0 ± 0.54[c]	8.8 ± 0.58[d]	8.5 ± 0.46[c]	9.6 ± 0.44	9.4 ± 0.91
Thymus	2.5 ± 0.26	1.9 ± 0.19[d]	1.9 ± 0.10[c]	1.9 ± 0.13[d]	2.3 ± 0.17	2.2 ± 0.14

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Organ-weight-to-body weight ratios are given as mg organ weight/g body weight (mean ± standard error); n=10 for all groups except where noted.
[b] For organ-weight-to-body-weight ratios, n=5 for males and n=7 for females.
[c] n=9
[d] n=8
[e] n=7

APPENDIX F
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA PROTOCOL

Testing was performed as reported by Ames *et al.* (1975) with modifications as listed below and described in greater detail in Mortelmans *et al.* (1986). Probenecid was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). Probenecid was incubated with the *Salmonella typhimurium* tester strain (TA98, TA100, TA1535, TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C prior to the addition of soft agar supplemented with *l*-histidine and *d*-biotin, and subsequent plating on minimal glucose agar plates. Incubation continued for an additional 48 hours.

Each trial consisted of triplicate plates of concurrent positive and negative controls and of at least 5 doses of probenecid. High dose was limited to 10 mg/plate. All trials were repeated.

A positive response in this assay is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants which was not dose-related, not reproducible, or of insufficient magnitude to support a determination of mutagenicity. A negative response was obtained when no increase in revertant colonies was observed following chemical treatment.

CHINESE HAMSTER OVARY CYTOGENETICS ASSAYS

Testing was performed as reported by Galloway *et al.* (1987) and presented briefly below. Probenecid was sent to the laboratories as coded aliquots from Radian Corporation (Austin, TX). Probenecid and positive control chemicals were tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of test chemical; the high dose was limited by toxicity or solubility, but did not exceed 160 μg/mL.

In the sister chromatid exchange test without S9, Chinese hamster ovary cells were incubated for 26 hours with probenecid in McCoy's 5A medium supplemented with 10% fetal bovine serum, *l*-glutamine (2mM), and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing the test chemical was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 more hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with the chemical, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing BrdU and no test chemical and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining procedures were the same as for cells treated without S9.

In the chromosome aberration (Abs) test without S9, cells were incubated in McCoy's 5A medium with the study chemical for 8 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with the study chemical and S9 for 2 hours, after which the treatment medium was removed and the cells incubated for 10 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9; the harvest time was based on the cell cycle information obtained in the SCE test.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind and those from a single test were read by the same person. For the SCE test, usually 50 second-division metaphase cells were scored for frequency of SCE per cell from each dose level; 200 first-division metaphase cells were scored at each dose level for the Abs test. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Statistical analyses were conducted on both the slopes of the dose-response curves and the individual dose points. A sister chromatid exchange frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. Chromosomal aberration data are presented as percentage of cells with aberrations. As with SCE, both the dose-response curve and individual dose points were statistically analyzed. For a single trial, a statistically significant ($P<0.05$) difference for one dose point and a significant trend ($P<0.015$) was considered weak evidence for a positive response (w+); significant differences for two or more doses indicated the trial was positive (+) (Galloway *et al.*, 1987).

RESULTS

Probenecid (33 to 10,000 μg/plate) was tested for induction of gene mutations in *Salmonella typhimurium* strains TA100, TA1535, TA1537, and TA98 using a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9. No increase in mutant colonies was observed in any of these four tester strains (Mortelmans *et al.*, 1986; Table F1).

In cytogenetic tests with CHO cells, probenecid induced SCEs over a concentration range of 5.0 to 160.0 μg/mL in two of three trials conducted in the absence of S9. The results of this SCE test were variable among trials: in the first trial a clear dose-response relationship was apparent, the second trial was negative, and the third trial had significant increases in SCE at the lowest and highest doses tested, with smaller increases observed at intermediate doses. Overall, the assay was judged to be positive. No increase in SCE was observed in the presence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 (Table F2).

Probenecid (500 to 1,250 μg/mL) was negative for induction of chromosomal aberrations in CHO cells, with or without S9 (Table F3).

TABLE F1
Mutagenicity of Probenecid in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA100	0	108 ± 4.4	149 ± 17.0	113 ± 4.0	222 ± 1.7	124 ± 4.3	226 ± 9.8
	33		116 ± 6.0		128 ± 13.6		174 ± 18.3
	100	88 ± 4.0	101 ± 13.0	118 ± 1.5	151 ± 6.9	98 ± 1.5	140 ± 20.8
	333	79 ± 2.0	107 ± 2.9	104 ± 5.3	145 ± 1.3	95 ± 0.9	154 ± 11.3
	1,000	87 ± 2.7	111 ± 1.0	100 ± 13.9	142 ± 1.9	123 ± 2.0	177 ± 29.4
	3,333	67 ± 1.2	109 ± 10.9	99 ± 1.5	146 ± 27.9	119 ± 7.3	162 ± 32.3
	10,000	80 ± 2.0		115 ± 4.8		135 ± 4.0	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[c]		492 ± 24.8	437 ± 24.4	1215 ± 22.4	2216 ± 32.0	1304 ± 19.4	2422 ± 93.2
TA1535	0	8 ± 0.9	8 ± 0.9	10 ± 2.1	12 ± 1.5	15 ± 4.5	12 ± 1.8
	33		4 ± 0.9		9 ± 1.3		5 ± 2.0
	100	6 ± 0.3	6 ± 0.0	7 ± 1.0	7 ± 1.2	12 ± 1.5	8 ± 0.7
	333	4 ± 0.6	4 ± 0.0	7 ± 0.9	6 ± 1.8	13 ± 2.0	6 ± 2.0
	1,000	6 ± 0.3	6 ± 0.3	5 ± 0.5	4 ± 1.2	11 ± 2.7	6 ± 1.8
	3,333	4 ± 0.3	3 ± 0.7	11 ± 1.2	7 ± 3.3	11 ± 1.7	6 ± 1.5
	10,000	4 ± 0.9		3 ± 0.3		6 ± 1.0	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		491 ± 31.1	727 ± 40.8	59 ± 4.7	118 ± 6.5	94 ± 12.8	226 ± 14.4
TA1537	0	3 ± 0.3	3 ± 0.3	5 ± 1.2	7 ± 2.7	4 ± 1.8	7 ± 1.3
	33		3 ± 1.5		3 ± 2.3		5 ± 1.8
	100	3 ± 0.9	2 ± 0.9	7 ± 0.9	8 ± 1.0	3 ± 0.6	3 ± 1.2
	333	3 ± 0.6	2 ± 0.9	6 ± 1.5	7 ± 1.0	9 ± 2.3	12 ± 3.0
	1,000	1 ± 0.3	3 ± 0.9	7 ± 1.2	8 ± 1.0	6 ± 1.7	8 ± 2.0
	3,333	1 ± 0.3	2 ± 0.5	5 ± 1.0	3 ± 2.1	2 ± 0.3	3 ± 0.0
	10,000	Toxic		6 ± 1.5		6 ± 0.9	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		769 ± 48.3	473 ± 104.5	135 ± 7.7	201 ± 12.8	89 ± 7.4	192 ± 20.2

TABLE F1
Mutagenicity of Probenecid in *Salmonella typhimurium* (continued)[a]

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA98	0	22 ± 4.7	15 ± 3.5	29 ± 2.0	28 ± 1.3	29 ± 4.9	23 ± 3.0
	33		12 ± 1.3		22 ± 1.8		21 ± 0.9
	100	23 ± 1.0	14 ± 0.9	17 ± 3.8	20 ± 2.3	20 ± 1.2	21 ± 2.7
	333	21 ± 1.9	11 ± 1.8	23 ± 0.9	23 ± 2.1	28 ± 3.7	24 ± 2.2
	1,000	18 ± 1.7	13 ± 0.7	25 ± 3.2	21 ± 3.7	35 ± 1.7	24 ± 5.9
	3,333	14 ± 0.6	12 ± 2.2	32 ± 0.6	28 ± 1.7	20 ± 3.6	22 ± 3.2
	10,000	19 ± 0.9		29 ± 3.2		30 ± 2.5	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		138 ± 9.9	184 ± 9.7	870 ± 42.1	1436 ± 21.4	889 ± 73.1	1551 ± 38.6

[a] Study performed at Case Western Reserve University. The detailed protocol and these data are presented in Mortelmans *et al.* (1986). Cells and study compound or solvent (dimethylsulfoxide) 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 to 10 mg/plate; 0 μg/plate dose is the solvent control.

[b] Revertants are presented as mean ± the standard error from 3 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 tested on TA98, sodium azide was tested on TA100 and TA1535, and 9-aminoacridine was tested on TA1537.

TABLE F2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Probenecid[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative SCEs/Chromosome (%)[b]
–S9[c]								
Trial 1 – Summary: Positive								
Dimethylsulfoxide		50	1048	388	0.37	7.8	26.0	
Mitomycin-C								
	0.0005	50	1047	500	0.47	10.0	26.0	28.99
	0.0050	10	210	308	1.46	30.8	26.0	296.16
Probenecid								
	5	50	1048	399	0.38	8.0	26.0	2.84
	16	50	1050	445	0.42	8.9	26.0	14.47
	50	50	1049	510	0.48	10.2	26.0	31.32*
	160	50	1047	539	0.51	10.8	26.0	39.05*
								P<0.001[d]
Trial 2 – Summary: Negative								
Dimethylsulfoxide		50	1039	417	0.40	8.3	26.0	
Mitomycin-C								
	0.0005	50	1042	542	0.52	10.8	26.0	29.60
	0.0050	10	207	285	1.37	28.5	26.0	243.05
Probenecid								
	5	50	1036	356	0.34	7.1	26.0	–14.38
	16	50	1040	424	0.40	8.5	26.0	1.58
	50	50	1035	379	0.36	7.6	26.0	–8.76
	160	50	1036	406	0.39	8.1	26.0	–2.36
								P=0.475
Trial 3 – Summary: Positive								
Dimethylsulfoxide		50	1046	383	0.36	7.7	26.0	
Mitomycin-C								
	0.0007	50	1047	501	0.47	10.0	26.0	30.69
	0.0050	10	210	317	1.50	31.7	26.0	312.27
Probenecid								
	5	50	1045	465	0.44	9.3	26.0	21.53*
	16	50	1044	458	0.43	9.2	26.0	19.81
	50	50	1042	440	0.42	8.8	26.0	15.32
	160	50	1043	545	0.52	10.9	26.0	42.71*
								P<0.001

TABLE F2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Probenecid[a] (continued)

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/Chromosome	SCEs/Cell	Hrs in BrdU	Relative SCEs/Chromosome (%)[b]
+S9[e]								
Trial 1 – Summary: Negative								
Dimethylsulfoxide		50	1045	479	0.45	9.6	26.0	
Cyclophosphamide								
	0.1500	50	1046	619	0.59	12.4	26.0	29.10
	0.6000	10	210	198	0.94	19.8	26.0	105.70
Probenecid								
	50	50	1047	455	0.43	9.1	26.0	-5.19
	160	50	1044	498	0.47	10.0	26.0	4.07
	500	50	1048	424	0.40	8.5	26.0	-11.74
	1250	50	1046	464	0.44	9.3	26.0	-3.23
								P=0.828

* Positive (≥20% increase over solvent control)

[a] Study performed at Environmental Health Research and Testing, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway *et al.* (1987). Briefly, Chinese hamster ovary cells were incubated with probenecid or solvent (dimethylsulfoxide) as described in [c] and [d] 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] Percent increase in SCEs/chromosome of culture exposed to probenecid relative to those of culture exposed to solvent.

[c] In the absence of S9, cells were incubated with probenecid 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] Significance of relative SCEs/chromosome tested by linear regression vs. log of the dose

[e] In the presence of S9, cells were incubated with probenecid or solvent for 2 hours at 37° C. The cells were then 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 livers of Aroclor 1254-induced male Sprague-Dawley rats.

TABLE F3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Probenecid[a]

-S9[b]					+S9[c]				
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[d]
Trial 1 – Harvest time: 12.0 hours					**Trial 1** – Harvest time: 13.5 hours				
Summary: Negative					Summary: Negative				
Dimethylsulfoxide					Dimethylsulfoxide				
	200	3	0.02	1.5		200	1	0.01	0.5
Mitomycin-C					Cyclophosphamide				
0.0625	200	18	0.09	8.5	2.500	200	24	0.12	11.5
0.2500	50	30	0.60	46.0	7.5000	50	22	0.44	40.0
Probenecid					Probenecid				
500	200	4	0.02	2.0	500	200	3	0.02	1.5
1,000	200	8	0.04	4.0	1,000	200	4	0.02	2.0
1,250	200	4	0.02	2.0	1,250	200	3	0.02	1.5
				P=0.158					P=0.146

[a] Study performed at Environmental Health Research and Testing, Inc. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway *et al.* (1987). Briefly, Chinese hamster ovary cells were incubated with probenecid or solvent (dimethylsulfoxide) as described in [b] and [c]. 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, cells were incubated with probenecid or solvent 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] In the presence of S9, cells were incubated with probenecid or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 11 hours. Colcemid was added for the last 2-3 hours of incubation before harvest. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

[d] Significance of percent cells with aberrations tested by linear regression trend test vs. log of the dose

APPENDIX G
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF PROBENECID

Probenecid was obtained from Ganes Chemical, Inc. (New York City, NY). One lot (lot number 9L008892) was used throughout the studies. Reports from the analytical chemistry laboratory, Midwest Research Institute (MRI; Kansas City, MO), on analyses performed in support of the probenecid studies are on file at the National Institute of Environmental Health Sciences.

The study chemical, a fine, white, fluffy crystalline powder, was identified as probenecid by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with those expected for the structure and with the literature description for the spectra of probenecid (Figures G1 and G2) (*Sadtler Standard Spectra*).

The purity of the lot was found to be greater than 99% by Karl Fischer water analysis, weight loss on drying, elemental analysis, thin-layer chromatography (TLC), high-performance liquid chromatography (HPLC), and titration. Titration of the carboxylic acid group was performed with 0.1 N sodium hydroxide in water in 95% ethanol.

Elemental analysis for carbon, hydrogen, nitrogen, and sulfur was in agreement with the theoretical values for probenecid. Thin-layer chromatography was performed on silica gel plates with two solvent systems: 1) absolute ethanol:acetic acid (99:1) and 2) diethylamine:methanol:toluene (40:35:25). Visualization was accomplished with short wavelength (254 nm) ultraviolet light by using a spray of 1% sodium nitrite solution in N hydrochloric acid followed a minute later by a spray of a 0.4% solution of N-(1-naphthyl)-ethylenediammonium dichloride in methanol. The plates were dried at 60° C and then were examined under long wavelength (366 nm) ultraviolet light. A major product spot was noted in both solvent systems using TLC. High-performance liquid chromatography was performed with a μBondpak C_{18} column and a mobile phase of two solvent systems: 1) water with 1% (v/v) glacial acetic acid and 2) acetonitrile with 1% (v/v) glacial acetic acid in an isocratic mode of 60% solvent 1) and 40% solvent 2), both at a flow rate of 1 mL/minute. Ultraviolet detection was at 254 nm. An impurity with an area of 0.15% of the major peak area was seen before the major peak using HPLC. The sample had a purity of 99.1% relative to the USP standard.

Stability studies were performed using HPLC with the system described above but the mobile phase was 50% solvent 1) and 50% solvent 2), both at a flow rate of 2 mL/minute and using 2-naphthol as an internal standard. These studies indicated that probenecid was stable as a bulk chemical for two weeks at temperatures up to 60° C when protected from light.

Supplementing the identity and purity tests listed above, a complete battery of USP tests was performed. All tests indicated that this lot met requirements for identity and purity specified by the USP (*The United States Pharmacopeia*, 1975).

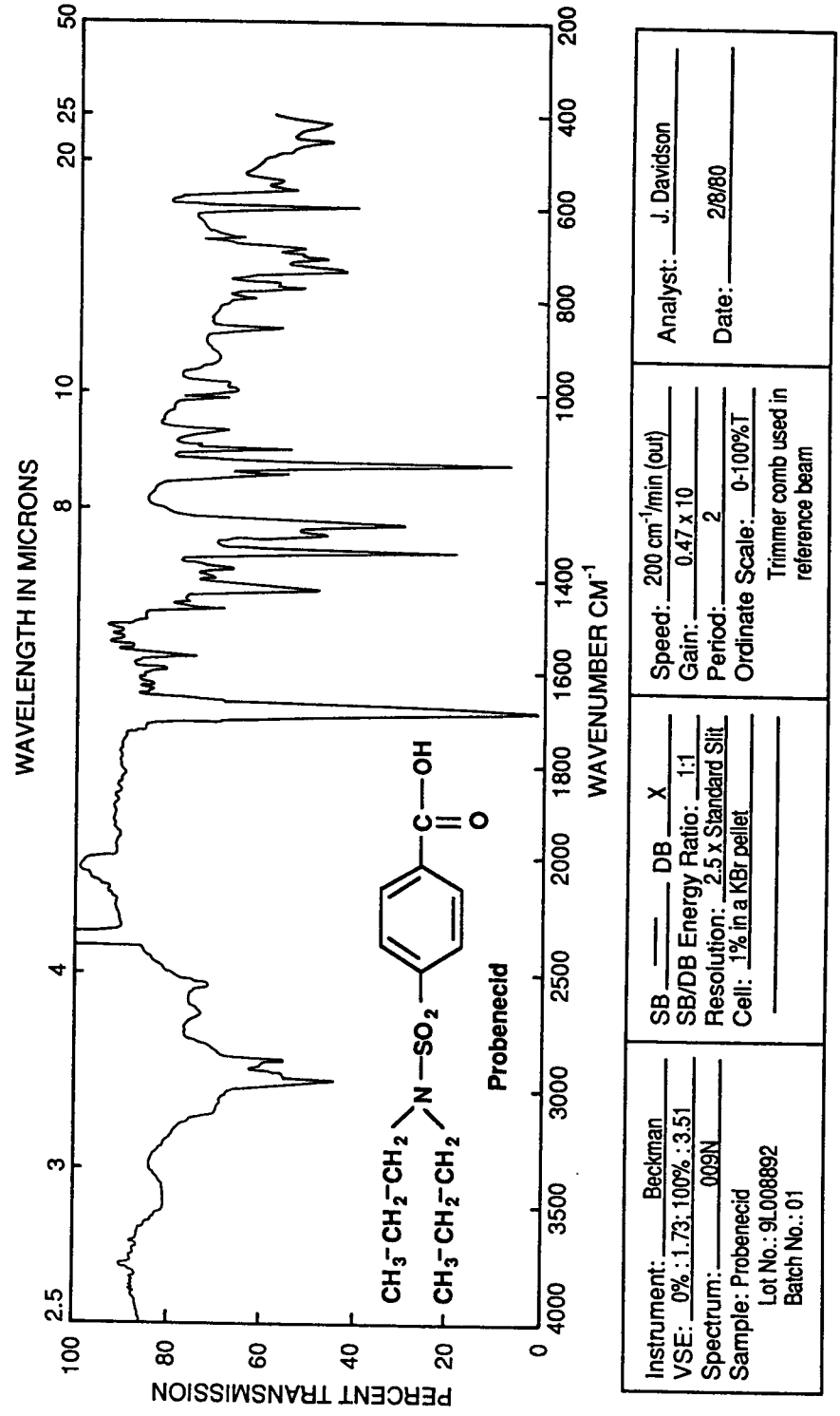

FIGURE G1
Infrared Absorption Spectrum of Probenecid

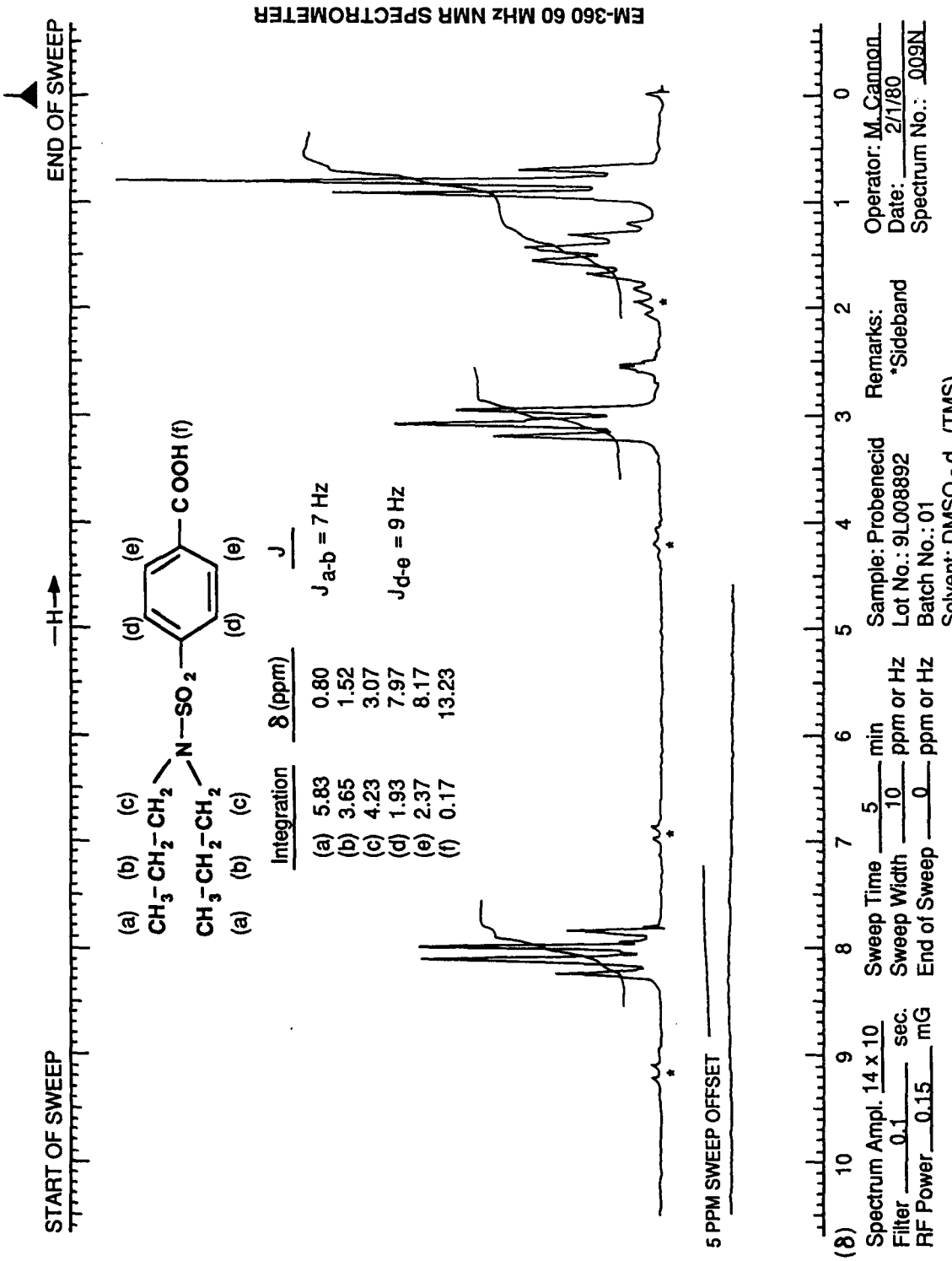

FIGURE G2
Nuclear Magnetic Resonance Spectrum of Probenecid

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared by mixing appropriate quantities of probenecid and corn oil to give the required concentrations (Table G1). The dose formulations were stored at 0° ± 5° C and brought to room temperature and hand agitated before administration. Dose formulations were discarded every 2 weeks and new dose formulations were prepared as needed.

Studies were conducted by the analytical chemistry laboratory to determine the homogeneity and stability of the corn oil suspensions. For the homogeneity analyses the formulations were extracted with methanol. The extract was further diluted with methanol and the concentration determined using an ultraviolet method at 247 nm. For the formulation stability studies a methanolic extract was injected into an HPLC system equipped with a Waters μBondpak C_{18} column (300 mm x 3.9 mm ID), Whatman CO: PELL ODS guard column (72 mm x 2 mm ID) and a 254 nm detector. The mobile phase was 37%[water:glacial acetic acid (99:1)] and 63%[methanol:glacial acetic acid (99:1)] with a flow rate of 1 mL/minute. Homogeneity of the formulation was confirmed and stability established for at least 2 weeks.

Periodic analyses of the dose formulations of probenecid were conducted at the study laboratory and at the analytical chemistry laboratory using the ultraviolet spectroscopy method at 247 nm. Dose formulations were analyzed once during the 14-day studies and twice during the 13-week studies. The results were within ± 10% of the target concentrations for the 14-day samples (Table G2). Dose formulation samples for the 13-week studies ranged from 2% to 9% greater than the target concentrations (Table G3). During the 2-year studies, samples from the dose formulation room were analyzed at 8-week intervals and samples from the animal room were analyzed at 24-week intervals. Samples were within ± 10% of the target concentrations 99% (73/74) of the time (Table G4).

Peroxide analyses of the corn oil vehicle by the study laboratory consistently demonstrated peroxide levels within the acceptable limit of 10 mEq/kg. Results of the referee analyses of the dose formulations supplied by the analytical laboratory indicated good agreement with the results obtained by the study laboratory (Table G5).

TABLE G1
Preparation and Storage of Dose Formulations in the Gavage Studies of Probenecid

14-Day Studies	13-Week Studies	2-Year Studies
Preparation		
Dose formulations were prepared (w/v) in corn oil as detailed by the MRI report of 18 March 1980 on file at NIEHS.	Dose formulations were mixed weekly (w/v) in corn oil using a magnetic stir bar and plate. Gavage formulations from cold storage were allowed to equilibrate to room temperature prior to administration.	Dose formulations were mixed weekly (w/w) in corn oil using a Brinkman Polytron; one minute at medium speed. Gavage formulations from cold storage were allowed to equilibrate to room temperature and were manually agitated prior to administration.
Lot		
9L008892	9L008892	9L008892
Maximum Storage Time		
14 days from date of preparation	14 days from date of preparation	14 days from date of preparation
Storage Conditions		
Sealed in labeled serum vials containing magnetic stir bars and stored at 0 ± 5° C	Sealed in labeled amber serum vials and stored in cold room at approximately 4° C	Sealed in labeled serum vials and stored in cold room at 0 ± 5° C.
Study Laboratory		
EG&G Mason Research Institute, Worcester, MA	EG&G Mason Research Institute, Worcester, MA	EG&G Mason Research Institute, Worcester, MA
Referee Laboratory		
Midwest Research Institute, Kansas City, MO	Midwest Research Institute, Kansas City, MO	Midwest Research Institute, Kansas City, MO

TABLE G2
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 14-Day Gavage Studies of Probenecid

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
3 March 1981	9 March 1981	20	22.0	+10
		40	43.8	+9
		80	84.8	+6
		160	167.5	+5
		320	308.0	–4

TABLE G3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Gavage Studies of Probenecid

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
15 May 1981	18 May 1981	10	10.9	+9
		20	20.5	+2
		40	42.4	+6
		80	84.7	+6
		160	166.8	+4
9 July 1981	10 July 1981	10	10.9	+9
		20	21.3	+6
		40	42.2	+6
		80	87.3	+9
		160	173.6	+9

TABLE G4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Probenecid

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)[a]	Difference from Target (%)
29 April 1982	3 May 1982	10	9.6	–4
		20	20.1	+1
		40	42.4	+6
		80	83.9	+5
29 April 1982	12 May 1982[b]	10	10.5	+5
		20	20.1	+3
		40	41.6	+4
		80	79.9	0
6 July 1982	7 July 1982	10	10.6	+6
		20	20.7	+3
		40	41.9	+5
		80	85.3	+7
31 August 1982	1 September 1982	10	10.5	+5
24 August 1982	25 August 1982	20	20.9	+4
31 August 1982	1 September 1982	40	40.6	+1
24 August 1982	25 August 1982	80	82.0	+2
22 November 1982	24 November 1982	10	10.1	+1
		20	20.7	+4
		40	41.4	+4
		80	80.5	+1
22 November 1982	1 December 1982[b]	10	10.3	+3
		20	19.9	–1
		40	40.3	+1
		80	80.4	0
21 December 1982	22 December 1982	10	10.3	+3
		20	20.4	+2
		40	39.0	–2
		80	80.5	+1
10 February 1983	10 February 1983	10	9.9	–1
8 February 1983		20	20.7	+3
10 February 1983		40	40.6	+1
8 February 1983		80	80.9	+1
19 April 1983	20 April 1983	10	10.4	+4
		20	20.6	+3
		40	40.0	0
		80	79.2	–1
19 April 1983	27 April 1983[b]	10	10.3	+3
		20	20.6	+3
		40	39.7	–1
		80	78.3	–2

TABLE G4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Probenecid (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)[a]	Difference from Target (%)
2 June 1983	3 June 1983	10	9.5	-5
1 June 1983		20	20.0	0
2 June 1983		40	40.0	0
1 June 1983		80	78.8	-1
16 August 1983	17 August 1983	10.9	11.4	+5
		21.7	23.0	+6
		43.2	44.7	+4
		85.3	86.2	+1
25 October 1983	27 October 1983	10.9	11.6	+6
		21.7	23.0	+6
		43.2	44.0	+2
		85.3	84.0	-2
25 October 1983	8 November 1983[b]	10.9	12.4	+14
		21.7	23.3	+8
		43.2	47.4	+10
		85.3	85.8	+1
20 December 1983	22 December 1983	10.9	11.3	+4
		21.7	22.3	+3
		43.2	43.9	+2
		85.3	81.8	-4
6 February 1984	9 February 1984	10.9	11.5	+6
		21.7	22.7	+5
		43.2	44.4	+3
		85.3	86.4	+1
17 April 1984	18 April 1984	10.9	11.6	+7
		21.7	22.9	+6
		43.2	44.6	+3
		85.3	87.7	+3
17 April 1984	3 May 1984[b]	10.9	11.8	+8
		21.7	22.2	+2
		43.2	45.3	+5
		85.3	85.9	+1
8 May 1984	10 May 1984	21.7	23.1	+6
		85.3	87.6	+3

[a] After 3 June 1983, units are mg probenecid/g dose formulation.
[b] Animal room sample

TABLE G5
Results of Referee Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Probenecid

Date Mixed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	
		Study Laboratory[a]	Referee Laboratory[b]
29 April 1982	20	20.1	20.5 ± 0.1
22 November 1982	40	40.3	40.3 ± 1.3
1 June 1983	80[c]	78.8	79.8 ± 0.4
20 December 1983	21.7[c]	22.3	21.9 ± 0.3
8 May 1984	21.7	23.1	22.5 ± 0.2

[a] Averaged values of results of duplicate analysis
[b] Averaged values of results of triplicate analysis
[c] Units are mg/g.

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

TABLE H1
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] NCI, 1976; NIH, 1978
[b] Ingredients ground to pass through a U.S. Standard Screen No. 16 before being mixed

TABLE H2
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 H3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	23.01 ± 1.19	21.2–25.9	26
Crude fat (% by weight)	5.09 ± 0.47	4.2–5.8	26
Crude fiber (% by weight)	3.50 ± 0.36	2.8–4.5	26
Ash (% by weight)	6.66 ± 0.21	6.3–7.1	26
Amino Acids (% of total diet)			
Arginine	1.320 ± 0.072	1.310–1.390	5
Cystine	0.319 ± 0.088	0.218–0.400	5
Glycine	1.146 ± 0.063	1.060–1.210	5
Histidine	0.571 ± 0.026	0.531–0.603	5
Isoleucine	0.914 ± 0.030	0.881–0.944	5
Leucine	1.946 ± 0.056	1.850–1.990	5
Lysine	1.280 ± 0.067	1.200–1.370	5
Methionine	0.436 ± 0.165	0.306–0.699	5
Phenylalanine	0.938 ± 0.158	0.655–1.050	5
Threonine	0.855 ± 0.035	0.824–0.898	5
Tryptophan	0.277 ± 0.221	0.156–0.671	5
Tyrosine	0.618 ± 0.086	0.564–0.769	5
Valine	1.108 ± 0.043	1.050–1.170	5
Essential Fatty Acids (% of total diet)			
Linoleic	2.290 ± 0.313	1.830–2.520	5
Linolenic	0.258 ± 0.040	0.210–0.308	5
Vitamins			
Vitamin A (IU/kg)	11,673 ± 4,238	4,200–22,000	26
Vitamin D (IU/kg)	4,450 ± 1,382	3,000–6,300	4
α–Tocopherol (ppm)	43.58 ± 6.92	31.1–48.0	5
Thiamine (ppm)	18.65 ± 4.14	12.0–31.0	26
Riboflavin (ppm)	7.60 ± 0.85	6.10–8.20	5
Niacin (ppm)	97.80 ± 31.68	65.0–150.0	5
Pantothenic acid (ppm)	30.06 ± 4.31	23.0–34.0	5
Pyridoxine (ppm)	7.68 ± 1.31	5.60–8.80	5
Folic acid (ppm)	2.62 ± 0.89	1.80–3.70	5
Biotin (ppm)	0.254 ± 0.053	0.19–0.32	5
Vitamin B_{12} (ppb)	24.21 ± 12.66	10.6–38.0	5
Choline (ppm)	3,122 ± 416.8	2,400–3,430	5
Minerals			
Calcium (%)	1.26 ± 0.10	1.04–1.43	26
Phosphorus (%)	0.96 ± 0.05	0.87–1.10	26
Potassium (%)	0.900 ± 0.098	0.772–0.971	3
Chloride (%)	0.513 ± 0.114	0.380–0.635	5
Sodium (%)	0.323 ± 0.043	0.258–0.371	5
Magnesium (%)	0.167 ± 0.012	0.151–0.181	5
Sulfur (%)	0.304 ± 0.064	0.268–0.420	5
Iron (ppm)	410.3 ± 94.04	262.0–523.0	5
Manganese (ppm)	90.29 ± 7.15	81.70–99.40	5
Zinc (ppm)	52.78 ± 4.94	46.10–58.20	5
Copper (ppm)	10.72 ± 2.76	8.090–15.39	5
Iodine (ppm)	2.95 ± 1.05	1.52–3.82	4
Chromium (ppm)	1.85 ± 0.25	1.44–2.09	5
Cobalt (ppm)	0.681 ± 0.14	0.490–0.780	4

TABLE H4
Contaminant Levels in NIH-07 Rat and Mouse Ration

	Mean ± Standard Deviation[a]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.51 ± 0.14	0.18–0.74	26
Cadmium (ppm)	0.11 ± 0.03	0.10–0.20	26
Lead (ppm)	0.66 ± 0.52	0.27–2.93	26
Mercury (ppm)	<0.05	–	26
Selenium (ppm)	0.31 ± 0.06	0.22–0.45	26
Aflatoxins (ppb)	<5.0	–	26
Nitrate nitrogen (ppm)[b]	9.69 ± 4.50	2.50–19.0	26
Nitrite nitrogen (ppm)[b]	1.63 ± 1.66	0.10–6.10	26
BHA (ppm)[c]	4.12 ± 4.96	2.00–20.00	26
BHT (ppm)[c]	2.89 ± 2.57	1.00–13.00	26
Aerobic plate count (CFU/g)[d]	138,450 ± 132,897	6,200–420,000	26
Coliform (MPN/g)[e]	676 ± 921	3.00–2400.00	26
E. coli (MPN/g)[f]	10.19 ± 28.88	3.00–150.00	26
E. coli (MPN/g)[g]	4.60 ± 4.65	3.00–23.00	25
Total nitrosamines (ppb)[h]	5.27 ± 5.86	0.80–30.30	26
N-Nitrosodimethylamine (ppb)[h]	4.43 ± 5.92	0.50–30.00	26
N-Nitrosopyrrolidine (ppb)[h]	0.83 ± 0.64	0.30–2.20	26
Pesticides (ppm)			
α-BHC[i]	<0.01	–	26
β-BHC	<0.02	–	26
γ-BHC	<0.01	–	26
δ-BHC	<0.01	–	26
Heptachlor	<0.01	–	26
Aldrin	<0.01	–	26
Heptachlor epoxide	<0.01	–	26
DDE	<0.01	–	26
DDD	<0.01	–	26
DDT	<0.01	–	26
HCB	<0.01	–	26
Mirex	<0.01	–	26
Methoxychlor	<0.05	–	26
Dieldrin	<0.01	–	26
Endrin	<0.01	–	26
Telodrin	<0.01	–	26
Chlordane	<0.05	–	26
Toxaphene	<0.1	–	26
Estimated PCB's	<0.2	–	26
Ronnel	<0.01	–	26
Ethion	<0.02	–	26
Trithion	<0.05	–	26
Diazinon	<0.1	–	26
Methyl parathion	<0.02	–	26
Ethyl parathion	<0.02	–	26
Malathion[j]	0.14 ± 0.17	0.05–0.81	26
Endosulfan I	<0.01	–	26
Endosulfan II	<0.01	–	26
Endosulfan sulfate	<0.03	–	26

TABLE H4
Contaminant Levels in NIH-07 Rat and Mouse Ration (continued)

[a] For values less than the limit of detection, the detection limit is given for the mean.
[b] Sources of contamination: alfalfa, grains, and fish meal
[c] Sources of contamination: soy oil and fish meal
[d] CFU = colony forming units
[e] MPN = most probable number
[f] The mean, SD, and range include one large value obtained in lot milled on 26 August 1982.
[g] The mean, SD, and range exclude one large value obtained in lot milled on 26 August 1982.
[h] All values were corrected for percent recovery
[i] BHC = hexachlorocyclohexane or benzene hexachloride
[j] Fourteen lots contained >0.05 ppm

APPENDIX I
FEED CONSUMPTION BY RATS AND MICE IN THE 2-YEAR GAVAGE STUDIES

TABLE I1
Feed Consumption by Male Rats in the 2-Year Gavage Study of Probenecid

Week	Vehicle Control		100 mg/kg			400 mg/kg		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)[a]	Body Weight (g)	Low/ Control[b]	Feed (g/day)[a]	Body Weight (g)	High/ Control[b]
1	15.6	136	15.5	134	0.99	15.4	139	0.99
2	19.0	168	18.0	166	0.95	16.3	168	0.86
4	14.7	223	14.4	222	0.98	13.7	220	0.93
5	14.9	243	15.0	242	1.01	14.5	237	0.97
9	14.6	299	14.0	298	0.96	14.3	288	0.98
12	14.2	325	13.2	321	0.93	14.3	313	1.01
13	14.4	334	13.5	332	0.94	13.6	324	0.94
17	12.9	359	11.9	356	0.92	12.3	345	0.95
21	13.3	377	11.9	377	0.89	11.1	369	0.83
25	14.2	401	12.6	397	0.89	12.2	386	0.86
29	13.6	416	12.2	413	0.90	13.0	403	0.96
33	14.7	429	13.8	427	0.94	9.7	410	0.66
37	15.0	434	13.2	431	0.88	13.2	417	0.88
41	12.8	440	12.3	439	0.96	13.6	423	1.06
45	14.1	459	13.6	456	0.96	12.9	438	0.91
49	14.9	470	14.7	470	0.99	13.5	450	0.91
53	12.1	481	10.9	477	0.90	12.3	459	1.02
57	13.8	485	12.1	481	0.88	11.7	460	0.85
61	12.4	489	11.3	482	0.91	12.1	462	0.98
65	11.9	492	10.9	486	0.92	11.5	471	0.97
69	11.1	486	9.9	478	0.89	12.4	465	1.12
73	10.5	484	10.7	481	1.02	10.3	465	0.98
77	9.4	481	10.4	483	1.11	9.2	462	0.98
81	6.6	473	10.4	479	1.58	6.8	455	1.03
85	13.3	474	12.0	477	0.90	9.7	454	0.73
89	12.3	481	9.6	473	0.78	11.6	462	0.94
93	14.6	476	12.4	473	0.85	15.8	462	1.08
97	7.5	458	7.6	461	1.01	8.9	453	1.19
101	7.3	449	7.3	450	1.00	7.9	441	1.08
104	5.6	442	6.0	439	1.07	7.8	434	1.39
Mean for weeks								
1–13	15.3	247	14.8	245	0.96	14.6	241	0.95
14–52	13.9	421	12.9	419	0.93	12.4	404	0.89
53–104	10.6	475	10.1	473	0.99	10.6	458	1.02

[a] Grams of feed consumed per animal per day
[b] Grams of feed per day for the dosed group divided by that for the controls

TABLE I2
Feed Consumption by Female Rats in the 2-Year Gavage Study of Probenecid

Week	Vehicle Control		100 mg/kg			400 mg/kg		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)[a]	Body Weight (g)	Low/ Control[b]	Feed (g/day)[a]	Body Weight (g)	High/ Control[b]
2	13.0	140	12.9	140	0.99	11.7	137	0.90
4	13.3	158	15.3	159	1.15	14.3	152	1.08
5	12.0	167	12.7	169	1.06	12.3	165	1.03
9	11.3	186	11.6	188	1.03	11.7	184	1.04
13	10.6	199	10.7	201	1.01	10.8	192	1.02
17	10.5	206	11.4	209	1.09	8.4	198	0.80
21	10.9	211	12.3	217	1.13	9.6	200	0.88
25	10.7	221	11.2	224	1.05	7.8	201	0.73
29	10.9	228	10.8	230	0.99	5.9	209	0.54
33	8.4	228	9.3	230	1.11	5.7	203	0.68
37	11.6	242	12.7	249	1.09	8.6	222	0.74
41	11.1	250	10.9	255	0.98	6.9	223	0.62
45	14.5	264	14.8	267	1.02	10.8	229	0.74
49	11.5	275	11.0	277	0.96	8.2	230	0.71
53	12.9	288	12.2	286	0.95	9.2	237	0.71
57	10.8	296	10.9	294	1.01	8.7	238	0.81
61	10.1	306	10.6	302	1.05	8.1	239	0.80
65	9.5	312	9.6	307	1.01	9.4	246	0.99
69	10.7	317	10.0	312	0.93	8.6	253	0.80
73	10.6	323	9.9	317	0.93	8.2	260	0.77
77	8.9	326	10.2	324	1.15	7.3	264	0.82
81	10.9	332	9.9	326	0.91	8.7	268	0.80
85	11.1	331	9.7	330	0.87	9.2	278	0.83
89	11.0	336	9.4	331	0.85	9.9	279	0.90
93	15.7	337	16.7	336	1.06	19.7	295	1.25
97	7.4	330	7.5	333	1.01	8.6	290	1.16
101	5.0	335	4.0	329	0.80	4.7	286	0.94
104	5.7	338	5.7	330	1.00	7.3	287	1.28
Mean for weeks								
1–13	12.0	170	12.6	171	1.05	12.1	166	1.01
14–52	11.1	236	11.6	240	1.05	8.0	213	0.72
53–104	10.0	321	9.7	318	0.97	9.1	266	0.92

[a] Grams of feed consumed per animal per day
[b] Grams of feed per day for the dosed group divided by that for the controls

TABLE I3
Feed Consumption by Male Mice in the 2-Year Gavage Study of Probenecid

Week	Vehicle Control		100 mg/kg			400 mg/kg		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)[a]	Body Weight (g)	Low/ Control[b]	Feed (g/day)[a]	Body Weight (g)	High/ Control[b]
2	5.6	24.9	6.1	24.9	1.09	6.2	24.7	1.11
5	5.1	27.2	5.1	26.8	1.00	5.1	26.9	1.00
9	5.9	29.6	5.7	29.7	0.97	5.8	29.0	0.98
13	6.0	31.7	5.9	31.7	0.98	5.6	31.5	0.93
21	4.8	33.4	4.7	32.3	0.98	4.5	32.4	0.94
25	5.8	35.1	5.8	34.1	1.00	5.6	35.2	0.97
29	5.2	35.9	5.4	35.2	1.04	5.1	36.1	0.98
37	1.2	37.7	1.1	36.3	0.92	1.2	35.8	1.00
41	5.2	38.7	5.0	36.4	0.96	4.8	37.5	0.92
45	4.2	38.0	4.3	37.0	1.02	4.4	37.7	1.05
49	5.8	38.4	5.6	37.6	0.97	5.9	37.8	1.02
53	5.5	39.9	5.5	38.3	1.00	5.4	38.7	0.98
57	4.7	40.2	4.8	38.8	1.02	5.2	38.9	1.11
61	4.9	39.9	5.2	38.3	1.06	5.7	39.0	1.16
65	5.0	40.4	5.1	38.1	1.02	5.7	38.9	1.14
69	4.4	39.5	4.8	37.6	1.09	5.3	38.1	1.20
73	5.6	39.9	5.8	38.6	1.04	6.7	38.6	1.20
77	4.2	38.9	5.1	37.5	1.21	6.8	38.4	1.62
81	4.6	39.1	5.7	38.1	1.24	7.4	38.5	1.61
85	4.3	38.3	5.2	37.7	1.21	6.3	37.7	1.47
89	4.7	37.9	6.1	37.7	1.30	7.1	37.6	1.51
93	4.2	37.4	5.4	36.5	1.29	7.2	36.9	1.71
97	4.5	36.6	6.4	37.4	1.42	6.9	37.2	1.53
101	4.6	36.3	5.6	36.3	1.22	8.4	36.4	1.83
104	4.9	37.5	6.4	37.0	1.31	7.9	37.8	1.61
Mean for weeks								
2–13	5.6	28.4	5.7	28.3	1.01	5.7	28.0	1.01
21–49	4.6	36.7	4.5	35.6	0.98	4.5	36.1	0.98
53–104	4.7	38.7	5.4	37.7	1.17	5.4	37.8	1.41

[a] Grams of feed consumed per animal per day
[b] Grams of feed per day for the dosed group divided by that for the controls

TABLE I4
Feed Consumption by Female Mice in the 2-Year Gavage Study of Probenecid

Week	Vehicle Control		100 mg/kg			400 mg/kg		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)[a]	Body Weight (g)	Low/ Control[b]	Feed (g/day)[a]	Body Weight (g)	High/ Control[b]
2	4.7	19.5	5.2	19.4	1.11	5.2	19.5	1.11
5	4.1	21.4	4.1	21.4	1.00	3.9	21.4	0.95
9	5.4	23.9	5.3	23.8	0.98	5.4	23.8	1.00
13	4.5	24.7	5.3	24.8	1.18	4.8	24.4	1.07
17	5.8	26.2	5.8	26.0	1.00	5.5	25.4	0.95
21	5.3	27.0	5.4	26.8	1.02	4.9	26.8	0.92
29	5.2	29.4	5.3	29.6	1.02	5.3	29.6	1.02
33	5.6	31.9	5.8	31.2	1.04	5.0	31.2	0.89
37	5.3	31.7	5.6	32.6	1.06	5.1	32.4	0.96
41	5.2	34.5	5.6	34.8	1.08	5.0	34.5	0.96
45	6.1	34.9	6.1	34.9	1.00	5.7	34.5	0.93
49	7.0	35.4	7.1	35.9	1.01	6.5	35.7	0.93
53	6.1	36.7	6.7	37.4	1.10	6.2	36.9	1.02
57	5.7	38.6	6.4	38.9	1.12	5.6	38.0	0.98
61	6.5	38.9	6.8	39.3	1.05	6.0	37.6	0.92
65	6.3	39.7	6.8	40.3	1.08	6.1	39.1	0.97
69	7.1	40.2	7.2	40.6	1.01	6.8	38.2	0.96
73	7.1	40.6	7.3	41.1	1.03	7.2	39.6	1.01
77	4.2	39.6	5.4	41.1	1.29	5.9	39.7	1.40
81	5.3	39.7	8.1	41.0	1.53	5.6	39.0	1.06
85	7.7	38.6	8.1	40.8	1.05	8.5	38.8	1.10
89	7.0	39.4	7.3	40.6	1.04	7.4	40.2	1.06
93	6.7	38.2	7.6	40.4	1.13	7.1	38.6	1.06
97	8.2	38.8	8.4	41.2	1.02	9.1	39.6	1.11
101	9.0	37.5	9.1	39.8	1.01	9.0	39.2	1.00
104	9.6	38.6	9.3	39.8	0.97	9.4	39.8	0.98
Mean for weeks								
2–13	4.7	22.4	5.0	22.4	1.07	4.8	22.3	1.03
17–49	5.7	31.4	5.8	31.5	1.03	5.4	31.3	0.95
53–104	6.9	38.9	7.5	40.2	1.10	7.1	38.9	1.05

[a] Grams of feed consumed per animal per day
[b] Grams of feed per day for the dosed group divided by that for the controls

APPENDIX J
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

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. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds, and these animals and the study animals are subject to identical environmental conditions.

Rats

Fifteen F344/N rats of each sex were maintained with the study animals to serve as sentinel animals. Blood was drawn from five rats of each sex at 6, 12, and 18 months following study initiation. Five randomly selected control animals of each sex were bled at study termination (24 months). Blood collected from each animal was allowed to clot, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates, Inc. (Bethesda, MD) for determination of antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Hemagglutination Inhibition	
PVM (pneumonia virus of mice)	6, 12, 18, and 24 months
Sendai	6, 12, 18, and 24 months
KRV (Kilham rat virus)	6, 12, 18, and 24 months
H-1 (Toolan's H-1 virus)	6, 12, 18, and 24 months
ELISA	
RCV/SDA (rat corona virus/sialodacryoadenitis virus)	12, 18, and 24 months
Mycoplasma pulmonis	12 months
Complement Fixation	
RCV (rat corona virus)	6 months

Mice

Fifteen B6C3F$_1$ mice of each sex were maintained with the study animals to serve as sentinel animals. Blood was drawn from five rats of each sex at 6, 12, and 18 months following study initiation. Five randomly selected control animals of each sex were bled at study termination (24 months). Blood collected from each animal was allowed to clot, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates, Inc. (Bethesda, MD) for determination of antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Hemagglutination Inhibition	
PVM (pneumonia virus of mice)	6, 12, 18, and 24 months
Reovirus 3	6, 12, 18, and 24 months
GDVII	6, 12, and 18 months
Polyoma virus	6, 12, 18, and 24 months
Sendai	6, 12, 18, and 24 months
MVM (minute virus of mice)	6, 12, 18, and 24 months
Ectromelia virus (mouse pox)	6, 12, 18, and 24 months
Complement Fixation	
Mouse adenoma virus	6, 12, 18, and 24 months
LCM (lymphocytic choriomeningitis virus)	6, 12, 18, and 24 months
ELISA	
MHV (mouse hepatitis virus)	6, 12, 18, and 24 months
GDVII (mouse encephalomyelitis virus)	24 months
Mycoplasma pulmonis	12 months

RESULTS

The serology results for sentinel animals are presented in Table J1.

TABLE J1
Murine Virus Antibody Determinations for Rats and Mice in the 2-Year Gavage Studies of Probenecid

	Interval (months)	Incidence of Antibody in Sentinel Animals[a]	Positive Serologic Reaction for
Rats	12	7/9	*Mycoplasma pulmonis*
		10/10	RCV/SDA
	18	9/9	RCV/SDA
	24	10/10	RCV/SDA
Mice	12	9/9	MHV
	18	8/10	MHV
	24	1/7	MHV

[a] Number of animals with positive sera/(number of animal sera tested – number of equivocal or invalid test results)

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TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Dermal)
206	1,2-Dibromo-3-chloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butyl Benzyl 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)
243	Trichloroethylene (Rats and Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
246	Chrysotile Asbestos (Hamsters)
247	L-Ascorbic Acid
248	4,4'-Methylenedianiline Dihydrochloride
249	Amosite Asbestos (Hamsters)
250	Benzyl Acetate
251	2,4- & 2,6-Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
254	Dichloromethane (Methylene Chloride)
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
266	Monuron
267	1,2-Propylene Oxide
269	1,3-Dichloropropane (Telone II®)
271	HC Blue No. 1
272	Propylene
273	Trichloroethylene (Four Rat Strains)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
277	Tremolite
278	2,6-Xylidine
279	Amosite Asbestos
280	Crocidolite Asbestos
281	HC 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(hydroxymethyl) phosphonium Sulfate & Tetrakis(hydroxymethyl) 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 (Methylene Chloride)
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
313	Mirex
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
330	4-Hexylresorcinol
331	Malonaldehyde, Sodium Salt
332	2-Mercaptobenzothiazole
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol
335	C.I. Acid Orange 3
336	Penicillin VK
337	Nitrofurazone

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TR No.	CHEMICAL
338	Erythromycin Stearate
339	2-Amino-4-nitrophenol
340	Iodinated Glycerol
341	Nitrofurantoin
342	Dichlorvos
343	Benzyl Alcohol
344	Tetracycline Hydrochloride
345	Roxarsone
346	Chloroethane
347	D-Limonene
348	*a*-Methyldopa Sesquihydrate
349	Pentachlorophenol
350	Tribromomethane
351	*p*-Chloroaniline Hydrochloride
352	N-Methylolacrylamide
353	2,4-Dichlorophenol
354	Dimethoxane
355	Diphenhydramine Hydrochloride
356	Furosemide
357	Hydrochlorothiazide
358	Ochratoxin A
359	8-Methoxypsoralen
360	N,N-Dimethylaniline
361	Hexachloroethane
362	4-Vinyl-1-Cyclohexene Diepoxide
363	Bromoethane (Ethyl Bromide)
364	Rhodamine 6G (C.I. Basic Red 1)
365	Pentaerythritol Tetranitrate
366	Hydroquinone
367	Phenylbutazone
368	Nalidixic Acid
369	Alpha-Methylbenzyl Alcohol
370	Benzofuran
371	Toluene
372	3,3'-Dimethoxybenzidine Dihydrochloride
373	Succinic Anhydride
374	Glycidol
375	Vinyl Toluene
376	Allyl Glycidyl Ether
377	*o*-Chlorobenzalmalononitrile
378	Benzaldehyde
379	2-Chloroacetophenone
380	Epinephrine Hydrochloride
381	*d*-Carvone
382	Furfural
386	Tetranitromethane
387	Amphetamine Sulfate
390	3,3'-Dimethylbenzidine Dihydrochloride
391	Tris(2-chloroethyl) Phosphate
393	Sodium Fluoride

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