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No. 367

TOXICOLOGY AND CARCINOGENESIS STUDIES OF PHENYLBUTAZONE

(CAS NO. 50-33-9)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF PHENYLBUTAZONE

(CAS NO. 50-33-9)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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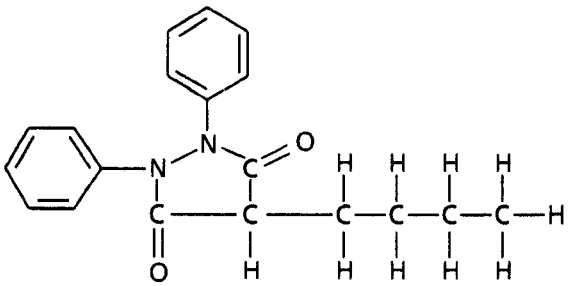

PHENYLBUTAZONE

CAS No. 50-33-9

$C_{19}H_{20}N_2O_2$ Molecular weight 308.4

Synonyms: 4-butyl-1,2-diphenyl-3,5-pyrazolidinedione;
3,5-dioxo-1,2-diphenyl-4-*n*-butylpyrazolidine

Trade Names: There have been over 100 registered trade names (IARC, 1977), including: Anerval; Azobutil; Bizolin 200; Butacote; Butadion; Butagesic; Butazolidin; Chembutazone; Equi Bute; Flexazone; Fenibutol; G 13,871; Pyrazolidin; Reumazol; Robizon-V; Uzone

ABSTRACT

Phenylbutazone is a nonsteroidal anti-inflammatory drug. Toxicology and carcinogenesis studies were conducted by administering phenylbutazone (greater than 99% pure) in corn oil by gavage to groups of F344/N rats and B6C3F$_1$ mice of each sex for 19 days, 13 weeks, or 2 years. Genetic toxicology studies were performed with *Salmonella typhimurium*, mouse L5178Y lymphoma cells, and Chinese hamster ovary (CHO) cells.

Nineteen-Day Studies: The deaths of 3/5 male and 4/5 female rats that received 600 mg/kg and of 2/5 females that received 300 mg/kg were considered to be chemical related. The final mean body weight of rats that received 300 or 600 mg/kg was 14%-15% or 46% lower than that of vehicle controls. No compound-related deaths occurred in mice (doses up to 600 mg/kg). The final mean body weights of dosed and vehicle control mice were similar.

Thirteen-Week Studies: Most rats that received 300 mg/kg and 1/10 male and 2/10 female rats that received 200 mg/kg died early. The final mean body weight of male rats at 300 mg/kg was 31% lower than that of the vehicle controls. The liver weight to body weight ratios were increased in the 200 and 300 mg/kg groups of rats. Compound-related lesions occurred mainly in the kidney and included papillary necrosis, papillary edema, and multifocal mineralization.

Five of 10 male mice and 4/10 female mice that received 600 mg/kg died early. No other compound-related deaths occurred in mice. Final mean body weights of dosed and vehicle control mice were comparable. The liver weight to body weight ratios were increased for mice at 300 and 600 mg/kg. No compound-related histopathologic effects were observed in mice.

Body Weight and Survival in the Two-Year Studies: Two-year studies were conducted by administering 0, 50, or 100 mg/kg phenylbutazone in corn oil by gavage to groups of 50 rats of each sex, 5 days

per week for 103 weeks. The doses given groups of 50 mice of each sex on the same schedule were 0, 150, or 300 mg/kg. Mean body weights of high dose rats were generally 6%-11% lower than those of vehicle controls. Mean body weights of mice were similar among all groups except for high dose female mice, which weighed 4%-11% less than vehicle controls. The survival of all groups was similar except for that of the low dose group of male rats, which was significantly lower than that of the vehicle controls at the end of the studies; the survival of the top dose group of female rats and the vehicle control group of female mice was low but not statistically reduced (final survival--male rats: vehicle control, 33/50; low dose, 20/50; high dose, 27/50; female rats: 31/50; 35/50; 22/50; male mice: 36/50; 40/50; 36/50; female mice: 22/50; 29/50; 32/50).

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: Mild pyelonephritis, renal papillary necrosis, and mineralization of the renal papillae in dosed male and female rats and hyperplasia of the renal pelvis epithelium, dilatation of the renal pelvis, and renal cysts in dosed female rats were observed at increased incidences compared with those in vehicle controls. A renal tubular cell carcinoma was observed in one low dose male rat, and renal tubular cell adenomas were observed in three high dose male rats. A carcinoma of uncertain histogenesis was observed in one low dose female rat. Carcinomas of the renal transitional epithelium were seen in two high dose female rats. When the kidneys were step-sectioned, additional tubular cell adenomas were diagnosed in four low dose and one high dose male rats and in three low dose and one high dose female rats; none was observed in vehicle controls.

Papillomas of the transitional epithelium of the urinary bladder were seen in 2/43 low dose male and in 1/49 low dose female F344/N rats. The historical incidence of urinary bladder transitional cell neoplasms in male corn oil vehicle control F344/N rats is 5/2,034 (0.2%; highest observed incidence, 2/50) and 4/2,026 (0.2%; highest observed incidence, 1/45) in females.

Adrenal medullary hyperplasia was observed at an increased incidence in high dose female rats (vehicle control, 3/50; low dose, 6/50; high dose, 19/50).

Ulcers of the forestomach were observed at increased incidences in high dose rats (male: 0/50; 5/50; 6/50; female: 2/49; 1/49; 12/49). In high dose female rats, acanthosis (4/49; 0/49; 12/49), hyperkeratosis (3/49; 0/49; 12/49), and basal cell hyperplasia (4/49; 1/49; 12/49) of the forestomach were observed at increased incidences. No neoplasms were associated with these stomach lesions.

Peliosis hepatis, centrilobular cytomegaly and karyomegaly, fatty change, hepatocellular degeneration, and coagulative necrosis of the liver were observed in dosed male mice; clear cell foci were observed in five high dose male mice. The incidences of hepatocellular adenomas and adenomas or carcinomas (combined) in male mice were increased in the high dose group (adenomas or carcinomas, combined: 16/50; 14/50; 31/50).

Genetic Toxicology: Phenylbutazone was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested with or without exogenous metabolic activation. Phenylbutazone produced a positive response in the mouse lymphoma assay in both the presence and absence of activation. Phenylbutazone induced chromosomal aberrations in CHO cells in the presence, but not the absence, of exogenous metabolic activation; no induction of sister chromatid exchanges was observed in CHO cells in the presence or absence of activation.

Conclusions: Under the conditions of these 2-year gavage studies, there was *equivocal evidence of carcinogenic activity** of phenylbutazone for male F344/N rats, as shown by the occurrence of small numbers of renal tubular cell adenomas and carcinomas. There was *some evidence of carcinogenic activity* for female F344/N rats, as shown primarily by the occurrence of two rare transitional cell carcinomas in the top dose group; none has ever been seen in vehicle control or untreated control female rats. Tubular cell adenomas may have been associated with the administration of phenylbutazone to female rats. There was *some evidence of carcinogenic activity* for male B6C3F$_1$ mice, as shown by the increased incidence of hepatocellular adenomas or carcinomas (combined). There was *no evidence of carcinogenicity* for female B6C3F$_1$ mice administered phenylbutazone in corn oil by gavage at doses of 150 or 300 mg/kg.

Phenylbutazone was also nephrotoxic to rats, as shown by the dose-related increase in the severity of age-related nephropathy, necrosis of the renal papilla, and mineralization of the collecting ducts in the papilla.

SUMMARY OF THE TWO-YEAR GAVAGE STUDIES OF PHENYLBUTAZONE

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses			
0, 50, or 100 mg/kg phenylbutazone in corn oil 5 d/wk	0, 50, or 100 mg/kg phenylbutazone in corn oil 5 d/wk	0, 150, or 300 mg/kg phenylbutazone in corn oil 5 d/wk	0, 150, or 300 mg/kg phenylbutazone in corn oil 5 d/wk
Body weights in the 2-year study			
High dose lower than vehicle controls	High dose lower than vehicle controls	Dosed similar to vehicle controls	High dose lower than vehicle controls
Survival rates in the 2-year study			
33/50; 20/50; 27/50	31/50; 35/50; 22/50	36/50; 40/50; 36/50	22/50; 29/50; 32/50
Nonneoplastic effects			
Kidney: pyelonephritis, papillary necrosis, mineralization; forestomach: ulcers	Kidney: pyelonephritis, papillary necrosis, mineralization, dilatation of the renal pelvis, cysts; forestomach: ulcers, acanthosis, hyperkeratosis, basal cell hyperplasia	Liver: peliosis hepatis, cytomegaly, karyomegaly, degeneration, coagulative necrosis, fatty change	None
Neoplastic effects			
Single section: tubular cell adenomas of the kidney (0/50; 1/49; 3/50); combined single and step sections: tubular cell adenomas or carcinomas (combined) (0/50; 5/49; 4/50)	Single section: transitional epithelial carcinomas of the kidney (0/50; 0/50; 2/50); combined single and step sections: tubular cell adenomas (0/50; 3/50; 1/50)	Hepatocellular adenomas or carcinomas (combined) (16/50; 14/50; 31/50)	None
Level of evidence of carcinogenic activity			
Equivocal evidence	Some evidence	Some evidence	No evidence

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 6.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 9-10.

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 because of major flaws cannot be evaluated ("Inadequate Study"). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Reports series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following quintet is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either potency or mechanism.

- **Clear Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.

- **Some Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.

- **Equivocal Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related.

- **No Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.

- **Inadequate Study of Carcinogenic Activity** is demonstrated by studies that because of major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

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

- The adequacy of the experimental design and conduct;
- Occurrence of common versus uncommon neoplasia;
- Progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic 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);
- The presence or absence of dose relationships;
- The statistical significance of the observed tumor increase;
- The concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- Survival-adjusted analyses and false positive or false negative concerns;
- Structure-activity correlations; and
- In some cases, genetic toxicology.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Phenylbutazone is based on 13-week studies that began in July 1980 and ended in October 1980 and on 2-year studies that began in August 1981 and ended in September 1983 at EG&G Mason Research Institute (Worcester, MA).

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PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on phenylbutazone on March 13, 1989, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF PHENYLBUTAZONE

On March 13, 1989, the draft Technical Report on the toxicology and carcinogenesis studies of phenylbutazone received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. F.W. Kari, NIEHS, began the discussion by reviewing the experimental design, results, and proposed conclusions (equivocal evidence of carcinogenic activity for male rats; some evidence of carcinogenic activity for female rats; some evidence of carcinogenic activity for male mice; no evidence of carcinogenic activity for female mice).

Dr. Kari reported that kidneys from this and several other studies were step-sectioned to evaluate potential renal lesions more rigorously. In this special examination, additional tubular cell adenomas were diagnosed in four low dose and one high dose male rats and in three low dose and one high dose female rats. Kidney tumors were not observed in any of the vehicle control rats in either the single or multiple sections.

Dr. Ashby, a principal reviewer, agreed in principle with the conclusions. His major concern was that the small and variable numbers of different types of renal tumors in rats, along with the additional tumors observed after step-sectioning, made interpretation somewhat more complicated. Dr. J. Huff, NIEHS, emphasized that the kidney is clearly a target organ for toxicity in both laboratory animals and humans. In particular, Dr. Ashby found it difficult to distinguish equivocal evidence for male rats from some evidence for female rats. Regarding liver tumors, which were found at high concurrent and historical vehicle control incidences in male mice, Dr. Ashby was unconvinced that there was chemical induction of neoplasia. Dr. Kari responded that the liver was clearly a target organ and that the incidence observed in the high dose group was nearly double the concurrent vehicle control incidence and was outside the historical vehicle control range. Dr. Ashby stated that, from the available genetic toxicity data, phenylbutazone appeared to be a specific clastogen.

Dr. Lijinsky, the second principal reviewer, agreed with Dr. Ashby that the levels of evidence for male and female rats could have been the same or even reversed. He praised the decision to do additional step-sections of the kidney in rats. Dr. Kari commented that for renal tubular cell tumors in male rats, the statistical evaluation indicated marginal significance for both dose-response trend and pairwise comparisons. Although the additional sections uncovered neoplasms in dosed animals, the limited data base for step-sections did not enable drawing a clear relationship between tumor incidence and chemical exposure. For female rats, the level of some evidence was based on the occurrence of the two transitional cell carcinomas, neoplasms that have never been observed in nearly 2,100 vehicle control or in about 1,600 untreated control female rats. Dr. Huff mentioned that kidney tumors of any type in F344 rats are particularly uncommon. The incidence of liver neoplasms in high dose male mice compared with that in vehicle controls indicated only equivocal evidence in Dr. Lijinsky's view. He wondered whether the poor survival in high dose female rats might not have been due to gavage errors and questioned use of the gavage route and the choice of corn oil rather than water as the vehicle.

Dr. Garman, the third principal reviewer, agreed with the conclusions. He said that the photomicrographs of the renal neoplasms included in the Technical Report were quite helpful, especially in supporting the conclusion for female rats. He asked for more documentation in the Report as to specifics

of the Pathology Working Group process, in particular regarding organs examined and numbers within an organ group.

Further discussion centered primarily on the rat kidney tumors and the levels of evidence. Dr. J. Haseman, NIEHS, said that the historical control data base was used informally to support the level of evidence for female rats. Dr. S. Eustis, NIEHS, commented that the anaplastic carcinoma of apparent uncertain origin seen in the kidney of a low dose female rat was more likely of transitional cell than tubular cell origin. Dr. McKnight asked that a table be included in the text to report statistical significances for trend and pairwise comparisons of the composite incidences for renal tubular cell adenomas or carcinomas (combined) that were identified by both single- and step-section evaluations (page 35).

Dr. Ashby moved that the conclusion for male rats be accepted as written, equivocal evidence of carcinogenic activity. Dr. Garman seconded the motion, which was accepted unanimously. Dr. Ashby moved that the conclusion for female rats be accepted as written, some evidence of carcinogenic activity. Dr. Garman seconded the motion, which was accepted by seven affirmative votes (Drs. Ashby, Gallo, Garman, Klaassen, Lijinsky, Perera, and Popp) to three negative votes (Drs. Gold, McKnight, and Newberne). Dr. Ashby moved that the conclusion for male mice be changed to equivocal evidence of carcinogenic activity. Dr. Lijinsky seconded the motion, which was rejected by six panelists (Drs. Garman, Gold, Klaassen, McKnight, Perera, and Popp) to four (Drs. Ashby, Gallo, Lijinsky, and Newberne). Dr. Ashby then moved to accept the motion as written, some evidence of carcinogenic activity. Dr. Perera seconded the motion, which was accepted by eight panelists with two abstentions (Drs. Lijinsky and Newberne). Dr. Ashby moved that the conclusion for female mice be accepted as written, no evidence of carcinogenic activity. Dr. Gallo seconded the motion, which was accepted unanimously by the Panel.

I. INTRODUCTION

USE, PRODUCTION, AND PROPERTIES

METABOLISM

SYSTEMIC TOXICITY

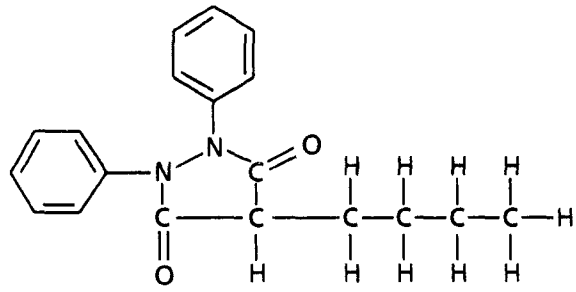
- Gastric Ulceration
- Nephrotoxicity
- Blood Dyscrasias in Human

GENETIC TOXICOLOGY

LONG-TERM TOXICITY AND CARCINOGENICITY

STUDY RATIONALE

I. INTRODUCTION



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USE, PRODUCTION, AND PROPERTIES

Phenylbutazone, first synthesized in 1914, was introduced in 1949 for the treatment of rheumatoid arthritis and related disorders for humans and was brought into the veterinary market in 1952. The antirheumatic and antiphlogistic properties of phenylbutazone result from potent nonsteroidal anti-inflammatory activity. Because of concerns about increased risks of aplastic anemia and agranulocytosis, its use in human medicine is now limited (Gilman et al., 1985). For example, the product license in the United Kingdom was revoked in 1984, and in the United States, physician labeling and contraindication warnings have been strengthened to reflect concerns regarding fatal blood dyscrasias (FDA Drug Bull., 1984; Am. Pharm., 1985). It has been estimated that in the United Kingdom, between 1964 and 1982, phenylbutazone caused 5.8 deaths per million prescriptions (Drug Ther. Bull., 1984).

Phenylbutazone is a white, crystalline, odorless powder; USP-grade phenylbutazone melts between 104° and 107° C (Ali, 1982). It is an enolic acid with lipophilic properties. The acidity is due to the presence of a dissociable proton on the carbon in the fourth position of the five-membered ring. The lipophilicity is attributable to the benzene rings and butyl group. It has a pK_a in water of 4.5-4.7 and an octanol/water partition coefficient of about 5.0. Since its solubility in water is low (Ali, 1982), most injectable preparations are alkaline solutions of the sodium salt (Faigle and Dieterle, 1977).

METABOLISM

Phenylbutazone binds avidly to serum proteins and is found in negligible quantities in saliva (Lambert and Kelly, 1978; Tobin et al., 1986). After administration of a single dose to humans (400 mg), the plasma concentration of unaltered drug is characterized by an early maximum of 36 µg/ml at 3 hours and by slow decay between 7 and 336 hours, corresponding to an elimination half-life of 88 hours (Hvidberg et al., 1974; Dieterle et al., 1976). Phenylbutazone is extensively metabolized before excretion. Studies in horses and rats indicate that less than 3% of an administered dose of phenylbutazone is excreted unchanged in the urine (Lees et al., 1983;

Alexander et al., 1985). Similar studies involving humans revealed that no detectable parent compound was excreted in the urine (Burns et al., 1953).

A generalized scheme for mammalian metabolism of phenylbutazone is depicted in Figure 1. Major metabolites that have been identified include oxyphenbutazone (ring hydroxylation), γ-hydroxyphenylbutazone (side-chain hydroxylation), γ-hydroxyoxyphenbutazone (dihydroxy metabolite), and 4-hydroxyphenylbutazone. In rats and horses, γ-hydroxyphenylbutazone represents a major (approximately 35%) metabolite and exists in two interchangeable forms: the lactone and the straight-chain forms. The production of the lactone form of γ-phenylbutazone requires cleavage of one of the amide bonds. The formation of this lactone isomer has been shown to be an insignificant reaction in humans (Faigle and Dieterle, 1977). Additional, but apparently minor, products of phenylbutazone oxidation include β-hydroxy- and γ-keto-derivatives of the parent compound (Wagner et al., 1971; McGilvery et al., 1974).

Phenylbutazone exists in solution in three forms--a diketo, an enol, and a mesomeric anion form. In solution, it exists primarily in the diketo form, and conversion between the forms is slow. These transformations probably contribute to its chemical instability and the ability of the cyclooxygenase system to generate the 4-hydroxyphenylbutazone metabolite (Reed et al., 1985) by a peroxide-dependent cooxygenation reaction. This reaction has been shown to produce reactive intermediates capable of inactivating prostacyclin synthase and prostaglandin H synthase, which may account for phenylbutazone's anti-inflammatory activity.

In addition to the primary metabolites, glucuronide/sulfate conjugates of these primary metabolites have been detected in varying proportions. No glucuronide metabolites have been reported in horses (Smith et al., 1985); in rats, approximately 35%-40% of the metabolites are excreted in the urine as conjugated metabolites (Alexander et al., 1985); in humans, conjugates represent about 50% of urinary metabolites (Dieterle et al., 1976).

SYSTEMIC TOXICITY

Gastric Ulceration

Mucosal ulceration resulting from phenylbutazone administration has been observed in rodents, dogs (Kirsner and Ford, 1955), horses, and humans. Signs of this have been most completely described in equine models. After administration to ponies, phenylbutazone (10 mg/kg per day for 14 days) induced ulceration of mucosal surfaces in the oral cavity, glandular stomach, and colon (MacAllister, 1983; Traub et al., 1983). In addition to confirming these lesions, Collins and Tyler (1985) reported that phenylbutazone caused central nervous system depression in foals. The administration of prostaglandin E_2 prevented the appearance of most of the signs of phenylbutazone toxicity.

Arai et al. (1985) found that, at doses that increased ulcer formation in rats (3-10 mg/kg), phenylbutazone also induced gastric acid secretion and reduced gastric mucosal prostaglandin content in a dose-dependent manner. Their evaluation of other drugs indicated that increased gastric acid secretion followed administration of vagal-mediated secretagogues, such as insulin and 2-deoxyglucose, but not peripheral secretagogues, such as gastrin and histamine. These findings led to the conclusion that phenylbutazone may influence gastric acid output by regulating vagus nerve activity. Other investigators showed that rats receiving phenylbutazone developed strong contractile activity in their stomachs, which led to ulceration. Surgical vagotomy or atropine administration prevented the contractile response to phenylbutazone, and these rats failed to develop ulceration even when their stomachs were perfused with acid. These findings suggest that the focal hemorrhagic lesions induced by the administration of phenylbutazone to rats result from mucosal compression secondary to passage of vagal-stimulated peristaltic waves and that gastric acid synergizes, but is not essential for, the observed mucosal erosion (Mersereau and Hinchey, 1981).

Nephrotoxicity

Administration of phenylbutazone (50-200 mg/kg) to rats and horses causes renal papillary

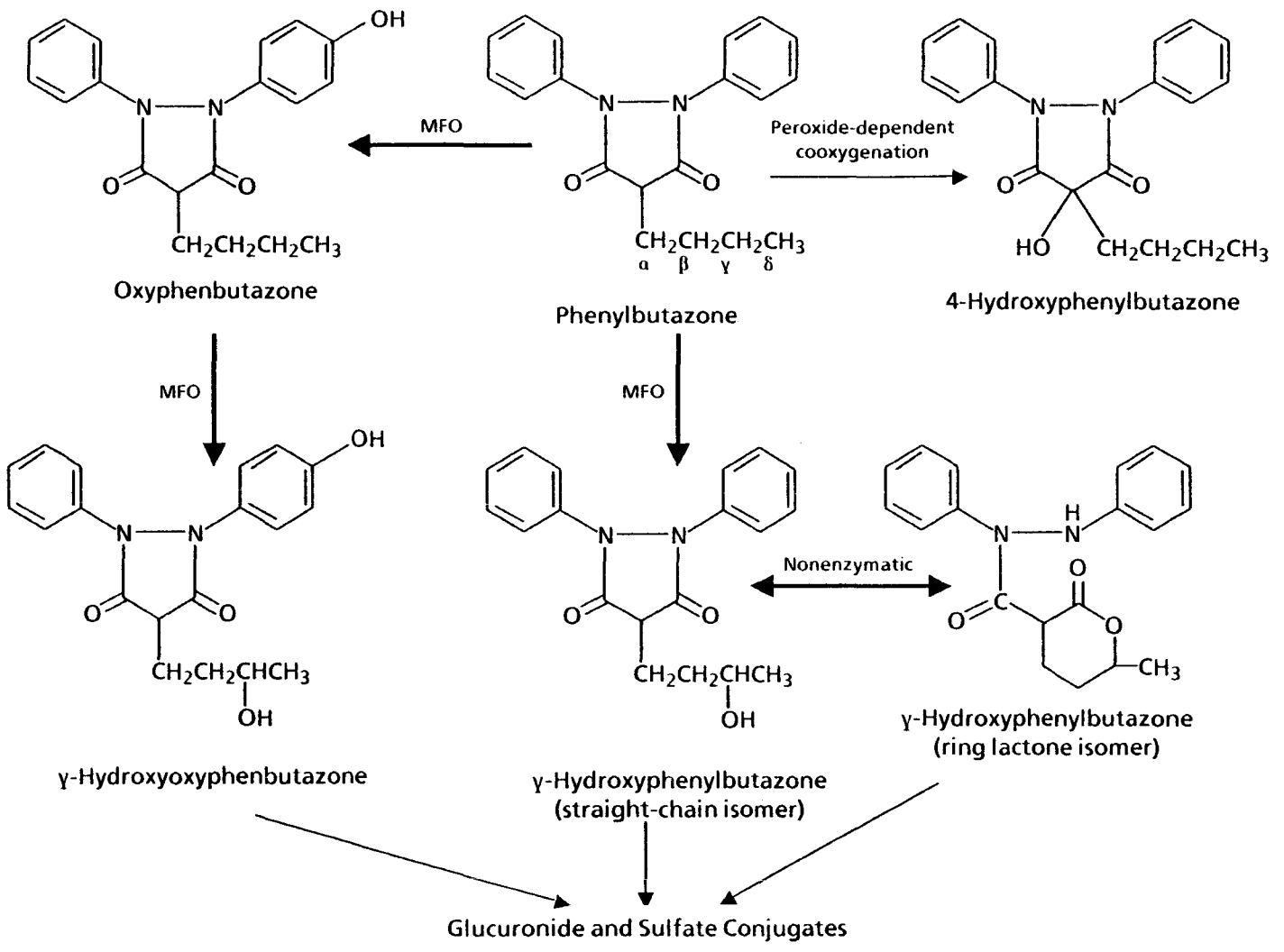

FIGURE 1. GENERALIZED METABOLISM OF PHENYLBUTAZONE

Generalization of metabolism from in vitro and in vivo studies with rats, horses, and humans; MFO = mixed function oxidase. Adapted from: Baake et al. (1974); Aarbakke et al. (1977); Lees et al. (1983); Alexander et al. (1985); Reed et al. (1985); and Tobin et al. (1986).

necrosis, progressive proteinuria, and concomitant hyperplastic changes in the collecting ducts (Arnold et al., 1976; Owen and Heywood, 1983). Acute renal papillary necrosis in horses given phenylbutazone is accentuated by water deprivation (Gunson and Soma, 1983). Similar lesions have been described in dogs and cats (Kincaid-Smith and Fiariley, 1971).

Blood Dyscrasias in Humans

Phenylbutazone has been shown to cause idiosyncratic bone marrow toxicity in some human patients. Although many of these reports are anecdotal and involve few observations, several large-scale clinical trials and epidemiologic investigations have confirmed these side effects in humans.

In a review of its efficacy for rheumatoid arthritis, Hazleton et al. (1953) noted that 47/140 patients receiving phenylbutazone experienced adverse side effects. Two of these patients developed anemia. A similar overall incidence of adverse effects was observed in a study of 188 patients with rheumatoid arthritis (Stevens et al., 1952). Of these, 31 (16%) were found to have thrombocytopenia. In 18 patients, anemia developed within 2 weeks. These abnormalities apparently regressed after the drug was withdrawn.

In a summary of data on 133 patients with phenylbutazone-induced blood dyscrasia, the incidence of fatal reactions was estimated to be 1 in 250,000 patient-months. The mortality was 100% in patients over 70 years old. Agranulocytosis was more common in the young, and aplastic anemia was more common in the elderly (Fowler, 1967).

Lymphocytes from rheumatoid arthritis patients undergoing phenylbutazone therapy have been evaluated cytogenetically. Significant increases in chromosomal aberrations were observed in patients treated with 300 mg/day for 3-7 months (Stevenson et al., 1971) or 600 mg/day by infusion for 10 days (Vormittag and Kolarz, 1979). For the infusion study, patients served as their own controls by having baseline chromosomal aberration frequencies established before treatment was begun. Other studies on the lymphocytes (Walker et al., 1975; Crippa et al., 1976) or bone marrow cells (Jensen, 1972) of these patients treated with phenylbutazone showed no increase in chromosomal aberrations over controls (typically, arthritic patients not previously exposed to phenylbutazone). The total doses of phenylbutazone to which patients were exposed in these negative studies were difficult to assess. Several confounding factors, including additional drug therapies, reliance on patients' reporting of medication intake, dosage differences, and diagnostic radiation exposure of the patients, limit the ability to interpret the data from these cited clinical studies.

GENETIC TOXICOLOGY

Phenylbutazone has undergone extensive testing for mutagenic activity. All reported tests for induction of gene mutation in various strains of Salmonella were negative for phenylbutazone, with or without exogenous metabolic activation (S9) (McCann et al., 1975; Sasaki et al., 1980; Ishidate et al., 1981). NTP-sponsored Salmonella tests with strains TA98, TA100, TA1535, and TA1537 were also negative, with and without S9 (Mortelmans et al., 1986; Table H1). No growth inhibition due to DNA damage was observed in *Bacillus subtilis* rec^-/rec^+, with or without S9; mutations were not induced by phenylbutazone in silkworms (Kawachi et al., 1980).

Positive results have been reported for phenylbutazone-induced chromosomal effects in mammalian cell cultures. Induction of chromosomal aberrations by phenylbutazone was reported in cultured hamster lung fibroblasts in the absence of S9 (Kawachi et al., 1980; Ishidate et al., 1981), in Chinese hamster ovary (CHO) cells in the presence of S9 (Galloway et al., 1987; Table H4), and in human lymphocyte cultures (Wissmuller and Gebhart, 1970), but not in human fibroblast cultures (Sasaki et al., 1980; Kawachi et al., 1980). The frequency of sister chromatid exchanges was not increased in CHO cells (Galloway et al., 1987; Table H3) or human fibroblasts (Sasaki et al., 1980; Kawachi et al., 1980) treated with phenylbutazone.

Phenylbutazone has been tested in several in vivo assays for clastogenicity. There is one positive report of induction of micronuclei in the bone marrow cells of Swiss albino mice given phenylbutazone orally or by intraperitoneal injection, with total doses of 75-200 mg/kg body weight (administered in two equal portions at 24-hour intervals; mice were killed 6 hours after the second administration) (Pentiah et al., 1980). All other reports were negative. A micronucleus test for induction of clastogenic damage in bone marrow polychromated erythrocytes (PCEs) of male BALB/c mice administered a dose of 400 mg/kg in a single intraperitoneal injection gave negative results (Charles and Leonard, 1978); this 400 mg/kg dose was higher than that used in the Pentiah et al. (1980) study. No induction of chromosomal aberrations was observed in bone marrow cells of mice (Charles and Leonard, 1978), hamsters (Muller and Strasser, 1972), or rats (Gebhart and Wissmuller, 1973; Kawachi et al., 1980) administered phenylbutazone. Spermatocytes from male mice administered phenylbutazone did not demonstrate an increase in chromosomal aberrations (Rathenberg and Muller, 1972; Charles and Leonard, 1978). No induction of dominant lethal mutations was detected in the germ cells of CLFP male mice given intraperitoneal injections of 100 mg/kg phenylbutazone (Machemer and Hess, 1971), in male BALB/c mice given intraperitoneal injections of 400 mg/kg phenylbutazone (Charles and Leonard, 1978), or in the ovum of female mice administered 400 mg/kg phenylbutazone orally at the time of estrus (Machemer and Hess, 1973).

Mutagenicity information is available on two compounds identified as metabolites of phenylbutazone, oxyphenbutazone (Varma, 1980) and γ-ketophenylbutazone (Smith et al., 1985). Both compounds, like phenylbutazone, were negative in bacterial studies for induction of gene mutation (McCann et al., 1975; Adam and Lim-Sylianco, 1976; Anderson and Styles, 1978; Simmon, 1979; Dayan et al., 1980; Florin et al., 1980; Chung et al., 1981; De Flora, 1981; Haworth et al., 1983). No cytogenetic data are available on these metabolites.

LONG-TERM TOXICITY AND CARCINOGENICITY

The long-term toxicity, carcinogenicity, and potential tumor-promoting effects of phenylbutazone were investigated in inbred DONRYU rats (Maekawa et al., 1987). In the carcinogenicity study, rats of each sex were fed diets containing 0, 1,250, or 2,500 ppm phenylbutazone for 2 years. Control groups of each sex contained 100 animals, and each dosed group contained 50 animals. In the female rats, dose-dependent positive trends were noted in the occurrence of leukemia, neoplastic nodules of the liver, and pheochromocytomas of the adrenal glands.

For the investigation of promoting effects, phenylbutazone was given as a dietary supplement (2,500 ppm) for 2 years subsequent to initiation with *N*-ethyl-*N*-nitrosourea (ENU; 15 ml/day of a 400-ppm solution for 4 weeks to 40 rats) or *N*-propyl-*N*-nitrosourea (PNU; a single gavage dose of 200 mg PNU/kg body weight to 80 rats) (Maekawa et al., 1987). After this exposure to the carcinogen, the groups were subdivided; half were maintained on a basal diet, and half were given a diet containing 2,500 ppm phenylbutazone for the next 104 weeks. In the rats given ENU and PNU, there were increased incidences of ovarian neoplasms, leukemia, renal neoplasms, gliomas, intestinal neoplasms, and cortical neoplasms; the incidences of these neoplasms were not increased by phenylbutazone exposure. A slight promoting effect, however, was demonstrated for renal and thyroid gland tumorigenesis.

STUDY RATIONALE

Phenylbutazone was selected for evaluation of long-term toxicity and carcinogenicity by the National Cancer Institute because of human exposure from medication and because of the lack of available data at the time these studies were begun. Gavage with corn oil suspensions was selected as the route of administration for the 2-year toxicity studies; bolus gavage doses mimic the route of human exposure to this drug.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF PHENYLBUTAZONE

CHARACTERIZATION OF DOSE MIXTURES

SINGLE-ADMINISTRATION STUDIES

NINETEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

- Study Design
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- Animal Maintenance
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II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF PHENYLBUTAZONE

Phenylbutazone (medicine NOIBN) was obtained in one lot (lot no. 62642) from the Ciba Geigy Corporation (Summit, NJ). Purity and identity analyses were conducted at Midwest Research Institute (Kansas City, MO) (Appendix G).

Lot no. 62642 was identified as phenylbutazone by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The lot was found to be greater than 99% pure, as determined by elemental analysis, Karl Fischer water analysis, a USP titration method using tetrabutylammonium hydroxide as the titrant, USP chloride and sulfate assays, thin-layer chromatography, and high-performance liquid chromatography.

The identity of the chemical at the study laboratory was confirmed by infrared spectroscopy. The stability of the bulk chemical was monitored by high-performance liquid chromatography. No deterioration of the study material was seen over the course of the studies.

CHARACTERIZATION OF DOSE MIXTURES

The 2-week stability of phenylbutazone mixed with NIH 07 Rat and Mouse Ration at 5,000 ppm and stored at temperatures ranging from −20° to 45° C was determined. The feed mixtures were extracted with a methanol/acetic acid solution (99:1) and analyzed by high-performance liquid chromatography with a μBondapak C_{18} column and ultraviolet detection at 254 nm. The formulated diets were found to be unstable at all storage temperatures; losses were 6% at 20° C, 8% at 5° C, 20% at room temperature, and 77% at 45° C.

Since the feed blends of phenylbutazone were found to be unstable and the chemical is only slightly soluble in water (less than 1 mg/ml), corn oil was chosen as the vehicle for a gavage study. Although the chemical is not significantly soluble in corn oil, suspensions suitable for gavage administration could be prepared at concentrations up to approximately 260 mg/ml. The 14-day stability of phenylbutazone/corn oil suspensions at 50 mg/ml, stored at room temperature or at 5° C, was determined. The suspensions were extracted with acetonitrile and analyzed by high-performance liquid chromatography with a μBondapak C_{18} column and ultraviolet detection at 254 nm. The phenylbutazone/corn oil suspensions were found to be stable for at least 14 days when stored in the dark at room temperature or at 5° C. During the studies, dose mixtures were stored for no longer than 2 weeks at 0° ± 5° C.

During the 2-year studies, the dose mixtures were analyzed at approximately 8-week intervals (Table G3). For the phenylbutazone studies, it is estimated that the mixtures were formulated within ±10% of the target concentrations approximately 98% (55/56) of the time throughout the studies. The one mixture that was found to be out of specifications was 112% of the target concentration. Results of periodic referee analysis performed by the analytical chemistry laboratory indicated generally good agreement with the results from the study laboratory (Table G4).

SINGLE-ADMINISTRATION STUDIES

Male and female F344/N rats were obtained from Harlan Industries, and male and female B6C3F_1 mice were obtained from Charles River Breeding Laboratories. Rats were observed for 14 days before the studies began, and mice were observed for 20 days.

Groups of five rats of each sex were fasted overnight and then were administered a single dose of 75, 150, 300, 600, or 1,200 mg/kg phenylbutazone in corn oil by gavage. Groups of five mice of each sex were fasted for 4 hours and then were administered a single dose of 150, 300, 600, 1,200, or 2,400 mg/kg. Controls were not used. Animals were observed one time per hour for 3 hours and then two times per day for 15 days. For rats, a necropsy was performed on one of each sex that received 75 mg/kg; on two of each sex that received 150, 300, or 1,200 mg/kg; and on three of each sex that received 600 mg/kg. For mice, a necropsy was performed on one of each sex that received 150, 300, or 600 mg/kg

and on one male and two females that received 1,200 or 2,400 mg/kg. Details of animal maintenance are presented in Table 1.

NINETEEN-DAY STUDIES

Male and female F344/N rats and $B6C3F_1$ mice were obtained from Charles River Breeding Laboratories and were held for 16 days before the studies began. The rats were 7 weeks old when placed on study, and the mice were 8-9 weeks old.

Groups of five rats and five mice of each sex were administered 0, 40, 80, 150, 300, or 600 mg/kg phenylbutazone in corn oil by gavage, 5 days per week for 12 doses over 19 days.

Animals were housed five per cage. Water and feed were available ad libitum. The rats and mice were observed two times per day and were weighed on days 1 and 7 and at the end of the studies. Details of animal maintenance are presented in Table 1. A necropsy was performed on all animals.

THIRTEEN-WEEK STUDIES

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

Four-week-old male and female F344/N rats and 5- to 6-week-old male and female $B6C3F_1$ mice were obtained from Harlan Industries, observed for 14 days, and then randomly assigned to dose groups. Rats were 6 weeks old when placed on study, and mice were 7-8 weeks old.

Groups of 10 rats of each sex were administered 0, 25, 50, 100, 200, or 300 mg/kg phenylbutazone in corn oil by gavage, 5 days per week for 13 weeks. Groups of 10 mice of each sex were administered 0, 40, 80, 150, 300, or 600 mg/kg phenylbutazone in corn oil by gavage, 5 days per week for 13 weeks.

Rats and mice were housed five per cage. Feed and water were available ad libitum. Further experimental details are summarized in Table 1. Animals were observed two times per day; moribund animals were killed. Individual animal weights were recorded once per week.

At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Histologic examinations were performed on all vehicle controls, rats in the 100 and 200 mg/kg groups, rats in the 300 mg/kg groups that died before the end of the studies, and mice in the 300 and 600 mg/kg groups. Tissues examined are listed in Table 1. The liver of all animals was weighed at necropsy.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats of each sex were administered 0, 50, or 100 mg/kg phenylbutazone in corn oil by gavage, 5 days per week for 103 weeks. Groups of 50 mice of each sex were administered 0, 150, or 300 mg/kg on the same schedule. On March 29, 1983 (month 19 of this study), 18 male rat vehicle controls were mistakenly given the 100 mg/kg dose mixture.

Source and Specifications of Animals

The male and female F344/N rats and $B6C3F_1$ (C57BL/6N, female $\times$ C3H/HeN MTV^-, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Animals were shipped to the study laboratory at 4-5 weeks of age. The animals were quarantined at the study laboratory for 3 weeks. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats were placed on study at 7-8 weeks of age and the mice at 7 weeks of age. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix E).

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF PHENYLBUTAZONE

Single-Administration Studies	Nineteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN			
Size of Study Groups			
5 males and 5 females of each species	5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses			
Rats--75, 150, 300, 600, or 1,200 mg/kg phenylbutazone in corn oil by gavage; dose vol--5 ml/kg; mice--150, 300, 600, 1,200, or 2,400 mg/kg; dose vol--10 ml/kg	0, 40, 80, 150, 300, or 600 mg/kg phenylbutazone in corn oil by gavage; dose vol--rats: 5 ml/kg; mice: 10 ml/kg	Rats--0, 25, 50, 100, 200, or 300 mg/kg phenylbutazone in corn oil by gavage; dose vol--5 ml/kg; mice--0, 40, 80, 150, 300, or 600 mg/kg; dose vol--10 ml/kg	Rats--0, 50, or 100 mg/kg phenylbutazone in corn oil by gavage; dose vol--5 ml/kg; mice--0, 150, or 300 mg/kg; dose vol--10 ml/kg
Date of First Dose			
Rats--3/13/80; mice--2/26/80	5/2/80	7/24/80	Rats--9/9/81; mice--8/25/81
Date of Last Dose			
N/A	5/20/80	10/22/80	Rats--8/30/83; mice--8/15/83
Duration of Dosing			
Single dose	12 doses over 19 d	5 d/wk for 13 wk	5 d/wk for 103 wk
Type and Frequency of Observation			
Observed 1 × h for the first 3 h and 2 × d thereafter; weighed at the start and end of the studies	Observed 2 × d; weighed initially and 1 × wk thereafter	Observed 2 × d; weighed initially and 1 × wk thereafter	Observed 2 × d; weighed initially, 1 × wk for 12 wk, and 1 × mo thereafter
Necropsy and Histologic Examinations			
Rats--necropsy performed on 1 male and 1 female in the 75 mg/kg groups, 2 males and 2 females in the 150, 300, and 1,200 mg/kg groups, and 3 males and 3 females in the 600 mg/kg groups; mice--necropsy performed on 1 male and 1 female in the 150, 300, and 600 mg/kg groups and on 1 male and 2 females in the 1,200 and 2,400 mg/kg groups	Necropsy performed on all animals; histologic exams not performed	Necropsy performed on all animals; histologic exams performed on all vehicle controls, rats in the 100 and 200 mg/kg groups, rats in the 300 mg/kg groups dying before the end of the studies, and mice in the 300 and 600 mg/kg groups; the following tissues were examined: adrenal glands, brain, colon, esophagus, eyes (if grossly abnormal), femur, gallbladder (mice), gross lesions, heart, kidneys, liver, lungs and bronchi, mammary gland, mandibular lymph nodes, pancreas, parathyroid glands, pituitary gland, prostate/testes or ovaries/uterus, salivary glands, skin, small intestine, spinal cord (if neurologic signs present), spleen, sternebrae, stomach, thymus, thyroid gland, tissue masses, trachea, and urinary bladder; liver, mandibular and mesenteric lymph nodes, spleen, testes, and thymus were examined in rats in the 100 mg/kg groups. Liver of all animals was weighed at necropsy	Necropsy performed on all animals; the following tissues examined histologically for vehicle control and high dose groups: adrenal glands, bone marrow, brain, colon, costochondral junction, duodenum, esophagus, gallbladder (mice), heart, ileum, jejunum, kidneys, larynx, liver, lungs and bronchi, mammary gland, mandibular and mesenteric lymph nodes, pancreas, parathyroid glands, pituitary gland, prostate/testes/seminal vesicles or ovaries/uterus, salivary glands, spleen, stomach, thymus, thyroid gland, tissue masses with abnormal regional lymph nodes, trachea, and urinary bladder. The following tissues from low dose animals were examined: male rats--adrenal glands, epididymis, kidneys, liver, stomach, and testes; female rats--adrenal glands, kidneys, pituitary gland, spleen, stomach, thyroid gland, and urinary bladder; male mice--kidneys and liver; female mice--kidneys, liver, ovaries, and uterus

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF PHENYLBUTAZONE (Continued)

Single-Administration Studies	Nineteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE			
Strain and Species			
F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice
Animal Source			
Rats--Harlan Industries (Indianapolis, IN); mice--Charles River Breeding Laboratories (Kingston, NY)	Charles River Breeding Laboratories (Kingston, NY)	Harlan Industries (Indianapolis, IN)	Charles River Breeding Laboratories (Kingston, NY)
Study Laboratory			
EG&G Mason Research Institute	EG&G Mason Research Institute	EG&G Mason Research Institute	EG&G Mason Research Institute
Method of Animal Identification			
Ear punch	Ear punch	Ear punch	Ear punch
Time Held Before Study			
Rats--14 d; mice--20 d	16 d	14 d	Rats--20 d; mice--19 d
Age When Placed on Study			
8 wk	Rats-- 7 wk; mice--8-9 wk	Rats--6 wk; mice--7-8 wk	Rats--7-8 wk; mice--7 wk
Age When Killed			
10 wk	Rats--10-11 wk; mice--11-13 wk	Rats--19-20 wk; mice--21-22 wk	Rats--110-111 wk; mice--113-114 wk
Necropsy Dates			
Rats--3/27/80; mice--3/11/80	Rats--5/21/80-5/28/80; mice--5/21/80-5/27/80	Rats--10/23/80-10/30/80; mice--10/24/80-10/29/80	Rats--9/7/83-9/15/83; mice--8/23/83-9/1/83
Method of Animal Distribution			
Assigned to groups such that for a given sex and species all cage weights were approximately equal	Same as single-administration studies	Same as single-administration studies	Animals assigned to cages and cages to groups according to a table of random numbers
Diet			
NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Bedding			
Aspen Bed (American Excelsior, Baltimore, MD)	Same as single-administration studies	Same as single-administration studies or Beta Chips hardwood chips (Agway, Inc., Syracuse, NY)	Aspen Bed heat-treated hardwood chips (American Excelsior Co., Baltimore, MD)
Water			
Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as single-administration studies; tap water filtered through an inline 5-μ filter	Same as single-administration studies	Same as 19-d studies
Cages			
Polycarbonate (Lab Products, Inc., Rochelle Park, NJ)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF PHENYLBUTAZONE (Continued)

Single-Administration Studies	Nineteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)			
Cage Filters			
Nonwoven fiber filters (Lab Products, Inc., Rochelle Park, NJ)	Same as single-administration studies	Nonwoven fiber filters (Snow Filtration, Cincinnati, OH)	Same as 13-wk studies
Animals per Cage			
5	5	5	5
Other Chemicals on Study in the Same Room			
None	None	None	None
Animal Room Environment			
Temp--21°-24° C; hum--31%-58%; fluorescent light 12 h/d; 10-12 room air changes/h	Temp--24°-27° C; hum--47%-78%; fluorescent light 12 h/d; 10-12 room air changes/h	Temp--average, 23° C, range, 20°- 27° C; hum--average, 73%, range, 50%-79%; fluorescent light 12 h/d; 10-12 room air changes/h	Temp--average, 23° C, range, 20°-27° C; hum--average, 44.8%, range, 0%-65%; fluorescent light 12 h/d; 10-12 (average 11.3) room air changes/h

A quality control skin grafting program has been in effect since early 1978 to monitor the genetic integrity of the inbred mice used to produce the hybrid B6C3F$_1$ study animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic integrity via isozyme and protein electrophoresis profiles that demonstrate phenotype expressions of known genetic loci.

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

Male mice from the C3H colony and female mice from the C57BL/6N colony were used as parents for the hybrid B6C3F$_1$ mice used in these studies. The influence of the potential genetic nonuniformity in the hybrid mice on these results is not known, but results of the studies are not affected because concurrent controls were included in each study.

Animal Maintenance

Animals were housed five per cage. Feed (Appendix F) and water were available ad libitum. Cages were not rotated during these studies. Sentinel animals were housed on the top of the racks, vehicle control animals were housed on the next two levels, low dose animals on the middle two levels, and high dose animals on the lower two levels. Further details of animal maintenance are given in Table 1.

Clinical Examinations and Pathology

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

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Histopathologic examination of tissues was performed according to an "inverse pyramid" design (McConnell, 1983a,b). That is, complete histopathologic examinations (Table 1) were performed on all high dose and vehicle control animals and on low dose animals dying before the end of the study. In addition, histopathologic examinations were performed on all grossly visible lesions in all dose groups. Potential target organs for chemically related neoplastic and nonneoplastic effects were identified from the short-term studies or the literature and were determined by examination of the pathology data; these target organs/tissues in the lower dose group were examined histopathologically. If mortality in the highest dose group exceeded that in the vehicle control group by 15%, complete histopathologic examinations were performed on all animals in the second highest dose group in addition to those in the high dose group.

When the pathology evaluation was completed by the laboratory pathologist and the pathology data entered into the Toxicology Data Management System, the slides, paraffin blocks, and residual formalin-fixed tissues were sent to the NTP Archives. The slides, blocks, and residual wet tissues were audited for accuracy of labeling and animal identification and for thoroughness of tissue trimming. The slides, individual animal necropsy records, and pathology tables were sent to an independent pathology quality assessment laboratory. The individual animal records and pathology tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tissues with a tumor diagnosis, all potential target tissues, and all tissues from a randomly selected 10% of the animals were re-evaluated microscopically by a quality assessment pathologist. Nonneoplastic lesions were evaluated for accuracy and consistency of diagnosis only in the potential target organs, the randomly selected 10% of animals, and in tissues with unusual incidence patterns or trends. Tissues are generally not evaluated in a "blinded" fashion (i.e., without knowledge of dose group) unless the lesions in question are subtle.

The quality assessment report and slides were submitted to a Pathology Working Group (PWG) Chairperson, who reviewed microscopically all potential target tissues and any other 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 shown to the PWG. The PWG, which included the laboratory pathologist, the quality assessment pathologist, and other pathologists experienced in rodent toxicology, 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 diagnosis was changed to reflect the opinion of the PWG. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final pathology data represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Prior to the PWG meeting, the chairperson selected a subset of 83 slides from the studies in rats for review. These included unresolved differences of opinion regarding diagnoses of neoplasms in nontarget organs and representative examples of neoplastic and nonneoplastic lesions in target tissues. In male rats, organs considered for evaluation included the kidney, urinary bladder, liver, stomach, and thyroid gland. Organs of female rats included the kidney, stomach, urinary bladder, and adrenal medulla.

Similarly, for the studies in mice, a subset of slides representing target organs and selected lesions were reviewed. For male mice, these included the liver, pituitary gland, coagulation gland, lungs, and kidneys. For females, slides of the liver and kidneys were reviewed.

Statistical Methods

Survival Analyses: The probability of survival was estimated by the product-limit procedure of

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

Calculation of Incidence: The incidence of neoplastic or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators include only those animals for which the site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) prior to histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Tumor Incidence: 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 vehicle 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 vehicle 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. (For further discussion of these statistical methods, see Haseman, 1984.)

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

III. RESULTS

RATS

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MICE

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III. RESULTS: RATS

SINGLE-ADMINISTRATION STUDIES

All rats that received 1,200 mg/kg phenylbutazone and 3/5 males and 2/5 females that received 600 mg/kg died on the first day (Table 2).

NINETEEN-DAY STUDIES

Four of five males and 5/5 females that received 600 mg/kg, 2/5 females that received 300 mg/kg, and 1/5 females that received 150 mg/kg died before the end of the studies (Table 3). The death at 150 mg/kg and the deaths of one male and one female that received 600 mg/kg were related to the gavage procedure. The final mean body weight of males that received 300 or 600 mg/kg was 14% or 46% lower than that of vehicle controls. The final mean body weight of females that received 300 mg/kg was 15% lower than that of vehicle controls.

THIRTEEN-WEEK STUDIES

Seven of 10 male rats and 8/10 female rats that received 300 mg/kg and 1/10 male and 2/10 female rats that received 200 mg/kg died before the end of the studies (Table 4). The final mean body weight of rats that received 200 or 300 mg/kg was 8% or 31% lower than that of vehicle controls for males and 12% or 13% lower for females. The liver weight to body weight ratios were significantly increased in the 200 and 300 mg/kg groups (Table 5). Compound-related clinical signs at 200 or 300 mg/kg included diarrhea, unkempt fur, a red exudate around the eyes, and decreased activity. Renal papillary necrosis, papillary edema, and multifocal mineralization were observed at increased incidences in dosed rats (Table 6); the severity of mineralization increased with increased dose. Testicular degeneration was observed in 4/6 males that received 300 mg/kg, 2/10 males that received 200 mg/kg,

TABLE 2. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF PHENYLBUTAZONE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)
MALE (d)				
75	5/5	108 ± 4	170 ± 7	+62 ± 3
150	5/5	108 ± 4	159 ± 5	+51 ± 2
300	5/5	108 ± 3	160 ± 7	+52 ± 5
600	(e) 2/5	108 ± 3	135 ± 22	+26 ± 27
1,200	(e) 0/5	108 ± 3	(f)	(f)
FEMALE (d)				
75	5/5	93 ± 2	127 ± 1	+34 ± 1
150	5/5	93 ± 2	124 ± 5	+31 ± 5
300	5/5	93 ± 1	114 ± 3	+21 ± 3
600	(g) 2/5	92 ± 3	111 ± 5	+21 ± 12
1,200	(e) 0/5	92 ± 1	(f)	(f)

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) LD_{50} by the Spearman-Karber procedure: 600 mg/kg with a 95% confidence interval of 401-781 mg/kg
(e) Day of death: all 1
(f) No data are reported due to 100% mortality in this group.
(g) Day of death: 1,1,2

TABLE 3. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE NINETEEN-DAY GAVAGE STUDIES OF PHENYLBUTAZONE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	145 ± 2	214 ± 6	+69 ± 5	
40	5/5	146 ± 2	217 ± 6	+71 ± 5	101
80	5/5	145 ± 5	222 ± 9	+77 ± 9	104
150	5/5	144 ± 3	206 ± 4	+62 ± 4	96
300	5/5	146 ± 1	184 ± 11	+38 ± 10	86
600	(d) 1/5	145 ± 8	116	−44	54
FEMALE					
0	5/5	119 ± 2	157 ± 3	+38 ± 4	
40	5/5	119 ± 2	162 ± 4	+43 ± 4	103
80	5/5	119 ± 2	154 ± 4	+35 ± 2	98
150	(e) 4/5	120 ± 2	155 ± 3	+37 ± 2	99
300	(f) 3/5	121 ± 2	134 ± 14	+12 ± 11	85
600	(g) 0/5	119 ± 2	(h)	(h)	(g)

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Day of death: 2,6,13; one death was due to gavage accident.
(e) Death was due to gavage accident.
(f) Day of death: all 3
(g) Day of death: 2,2,4,20 (day of scheduled necropsy); one death was due to gavage accident.
(h) No data are reported due to 100% mortality in this group.

TABLE 4. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF PHENYLBUTAZONE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final (c)	Change (d)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	117 ± 3	306 ± 5	+189 ± 5	
25	10/10	118 ± 3	319 ± 4	+201 ± 5	104
50	10/10	118 ± 3	322 ± 4	+204 ± 4	105
100	10/10	116 ± 3	313 ± 6	+197 ± 7	102
200	(e) 9/10	115 ± 3	280 ± 7	+164 ± 6	92
300	(f) 3/10	116 ± 3	211 ± 13	+103 ± 11	69
FEMALE					
0	10/10	98 ± 2	198 ± 4	+100 ± 4	
25	10/10	98 ± 2	193 ± 4	+95 ± 3	97
50	10/10	97 ± 2	188 ± 3	+91 ± 3	95
100	10/10	97 ± 2	192 ± 4	+95 ± 4	97
200	(g) 8/10	97 ± 2	175 ± 3	+76 ± 4	88
300	(h) 2/10	98 ± 2	173 ± 10	+72 ± 10	87

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Final body weights are those taken at week 12.
(d) Mean body weight change of the survivors ± standard error of the mean
(e) Week of death: 5
(f) Week of death: 1,3,3,7,7,7,9
(g) Week of death: 1,12
(h) Week of death: 1,2,2,3,4,5,7,7

TABLE 5. ANALYSIS OF LIVER WEIGHTS FOR RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF PHENYLBUTAZONE (a)

Dose (mg/kg)	Number Weighed	Necropsy Body Weight (grams)	Liver Weight (mg)	Liver Weight/ Necropsy Body Weight (mg/g)
MALE				
0	10	318.1 ± 5.93	13,490 ± 702	42.3 ± 1.73
25	10	327.0 ± 3.87	13,597 ± 298	41.6 ± 0.75
50	(b) 9	332.0 ± 3.63	13,877 ± 379	42.0 ± 2.22
100	10	316.5 ± 6.62	14,488 ± 564	45.7 ± 1.29
200	9	**289.7 ± 6.56	**15,949 ± 634	**54.9 ± 1.22
300	3	**202.7 ± 1.59	14,493 ± 499	**72.3 ± 5.31
FEMALE				
0	10	198.1 ± 4.40	7,531 ± 245	38.1 ± 1.25
25	10	195.8 ± 3.48	7,168 ± 131	36.7 ± 0.65
50	10	190.2 ± 3.79	7,593 ± 256	39.9 ± 0.80
100	10	195.7 ± 3.87	8,036 ± 274	41.0 ± 0.84
200	8	*181.2 ± 3.50	**10,983 ± 351	**60.6 ± 1.26
300	2	*170.8 ± 6.70	**12,685 ± 235	**74.4 ± 4.30

(a) Mean ± standard error; P values vs. the vehicle controls by Dunnett's test (Dunnett, 1955).
(b) One body weight not taken; ratio represents nine animals.
*P<0.05
**P<0.01

TABLE 6. NUMBERS OF RATS WITH SELECTED RENAL LESIONS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF PHENYLBUTAZONE

Lesion	Male					Female					
	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	300 mg/kg	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg	300 mg/kg
Number examined	10	10	10	10	7	10	10	10	10	10	8
Papillary edema	0	0	5	0	0	0	0	5	3	2	1
Multifocal mineralization	1	1	2	9	4	0	0	4	7	10	6
Papillary necrosis	0	0	1	3	3	0	0	0	2	3	3

and 1/10 males that received 100 mg/kg. Lymphoid depletion of the thymus, spleen, mesenteric lymph node, or mandibular lymph node was seen in 6/7 males and 6/8 females that received 300 mg/kg and 1/10 males and 1/10 females that received 200 mg/kg but in none of the vehicle controls. Lymphoid depletion was observed only in rats that died before the end of the studies.

Dose Selection Rationale: Based on the incidences of deaths and kidney lesions observed at 200 and 300 mg/kg, doses selected for rats for the 2-year studies were 50 and 100 mg/kg phenylbutazone administered in corn oil by gavage 5 days per week.

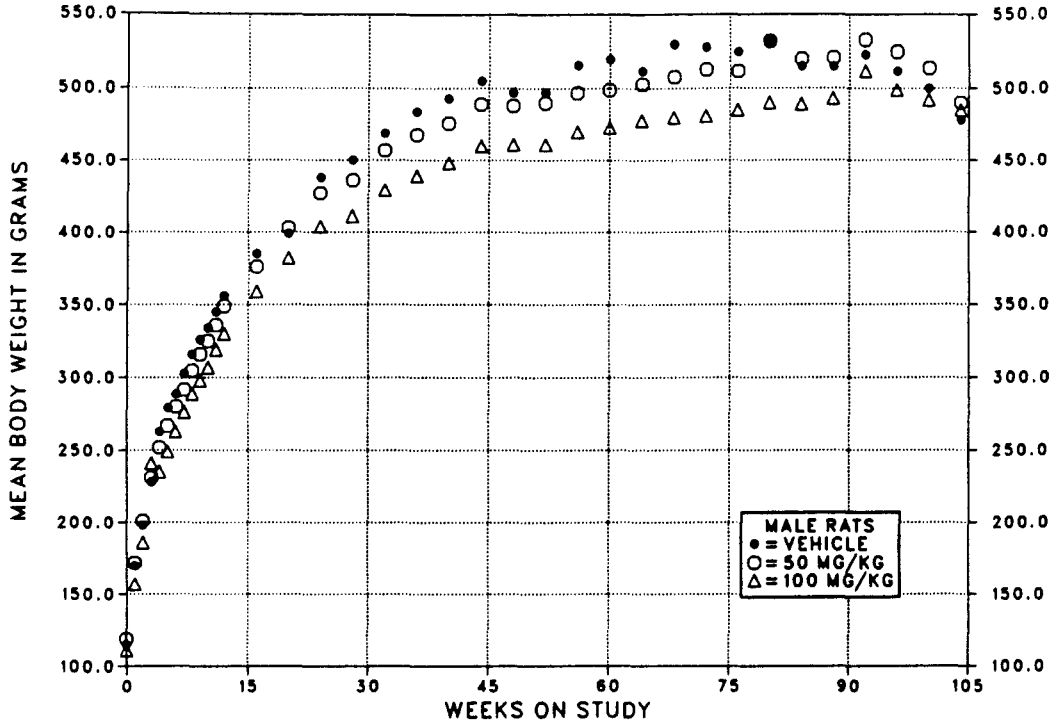
TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male rats were generally 7%-11% lower than those of vehicle controls between week 4 and week 80 (Table 7 and Figure 2). Mean body weights of high dose female rats were 6%-10% lower than those of vehicle controls between week 56 and the end of the study. No compound-related clinical signs were seen.

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

Weeks on Study	Vehicle Control		50 mg/kg			100 mg/kg		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors
MALE								
0	115	50	119	103	50	111	97	50
1	170	50	172	101	50	157	92	50
2	198	50	201	102	50	186	94	50
3	228	50	231	101	50	241	106	50
4	263	50	252	96	50	235	89	50
5	279	50	267	96	50	249	89	50
6	289	50	280	97	50	263	91	50
7	303	50	292	96	50	276	91	50
8	316	50	305	97	50	289	91	50
9	326	50	316	97	50	298	91	50
10	334	50	325	97	50	307	92	50
11	345	50	336	97	50	319	92	50
12	356	50	349	98	50	330	93	50
16	385	50	376	98	50	359	93	50
20	399	50	403	101	50	382	96	50
24	438	50	427	97	50	404	92	50
28	450	50	436	97	50	411	91	50
32	469	50	457	97	50	429	91	50
36	484	50	468	97	50	439	91	50
40	493	50	476	97	50	448	91	50
44	505	50	489	97	49	460	91	50
48	497	50	488	98	49	461	93	50
52	497	50	490	99	49	461	93	50
56	516	50	497	96	48	470	91	50
60	520	50	499	96	48	473	91	50
64	512	50	503	98	47	478	93	50
68	530	49	508	96	46	480	91	50
72	528	49	513	97	46	481	91	48
76	525	46	512	98	45	485	92	46
80	532	46	532	100	43	490	92	45
84	515	46	520	101	41	489	95	41
88	515	41	521	101	36	493	96	40
92	523	38	533	102	29	512	98	38
96	512	36	525	103	26	499	97	37
100	500	33	514	103	24	492	98	34
104	478	33	490	103	20	485	101	27
FEMALE								
0	102	50	104	102	50	104	102	50
1	134	50	132	99	50	126	94	50
2	142	50	144	101	50	142	100	50
3	154	50	154	100	50	156	101	50
4	162	50	162	100	50	164	101	50
5	168	50	168	100	50	171	102	50
6	175	50	176	101	50	177	101	50
7	179	50	179	100	50	181	101	50
8	184	50	185	101	50	186	101	50
9	187	50	189	101	50	188	101	50
10	190	50	191	101	50	189	99	50
11	193	50	196	102	50	194	101	50
12	197	50	200	102	50	197	100	50
16	207	50	207	100	50	204	99	50
20	215	50	216	100	50	212	99	49
24	225	50	223	99	50	222	99	49
28	233	50	232	100	50	231	99	49
32	241	49	238	99	50	239	99	49
36	243	49	239	98	50	235	97	49
40	253	49	248	98	50	245	97	49
44	263	49	256	97	49	253	96	49
48	266	49	261	98	48	255	96	49
52	271	49	272	100	47	266	98	49
56	286	49	278	97	46	265	93	49
60	296	49	289	98	46	277	94	48
64	306	48	299	98	46	283	92	48
68	318	48	308	97	46	290	91	48
72	322	46	320	99	46	298	93	45
76	334	44	329	99	46	309	93	41
80	343	43	340	99	45	310	90	40
84	348	43	346	99	44	317	91	36
88	351	42	350	100	44	326	93	34
92	367	39	362	99	43	339	92	32
96	361	37	364	101	41	332	92	27
100	365	34	361	99	37	329	90	27
104	364	31	364	100	35	327	90	22



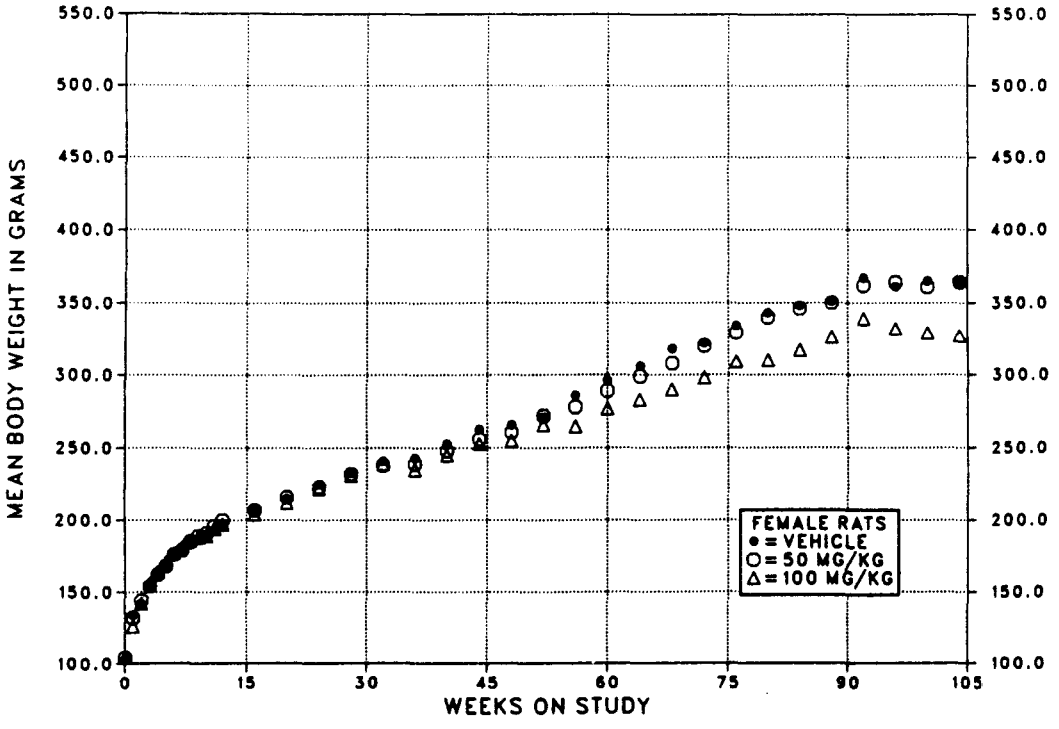


FIGURE 2. GROWTH CURVES FOR RATS ADMINISTERED PHENYLBUTAZONE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats administered phenylbutazone at the doses used in these studies and for vehicle controls are shown in Table 8 and in the Kaplan and Meier curves in Figure 3. The survival of the low dose group of male rats was significantly lower than that of the vehicle controls after day 725. No other significant differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the kidney, urinary bladder, adrenal gland, forestomach, lung, and mammary gland.

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 animal group, and historical control incidences for the neoplasms mentioned in this section are presented in Appendixes A and B for male and female rats, respectively.

Kidney: A spectrum of nonneoplastic toxic lesions occurred in the kidney of male and female rats given phenylbutazone, including a dose-related increase in the severity of the aging-related nephropathy (Table 9), necrosis of the papilla, mineralization (Figure 4) of the collecting tubules in the papilla (Table 10), and acute inflammation of the proximal convoluted tubules (pyelonephritis) (male: vehicle control, 6/50; low dose, 13/49; high dose, 27/50; female: 2/50; 4/50; 26/50). The nephropathy consisted of degeneration of renal tubular epithelium in the cortex with atrophy and dilation of the tubules, formation of hyaline and granular casts, regeneration of the tubular epithelium, interstitial fibrosis, and glomerulosclerosis. The less severe stages of papillary necrosis were characterized

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

	Vehicle Control	50 mg/kg	100 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Natural deaths	6	16	7
Moribund kills	11	13	16
Animals surviving until study termination	33	20	27
Killed accidentally	0	1	0
Survival P values (b)	0.374	0.025	0.385
FEMALE (a)			
Animals initially in study	50	50	50
Natural deaths	5	5	15
Moribund kills	14	9	14
Animals surviving until study termination	31	35	(c) 21
Killed accidentally	0	1	0
Survival P values (b)	0.066	0.389	0.091

(a) First day of termination period: male--730; female--732
(b) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.
(c) Number killed at study termination; one animal died or was killed in a moribund condition during the termination period and was combined, for statistical purposes, with those killed at termination.

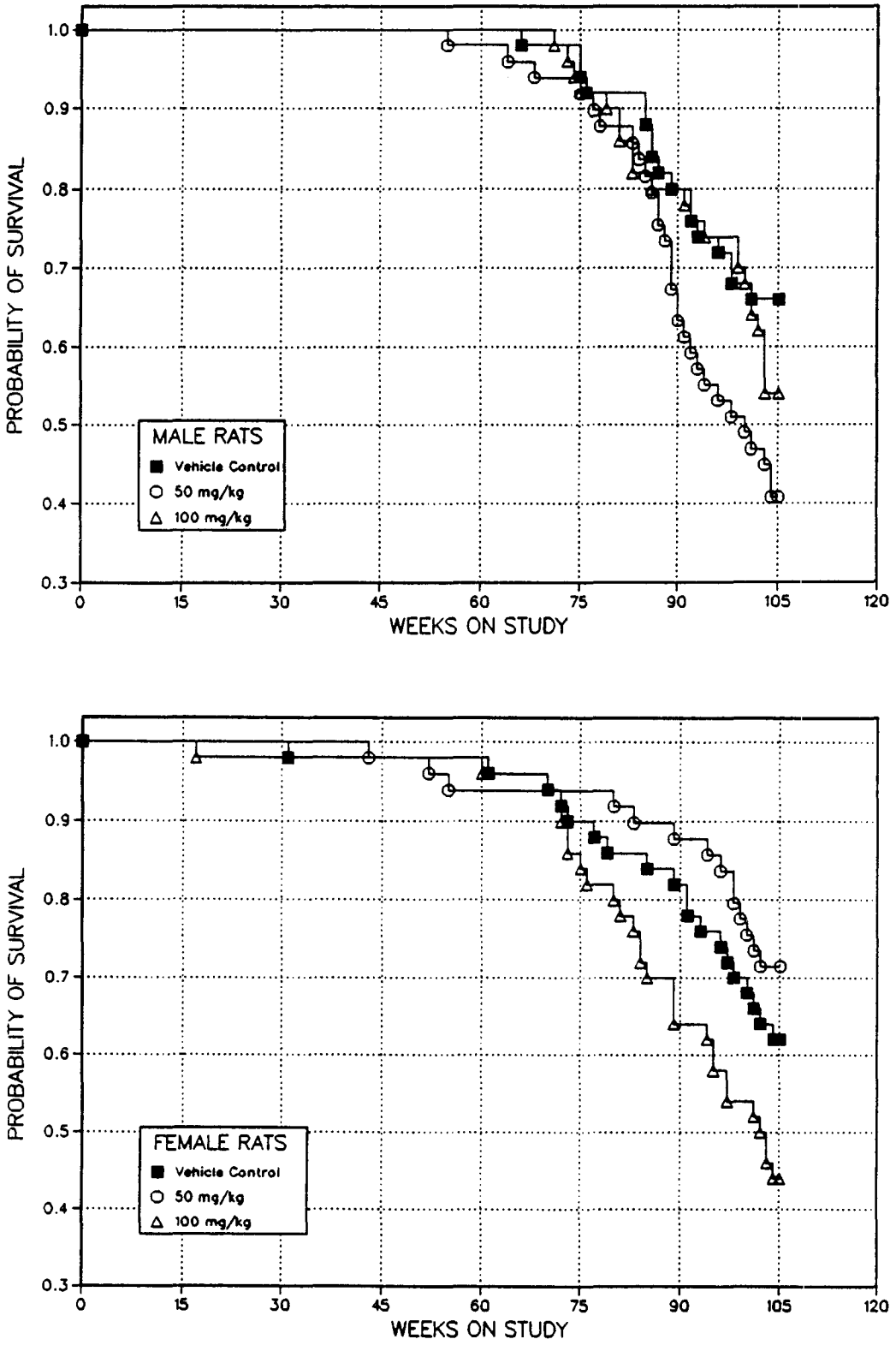


FIGURE 3. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED PHENYLBUTAZONE IN CORN OIL BY GAVAGE FOR TWO YEARS

TABLE 9. INCIDENCES AND SEVERITY OF NEPHROPATHY IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF PHENYLBUTAZONE

Nephropathy	Male			Female		
	Vehicle Control	50 mg/kg	100 mg/kg	Vehicle Control	50 mg/kg	100 mg/kg
Incidence of nephropathy	49/50	49/49	50/50	38/50	46/50	47/50
Severity (a)						
None	1	0	0	12	4	3
Minimal	11	6	5	22	11	1
Mild	25	19	11	14	19	6
Moderate	9	12	15	2	16	17
Marked	4	12	19	0	0	23
Mean severity (b)	2.08	**2.61	**2.96	1.12	**1.94	**3.12

(a) Number of animals with indicated severity
(b) Mean severity of animals with lesion; 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
**P<0.01 vs. vehicle controls (Mann-Whitney U test)

TABLE 10. NUMBERS OF RATS WITH SELECTED URINARY SYSTEM LESIONS IN THE TWO-YEAR GAVAGE STUDIES OF PHENYLBUTAZONE (ORIGINAL SECTIONS)

Site/Lesion	Male			Female		
	Vehicle Control	50 mg/kg	100 mg/kg	Vehicle Control	50 mg/kg	100 mg/kg
Kidney						
Number examined	50	49	50	50	50	50
Kidney (not otherwise specified)						
Cyst	2	0	2	1	2	**16
Pelvis						
Dilatation	1	1	1	1	0	**22
Papilla						
Necrosis	1	**10	**25	0	**18	**41
Collecting tubule						
Mineralization	5	10	**35	3	**31	**46
Tubule						
Hyperplasia	3	1	4	1	1	2
Adenoma	0	0	3	0	0	0
Carcinoma	0	1	0	0	0	0
Pelvis epithelium						
Hyperplasia	14	7	12	7	**20	**37
Carcinoma	0	0	0	0	0	2
Kidney (not otherwise specified)						
Carcinoma	0	0	0	0	1	0
Urinary Bladder						
Number examined	45	43	48	50	49	49
Transitional epithelium						
Hyperplasia	0	0	0	1	0	3
Papilloma	0	2	0	0	1	0

**P<0.01 vs. vehicle controls

by loss of cellular detail in the mid or distal papilla due to degeneration and loss of epithelial cells, necrosis of interstitial cells, and hyalinization of the vasa recta. In more advanced lesions, the distal papilla was completely necrotic with dystrophic mineralization of the devitalized tissue, or the necrotic tissue had sloughed completely causing a deformity of the papilla. In addition, there was mild inflammation consisting of accumulations of neutrophils and cellular debris in the lumina of individual tubules in the cortex of dosed rats. Hyperplasia of the renal pelvis epithelium, dilatation of the pelvic lumen, and cortical cysts also were increased in dosed female rats relative to vehicle controls.

Renal tubular cell adenomas (Figure 5) occurred in 3/50 high dose male rats, and a tubular cell carcinoma occurred in one low dose male rat. The historical incidence of renal tubular cell neoplasms in corn oil vehicle control male F344/N rats is 11/2,092 (0.5%). Tubular cell hyperplasia was not increased in dosed male rats. An anaplastic carcinoma of uncertain histogenesis was seen in the kidney of a low dose female rat (Figures 6-8); because of the undifferentiated nature of the neoplasm, it could not be determined if it was of tubular or transitional cell origin. Transitional cell carcinomas of the renal pelvis occurred in two high dose females (Figure 9). No renal transitional cell neoplasms have been observed in 2,094 corn oil vehicle control female F344/N rats.

An additional histopathologic review was undertaken on kidneys from all male and female rats. All left and right halves of kidneys remaining after the original histopathologic examination were embedded and step-sectioned every millimeter until the tissue was exhausted (usually three to four tissue sections per kidney). Only diagnoses relating to either proliferative or neoplastic lesions were recorded. As shown in Table 11, the incidences of hyperplasia and of tubular neoplasms increased in the dosed groups of each sex. The composite results are shown in Table 12. No additional neoplasms of the renal pelvis were observed in the step-section.

Cystic hyperplasia was observed in several male rats in vehicle control and dosed groups. This lesion consisted of markedly dilated tubules with a large open lumen lined by an irregular layer (one to several cell layers thick) of normal-appearing tubular epithelial cells, which often formed small papillary projections into the lumen.

TABLE 11. INCIDENCE OF SELECTED TUBULE LESIONS OBSERVED IN THE ADDITIONAL REVIEW OF RAT KIDNEYS (a)

Lesion	Male			Female		
	Vehicle Control	50 mg/kg	100 mg/kg	Vehicle Control	50 mg/kg	100 mg/kg
Number examined	50	49	50	50	49	49
Cystic hyperplasia	(b) 2	4	(b) 3	0	0	0
Hyperplasia	2	6	1	1	0	2
Adenoma	0	4	(c) 2	0	3	1
Oncocytic hyperplasia	0	1	0	0	0	0
Oncocytoma	0	0	0	0	0	1

(a) Diagnoses from original sections are not included.
(b) One animal had a diagnosis of renal tubule hyperplasia on the original section.
(c) One animal had a diagnosis of renal tubule adenoma on the original section.

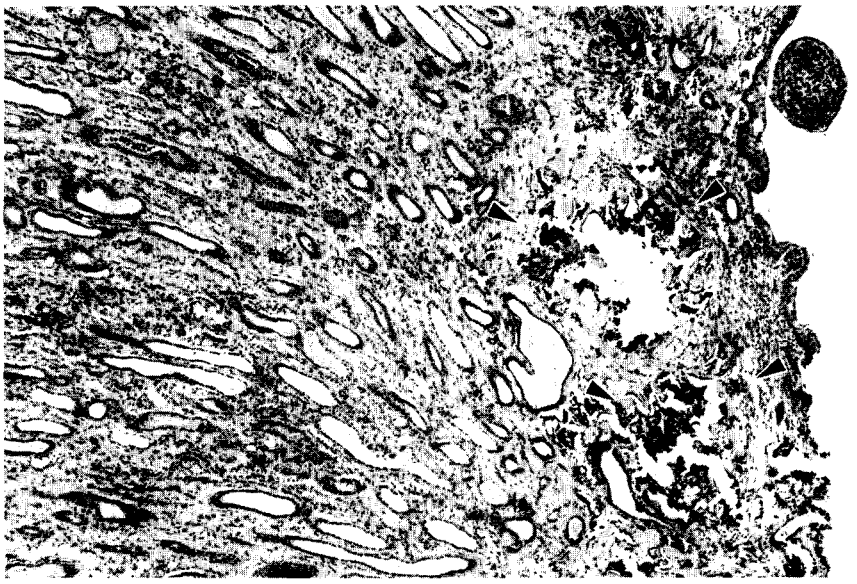


Figure 4. Kidney of high dose female rat CID #604. Note the areas of mineralization and scarring in the papillae (arrows).

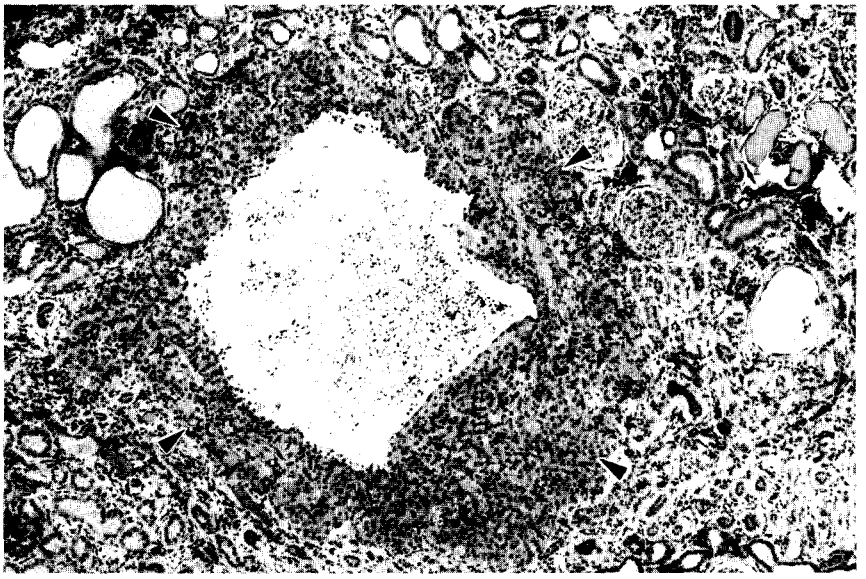


Figure 5. Kidney of high dose male rat CID #214. Note the tubular cell adenoma (arrows) with the large clear space in the center.

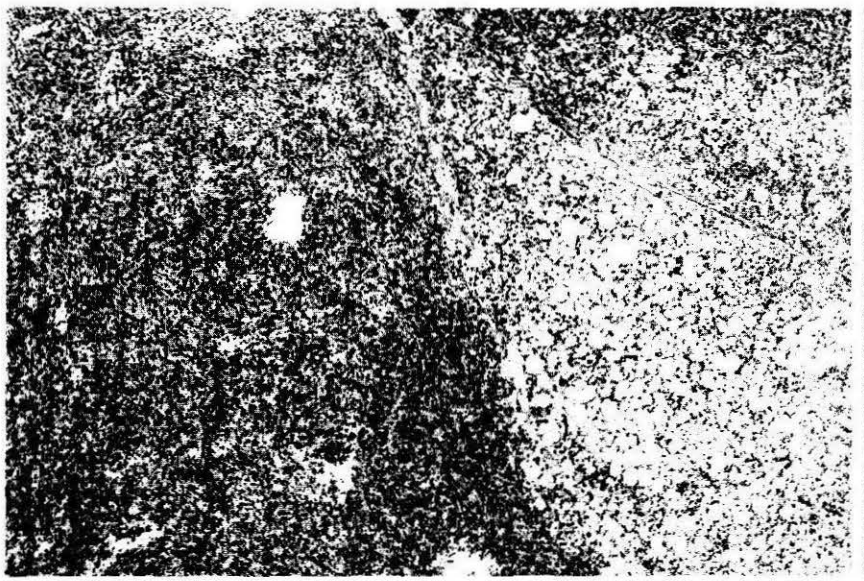


Figure 6. Renal neoplasm in low dose female rat CID #451. Note the two different morphologic patterns that merge together.

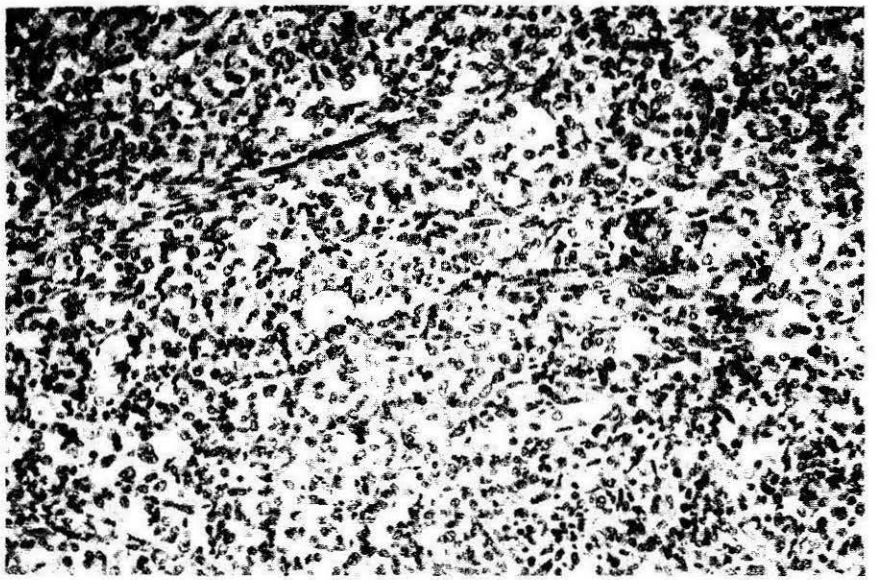


Figure 7. Higher magnification of renal neoplasm in low dose female rat CID #451. This pattern is more typical of a tubular cell carcinoma.

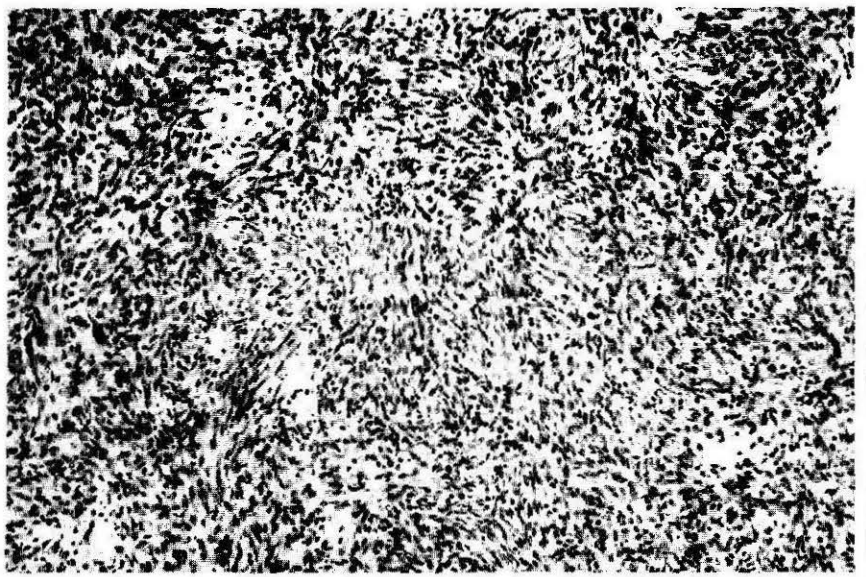


Figure 8. Higher magnification of renal neoplasm in low dose female rat CID #451, demonstrating the sarcomatous pattern.

Figure 9. Kidney of high dose female rat CID #552. Note the transitional cell carcinoma (arrows) originating from the urothelium lining the renal pelvis.

TABLE 12. NUMBERS OF RATS WITH RENAL TUBULAR CELL ADENOMAS OR CARCINOMAS (COMBINED) DETERMINED BY SINGLE-SECTION AND MULTIPLE-SECTION SAMPLING IN THE TWO-YEAR GAVAGE STUDIES OF PHENYLBUTAZONE

	Vehicle Control	50 mg/kg	100 mg/kg
MALE			
Single section	0	1	3
Multiple sections	0	4	(a) 2
Composite values (combined)	0	5	4
Overall Rates	0/50 (0%)	5/50 (10%)	4/50 (8%)
Terminal Rates	0/33 (0%)	3/20 (15%)	2/27 (7%)
First Day of Observation		630	705
Logistic Regression Tests	P=0.070	P=0.019	P=0.058
FEMALE			
Single section	0	0	(b) 0
Multiple sections	0	3	1
Composite values (combined)	0	(c) 3	(d) 1
Overall Rates	0/50 (0%)	3/50 (6%)	1/50 (2%)
Terminal Rates	0/31 (0%)	3/35 (9%)	0/22 (0%)
First Day of Observation		732	673
Logistic Regression Tests	P=0.319	P=0.143	P=0.495

(a) One of these adenomas was also diagnosed in the single-section sampling.
(b) Carcinomas of the transitional epithelium were also observed in two high dose female rats.
(c) An additional neoplasm of uncertain classification was observed with both sectioning techniques in one low dose female rat.
(d) An oncocytoma was also observed in one high dose female rat.

The tubular cell adenomas consisted of cells with a morphologic appearance similar to that of hyperplasia but differed by being larger (approximately five or more tubular diameters) and by generally having a more complex structure.

Adenomas often consisted of multiple nodules of solidly packed cells with large, round, vesicular nuclei and moderately abundant eosinophilic-to-amphophilic-staining cytoplasm. The oncocytomas consisted of irregular masses, having up to 10 times the diameter of a normal tubule; large polyhedral cells with small basophilic, often eccentrically placed nuclei; and abundant, brightly eosinophilic, granular cytoplasm.

Urinary Bladder: Papillomas of the transitional epithelium were seen in 2/43 low dose male rats and in 1/49 low dose female rats (see Table 10). The historical incidence of urinary bladder transitional cell neoplasms in corn oil vehicle control F344/N rats is 5/2,034 (0.2%; highest observed incidence, 2/50) for males and 4/2,026 (0.2%; highest observed incidence, 1/45) for females.

Adrenal Gland: Medullary hyperplasia was observed at increased ($P<0.01$) incidences in high dose female rats (male: vehicle control, 11/50; low dose, 15/49; high dose, 12/49; female: 3/50; 6/50; 19/50). The incidences of pheochromocytomas in female rats were not increased (3/50; 1/50; and 3/50).

Forestomach: Ulcers were observed at increased ($P<0.05$) incidences in dosed male and high dose female rats (male: vehicle control, 0/50; low dose, 5/50; high dose, 6/50; female: 2/49; 1/49; 12/49). In high dose female rats, acanthosis (4/49; 0/49; 12/49), hyperkeratosis (3/49; 0/49; 12/49), and basal cell hyperplasia (4/49; 1/49; 12/49) were observed at increased ($P<0.05$) incidences. A squamous cell papilloma was observed in one female vehicle control.

Lung: Histiocytic cellular infiltration was observed at an increased ($P<0.01$) incidence in high dose female rats (male: vehicle control, 13/50; low dose, 13/34; high dose, 12/50; female: 9/50; 6/20; 22/50).

Mammary Gland: Fibroadenomas and fibroadenomas or adenocarcinomas (combined) in female rats occurred with significant negative trends; the incidences in the high dose group were significantly lower than those in the vehicle controls (Table 13).

TABLE 13. MAMMARY GLAND LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF PHENYLBUTAZONE (a)

	Vehicle Control	50 mg/kg	100 mg/kg
Hyperplasia			
Overall Rates	41/46 (89%)	5/18 (28%)	32/40 (80%)
Fibroadenoma			
Overall Rates	22/50 (44%)	15/50 (30%)	7/50 (14%)
Terminal Rates	18/31 (58%)	9/35 (26%)	3/22 (14%)
Day of First Observation	485	578	590
Logistic Regression Tests	P=0.002N	P=0.076N	P=0.003N
Adenocarcinoma			
Overall Rates	1/50 (2%)	1/50 (2%)	0/50 (0%)
Fibroadenoma or Adenocarcinoma (b)			
Overall Rates	23/50 (46%)	15/50 (30%)	7/50 (14%)
Terminal Rates	18/31 (58%)	9/35 (26%)	3/22 (14%)
Day of First Observation	485	578	590
Logistic Regression Tests	P<0.001N	P=0.051N	P=0.002N

(a) For a complete explanation of the entries in this table, see Table B3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence of mammary gland neoplasms at study laboratory (mean ± SD): 107/300 (36% ± 4%); historical incidence in NTP studies: 647/2,100 (31% ± 10%)

SINGLE-ADMINISTRATION STUDIES

All mice that received 1,200 or 2,400 mg/kg phenylbutazone and 1/5 females that received 600 mg/kg died on the day of dosing (Table 14).

NINETEEN-DAY STUDIES

No compound-related deaths occurred (Table 15). The final mean body weights of dosed and vehicle control mice were similar. No compound-related clinical signs were observed.

THIRTEEN-WEEK STUDIES

Five of 10 male mice and 4/10 female mice that received 600 mg/kg died before the end of the studies (Table 16). No other compound-related deaths occurred. The final mean body weights of dosed and vehicle control mice were similar. No compound-related clinical signs were observed. The liver weight to body weight ratios were significantly increased for mice that received 300 and 600 mg/kg (Table 17). No compound-related histopathologic effects were observed.

Dose Selection Rationale: Because of the deaths at 600 mg/kg and the absence of effects on body weight at 300 mg/kg, doses selected for mice for the 2-year studies were 150 and 300 mg/kg phenylbutazone administered in corn oil by gavage 5 days per week.

TABLE 14. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF PHENYLBUTAZONE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams)		
		Initial (b)	Final	Change (c)
MALE				
150	5/5	28.7 ± 0.6	31.2 ± 0.7	+2.5 ± 0.4
300	5/5	28.8 ± 0.4	32.0 ± 0.5	+3.2 ± 0.2
600	5/5	28.6 ± 0.6	29.1 ± 0.9	+0.5 ± 0.5
1,200	0/5	28.4 ± 0.7	(d)	(d)
2,400	0/5	28.2 ± 0.4	(d)	(d)
FEMALE (e)				
150	5/5	20.7 ± 0.4	21.8 ± 0.4	+1.1 ± 0.2
300	5/5	20.7 ± 0.3	22.0 ± 0.3	+1.3 ± 0.2
600	4/5	20.9 ± 0.4	21.3 ± 0.3	+0.4 ± 0.3
1,200	0/5	20.6 ± 0.4	(d)	(d)
2,400	0/5	20.8 ± 0.4	(d)	(d)

(a) Number surviving/number initially in group; all deaths occurred on the day of dosing.
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) No data are reported due to 100% mortality in this group.
(e) LD_{50} by the Spearman-Karber procedure: 739 mg/kg with a 95% confidence interval of 563-969 mg/kg

TABLE 15. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE NINETEEN-DAY GAVAGE STUDIES OF PHENYLBUTAZONE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	24.3 ± 0.6	26.4 ± 1.0	+2.1 ± 0.6	
40	5/5	24.4 ± 0.7	27.2 ± 1.1	+2.8 ± 0.5	103
80	5/5	24.3 ± 0.7	28.1 ± 0.6	+3.8 ± 0.4	106
150	5/5	24.8 ± 0.5	27.9 ± 0.7	+3.1 ± 0.4	106
300	5/5	24.8 ± 0.4	26.9 ± 0.9	+2.1 ± 0.6	102
600	5/5	24.8 ± 0.4	27.9 ± 0.4	+3.1 ± 0.2	106
FEMALE					
0	5/5	19.4 ± 0.3	22.0 ± 0.4	+2.6 ± 0.1	
40	5/5	19.5 ± 0.3	22.8 ± 0.5	+3.3 ± 0.4	104
80	5/5	19.5 ± 0.3	22.3 ± 0.2	+2.8 ± 0.2	101
150	5/5	19.3 ± 0.3	22.1 ± 0.5	+2.8 ± 0.3	100
300	(d) 4/5	19.5 ± 0.2	21.4 ± 0.5	+1.7 ± 0.3	97
600	5/5	19.6 ± 0.5	21.5 ± 0.5	+1.9 ± 0.2	98

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Death was due to gavage accident.

TABLE 16. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF PHENYLBUTAZONE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	22.7 ± 0.4	29.1 ± 0.7	+6.4 ± 0.5	
40	10/10	22.4 ± 0.4	29.8 ± 0.9	+7.4 ± 0.9	102
80	(d) 9/10	22.8 ± 0.4	30.0 ± 0.9	+7.1 ± 0.7	103
150	10/10	22.4 ± 0.4	30.1 ± 0.5	+7.7 ± 0.4	103
300	10/10	22.8 ± 0.5	29.0 ± 0.8	+6.2 ± 0.5	100
600	(e) 5/10	22.8 ± 0.4	28.6 ± 0.9	+5.2 ± 0.9	98
FEMALE					
0	(d) 9/10	18.2 ± 0.3	24.5 ± 0.4	+6.2 ± 0.4	
40	(d) 9/10	18.1 ± 0.3	24.6 ± 0.5	+6.4 ± 0.4	100
80	10/10	17.8 ± 0.3	23.8 ± 0.6	+6.0 ± 0.5	97
150	10/10	18.1 ± 0.4	24.8 ± 0.6	+6.7 ± 0.6	101
300	10/10	18.3 ± 0.4	24.4 ± 0.5	+6.1 ± 0.4	100
600	(f) 6/10	18.3 ± 0.4	24.1 ± 0.6	+5.7 ± 0.5	98

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean weight change of the survivors ± standard error of the mean
(d) Week of death: 1
(e) Week of death: 1,1,9,10,10
(f) Week of death: 1,2,9,9

TABLE 17. LIVER WEIGHTS FOR MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF PHENYLBUTAZONE (a)

Dose (mg/kg)	Number Weighed	Necropsy Body Weight (grams)	Liver Weight (mg)	Liver Weight/ Necropsy Body Weight (mg/g)
MALE				
0	10	30.3 ± 0.90	1,476 ± 32	48.9 ± 1.30
40	10	30.7 ± 1.14	1,629 ± 40	53.5 ± 1.72
80	9	30.3 ± 1.02	1,571 ± 48	52.0 ± 1.42
150	10	30.5 ± 0.46	1,488 ± 52	48.8 ± 1.50
300	10	28.9 ± 0.81	**1,821 ± 84	**62.7 ± 1.44
600	5	28.5 ± 0.63	**2,616 ± 79	**91.8 ± 2.88
FEMALE				
0	9	24.7 ± 0.43	1,293 ± 38	52.4 ± 1.35
40	9	25.1 ± 0.77	1,361 ± 61	54.2 ± 1.85
80	10	23.6 ± 0.65	1,188 ± 42	50.4 ± 1.40
150	10	23.6 ± 0.67	1,159 ± 42	49.0 ± 1.11
300	10	24.0 ± 0.63	*1,524 ± 58	**63.3 ± 1.08
600	6	24.4 ± 0.52	**2,095 ± 136	**86.7 ± 6.85

(a) Mean ± standard error; P values vs. the vehicle controls by Dunnett's test (Dunnett, 1955).
*P<0.05
**P<0.01

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of low dose mice were 98%-108% those of vehicle controls throughout the study (Table 18 and Figure 10). Mean body weights of high dose male mice were within 4% of those of vehicle controls until week 84 and within 7% thereafter. Mean body weights of high dose female mice were generally 4%-11% lower than those of vehicle controls after week 36. No compound-related clinical signs were observed.

TABLE 18. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF PHENYLBUTAZONE

Weeks on Study	Vehicle Control		150 mg/kg			300 mg/kg		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors
MALE								
0	23.8	50	23.9	100	50	23.7	100	50
1	24.3	50	25.8	106	48	25.6	105	50
2	26.5	50	27.3	103	48	26.7	101	50
3	27.0	50	27.9	103	48	27.2	101	50
4	27.6	50	28.5	103	48	27.6	100	50
5	28.6	50	29.6	103	48	28.5	100	50
6	29.5	50	30.5	103	48	28.7	97	50
7	30.3	50	31.2	103	48	30.1	99	50
8	30.1	50	29.7	99	48	29.1	97	50
9	30.8	50	31.3	102	48	30.7	100	50
10	32.0	50	32.5	102	48	31.3	98	50
11	32.9	50	33.2	101	48	32.7	99	50
12	32.8	50	33.5	102	48	31.9	97	50
16	34.3	50	35.6	104	48	33.6	98	50
20	35.1	50	36.7	105	48	34.9	99	50
24	36.9	50	38.5	104	48	36.5	99	50
28	37.6	50	38.8	103	48	37.5	100	50
32	39.4	50	40.2	102	48	38.3	97	50
36	41.0	50	42.1	103	48	39.6	97	50
40	40.1	50	41.3	103	48	39.4	98	50
44	40.6	50	42.2	104	48	39.5	97	50
48	40.7	50	43.4	107	48	39.9	98	50
52	40.8	50	43.4	106	48	40.5	99	50
56	41.4	50	44.3	107	48	40.5	98	50
60	41.2	50	43.7	106	48	40.6	99	48
64	41.6	49	44.1	106	48	40.8	98	48
68	42.0	49	43.9	105	48	40.9	97	48
72	41.9	49	44.0	105	48	41.7	100	47
76	42.8	49	45.4	106	48	42.0	98	46
80	43.6	48	45.3	104	48	42.4	97	46
84	43.2	47	44.8	104	48	41.4	96	46
88	44.3	45	45.2	102	47	41.1	93	44
92	43.4	43	45.0	104	45	41.0	94	42
96	43.1	41	43.5	101	43	40.4	94	41
100	42.1	39	42.8	102	41	40.7	97	38
104	40.4	36	41.2	102	40	41.1	102	36
FEMALE								
0	19.1	50	18.9	99	50	18.8	98	50
1	20.0	50	19.8	99	50	19.9	100	49
2	21.4	50	21.2	99	50	21.1	99	49
3	21.6	50	22.1	102	50	21.9	101	49
4	22.4	50	22.0	98	50	22.3	100	49
5	22.9	50	23.3	102	49	23.0	100	49
6	23.5	50	23.7	101	49	23.6	100	49
7	24.4	50	24.1	99	49	24.2	99	49
8	23.6	50	24.0	102	49	23.1	98	49
9	24.7	50	24.9	101	49	23.8	96	46
10	25.1	50	25.5	102	49	24.9	99	46
11	26.3	50	26.1	99	49	25.7	98	46
12	26.0	50	26.9	103	49	25.5	98	46
16	26.6	50	26.6	100	49	26.6	100	46
20	28.5	50	29.4	103	49	27.2	95	46
24	29.7	50	30.8	104	49	28.9	97	46
28	30.2	50	30.7	102	49	29.6	98	46
32	31.4	50	33.5	107	47	30.5	97	46
36	33.4	50	35.4	106	45	31.7	95	46
40	32.8	50	34.2	104	45	31.0	95	45
44	34.2	50	35.8	105	45	31.8	93	45
48	34.5	50	35.8	104	45	31.5	91	45
52	34.8	50	36.6	105	45	32.2	93	45
56	36.0	50	36.6	102	45	32.1	89	44
60	36.0	50	36.6	102	45	32.3	90	44
64	37.0	50	38.6	104	43	33.6	91	44
68	37.5	50	37.6	100	42	34.3	91	43
72	37.1	49	38.5	104	42	35.3	95	40
76	38.5	49	40.2	104	41	36.4	95	39
80	39.3	49	41.4	105	40	37.4	95	39
84	40.1	47	41.4	103	38	37.7	94	38
88	40.4	41	42.5	105	35	38.2	95	37
92	39.2	37	42.2	108	33	37.7	96	36
96	39.4	32	42.0	107	32	37.2	94	36
100	38.1	29	40.4	106	31	38.3	101	33
104	37.6	22	38.5	102	29	35.3	94	32

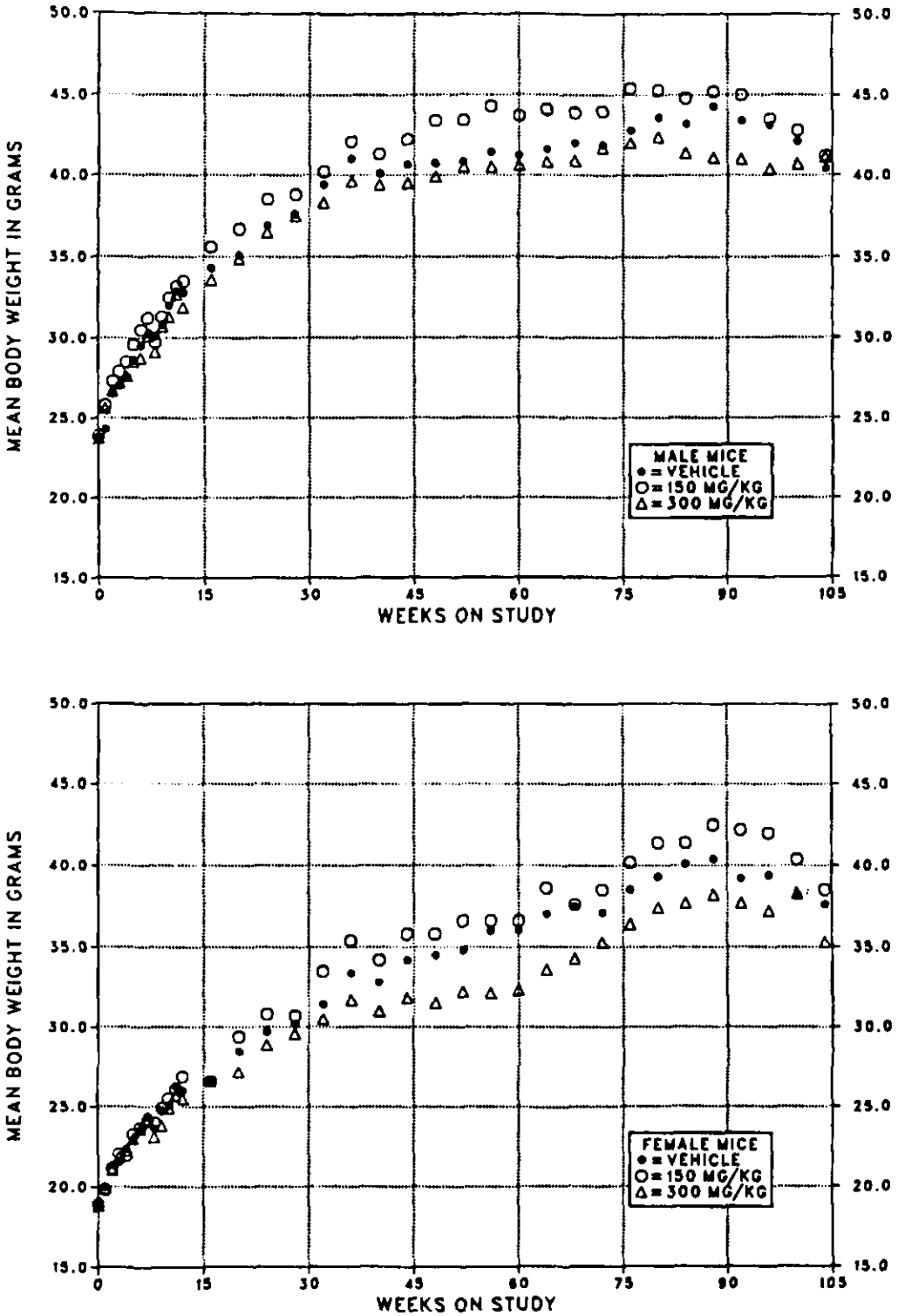


FIGURE 10. GROWTH CURVES FOR MICE ADMINISTERED PHENYLBUTAZONE IN CORN OIL BY GAVAGE FOR TWO YEARS

III. RESULTS: MICE

Survival

Estimates of the probabilities of survival for male and female mice administered phenylbutazone at the doses used in these studies and for vehicle controls are shown in Table 19 and in the Kaplan and Meier curves in Figure 11. No significant differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the liver, uterus, and hematopoietic system.

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 animal group, and historical control incidences for the neoplasms mentioned in this section are presented in Appendixes C and D for male and female mice, respectively.

TABLE 19. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF PHENYLBUTAZONE

	Vehicle Control	150 mg/kg	300 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Natural deaths	3	2	3
Moribund kills	12	6	11
Animals surviving until study termination	(b) 35	40	36
Killed accidentally	0	2	0
Survival P values (c)	0.962	0.254	0.899
FEMALE (a)			
Animals initially in study	50	50	50
Natural deaths	8	10	12
Moribund kills	20	11	5
Animals surviving until study termination	22	29	32
Killed accidentally	0	0	1
Survival P values (c)	0.133	0.539	0.132

(a) First day of termination period: male--730; female--731
(b) Number killed at study termination; one animal died or was killed in a moribund condition during the termination period and was combined, for statistical purposes, with those killed at termination.
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

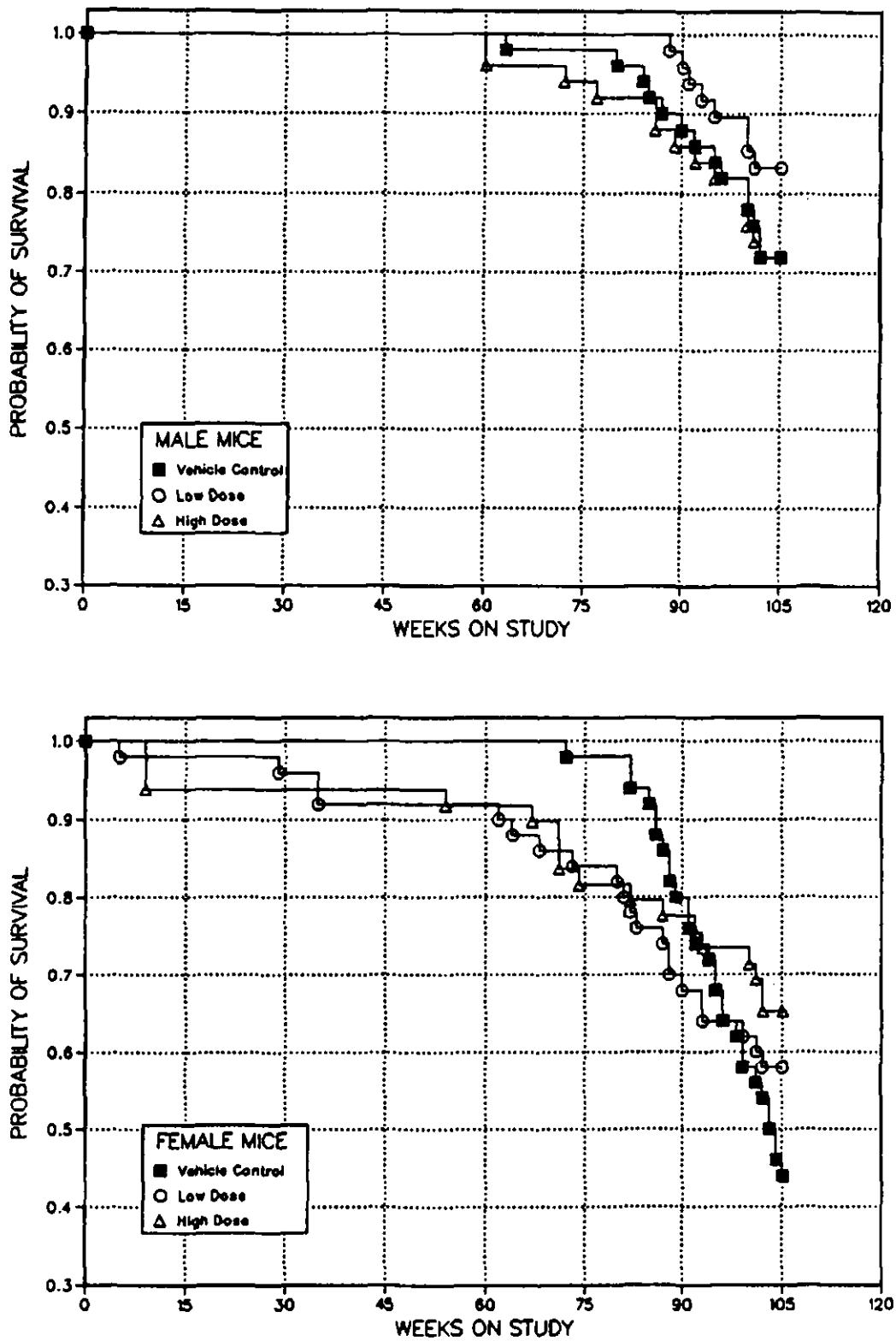


FIGURE 11. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED PHENYLBUTAZONE IN CORN OIL BY GAVAGE FOR TWO YEARS

Liver: The administration of phenylbutazone to male mice caused a variety of toxic lesions in the liver. These lesions included cytomegaly, karyomegaly, hepatocellular degeneration and necrosis, fatty change, peliosis hepatis (referred to as hemorrhage in Tables C5 and D5), and pigment accumulation (Table 20). The cytomegaly was primarily centrilobular in distribution and consisted of enlarged hepatocytes with homogeneous eosinophilic cytoplasm and usually contained enlarged nuclei (karyomegaly). There were multiple foci of hepatocellular degeneration characterized by shrunken, deeply basophilic cells with pyknotic nuclei or individual vacuolated cells. Individual necrotic hepatocytes with or without a minimal inflammatory response often accompanied this change. The lesion diagnosed as hemorrhage consisted of widely dilated sinusoids filled with blood (angiectasis or peliosis hepatis). A granular yellow-green pigment (possibly bile pigment) was present in widely scattered macrophages in the liver sinosoids. Clear cell foci (discrete areas of hepatocytes with pale cytoplasm) occurred in five high dose male mice.

Hepatocellular adenomas and adenomas or carcinomas (combined) in male mice occurred with significant positive trends, and the incidences in the high dose group were significantly greater than those in the vehicle controls (Table 21). Hepatocellular neoplasms were not increased in female mice (vehicle control, 5/50; low dose, 5/49; high dose, 7/50).

Uterus: Adenocarcinomas were observed in 2/49 low dose female mice. The historical incidence of uterine glandular tumors in corn oil vehicle control B6C3F$_1$ female mice is 7/2,077 (0.3%); the highest observed incidence is 3/49.

Hematopoietic System: The incidence of lymphomas in the high dose male mice was significantly lower than that in the vehicle controls (Table 22). Lymphomas were seen in 11/50 vehicle control, 8/50 low dose, and 8/50 high dose female mice.

TABLE 20. NUMBERS OF MICE WITH SELECTED LIVER LESIONS IN THE TWO-YEAR GAVAGE STUDIES OF PHENYLBUTAZONE

Lesion	Male			Female		
	Vehicle Control	150 mg/kg	300 mg/kg	Vehicle Control	150 mg/kg	300 mg/kg
Number examined	50	50	50	50	49	50
Clear cell focus	0	0	*5	0	0	1
Hemorrhage (peliosis hepatis)	1	**16	**27	0	*6	1
Pigmentation	1	1	**26	0	2	0
Fatty change	11	7	**20	5	6	0
Centrilobular cytomegaly	0	**34	**45	0	0	0
Centrilobular karyomegaly	0	**34	**44	0	0	0
Degeneration	0	**22	**38	0	1	0
Coagulative necrosis	4	*11	**36	8	14	12
Hepatocellular adenoma	8	12	**24	4	5	7
Hepatocellular carcinoma	8	4	11	1	0	0

*P<0.05 vs. vehicle controls
**P<0.01 vs. vehicle controls

TABLE 21. HEPATOCELLULAR TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF PHENYLBUTAZONE (a)

	Vehicle Control	150 mg/kg	300 mg/kg
Adenoma			
Overall Rates	8/50 (16%)	12/50 (24%)	24/50 (48%)
Terminal Rates	5/36 (14%)	11/40 (28%)	21/36 (58%)
Day of First Observation	627	647	500
Logistic Regression Tests	P<0.001	P=0.231	P<0.001
Carcinoma			
Overall Rates	8/50 (16%)	4/50 (8%)	11/50 (22%)
Terminal Rates	3/36 (8%)	4/40 (10%)	4/36 (11%)
Day of First Observation	440	730	500
Logistic Regression Tests	P=0.252	P=0.165N	P=0.355
Adenoma or Carcinoma (b)			
Overall Rates	16/50 (32%)	14/50 (28%)	31/50 (62%)
Terminal Rates	8/36 (22%)	13/40 (33%)	23/36 (64%)
Day of First Observation	440	647	500
Logistic Regression Tests	P=0.001	P=0.421N	P=0.002

(a) For a complete explanation of the entries in this table, see Table C3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence at study laboratory (mean ± SD): 111/348 (32% ± 8%); historical incidence in NTP studies: 688/2,084 (33% ± 9%)

TABLE 22. HEMATOPOIETIC SYSTEM TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF PHENYLBUTAZONE (a)

	Vehicle Control	150 mg/kg	300 mg/kg
Lymphomas (b)			
Overall Rates	7/50 (14%)	8/50 (16%)	1/50 (2%)
Terminal Rates	5/36 (14%)	5/40 (13%)	1/36 (3%)
Day of First Observation	558	612	730
Life Table Tests	P=0.040N	P=0.565	P=0.036N
Logistic Regression Tests	P=0.038N	P=0.501	P=0.031N

(a) For a complete explanation of the entries in this table, see Table C3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence of lymphomas or leukemia (combined) at study laboratory (mean ± SD): 51/349 (15% ± 3%); historical incidence in NTP studies: 253/2,091 (12% ± 4%)

Phenylbutazone was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested with or without exogenous metabolic activation. Phenylbutazone produced a positive response in the mouse lymphoma assay both in the presence and absence of activation. Phenylbutazone induced chromosomal aberrations in Chinese hamster ovary (CHO) cells in the presence, but not the absence, of exogenous metabolic activation; no induction of sister chromatid exchanges was observed in CHO cells in the presence or absence of activation. The methodology and full results are presented in Appendix H.

IV. DISCUSSION AND CONCLUSIONS

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Studies of the toxicity and carcinogenicity of phenylbutazone were conducted in F344/N rats and B6C3F$_1$ mice of each sex. For the 2-year studies, phenylbutazone was administered in corn oil by gavage to groups of 50 rats of each sex at doses of 0, 50, or 100 mg/kg, 5 days per week for 103 weeks. Groups of 50 mice of each sex were administered 0, 150, or 300 mg/kg phenylbutazone on the same schedule. The selection of these doses was based on results of 19-day and 13-week studies. For rats, dose selection was based primarily on effects on the kidney, and for mice, on deaths at 600 mg/kg and the absence of effects on body weight at 300 mg/kg.

Throughout the 2-year studies with rats, there were no major differences in body weight between vehicle controls and low dose animals of each sex. High dose males weighed 6%-11% less than vehicle controls beginning as early as week 4 in the study, whereas high dose females showed similar weight reductions relative to vehicle controls after week 56. The survival of male rats in the low dose group was significantly lower than that of the vehicle controls; the increase in mortality began about week 85 and is unexplained. The survival of high dose female rats was substantially decreased compared with that of vehicle controls. This is likely related to renal failure, as evidenced by the number of high dose female rats with severe nephropathy and/or renal papillary necrosis. The chemical-related decrease in body weights in high dose rats and evidence for phenylbutazone-associated renal toxicity in all dosed groups, combined with the observation that 80% of all rats survived for at least 20 months, suggest that the selected doses were adequate for assessing the long-term toxicity and carcinogenicity of phenylbutazone and that higher doses would not have been appropriate.

The findings in the current studies that the kidney is the major target organ for phenylbutazone-induced toxicity in male and female rats are consistent with those in other reported studies of phenylbutazone (Arnold et al., 1976; Owen and Heywood, 1983, 1986) and in studies involving many other nonsteroidal analgesics. In the current 13-week studies, renal papillary necrosis was observed in 1/10 male and 2/10 female rats given doses as low as 100 mg/kg body weight phenylbutazone. In the 2-year studies, papillary necrosis was seen in over 80% of the females and 50% of the males given the top dose of 100 mg/kg; the lesions were often more severe or extensive in females than in males. Greater incidences and severity of renal papillary necrosis in female rats than in male rats were observed in studies of sudoxicam (Wiseman and Reinert, 1975) and of C.I. Acid Orange 3 (NTP, 1988) and may be related to the fact that females have more concentrated urine than males; the urine volume and glomerular filtration rate of female rats are lower than those of males. In studies of the experimental induction of papillary necrosis with 2-bromoethylamine hydrobromide, increasing the urine flow and decreasing the papillary solute concentration protected against the development of the lesion (Fuwa and Waugh, 1968; Sabatini et al., 1983). Conversely, dehydration enhances the severity of papillary necrosis induced by high doses of aspirin or combinations of aspirin, phenacetin, and caffeine (Shelley, 1978).

Although the precise mechanism of papillary necrosis caused by nonsteroidal analgesics has not been clarified, the lesion is most characteristic of an infarct caused by ischemia due to impairment of the blood supply to regions of the papilla (Kincaid-Smith et al., 1968). Within the affected region of the papilla, necrosis of the cells forming the interstitial tissue, necrosis of interstitial capillaries, and necrosis of the thin loops of Henle are present. Electron microscopic studies with various analgesics have shown that the earliest lesions appear in interstitial cells, the vasa recta that supply blood to the medulla and papilla, and the long loop of Henle (Molland, 1978). A major effect of nonsteroidal analgesics is the inhibition of prostaglandin synthesis, and it has been proposed that a decrease in prostaglandin production in the renal papilla may play a primary role in the pathogenesis of papillary necrosis, possibly by decreasing blood flow and thereby leading to ischemia. Prostaglandin E_2 is produced in the renal medulla and may be involved in the autoregulation of medullary blood flow (Shelley, 1978); an increase in prostaglandin synthesis has been reported to occur in response to a variety of stimuli that reduce renal blood flow. It has also been demonstrated that analgesics, including aspirin,

phenylbutazone, indomethacin, and paracetamol, all lower medullary blood flow. Because of the countercurrent exchange mechanism in the kidney, the concentration of diffusible analgesic metabolites will be highest in the papilla.

Although no microscopic evidence of injury to the renal tubules in the cortex was found in the current 13-week studies, other studies have reported cortical tubule necrosis after administration of a single dose of oxyphenbutazone, a major metabolite of phenylbutazone (Arnold et al., 1976). Thus, it is not surprising that there was a dose-related increased severity of nephropathy in male and female rats in the current 2-year studies of phenylbutazone. Age-related nephropathy primarily involves the convoluted tubules of the renal cortex and the glomeruli; some degree of nephropathy is seen in nearly all 2-year-old rats. This spontaneous renal disease of rats is not what has been described as "analgesic nephropathy" in humans (Shelley, 1978). The pathogenesis of spontaneous nephropathy in rats has not been fully elucidated, but high-protein diets are known to exacerbate the lesions. Because of the complex lesions involving the nephron in this disease and the limited manner in which individual cells are able to respond to injury, drug- or chemical-induced damage to the tubular epithelium is often manifested by a dose-related increase in severity of nephropathy.

Although phenylbutazone has been widely reported to cause acute ulceration of the glandular stomach (MacAllister, 1983; Traub et al., 1983), these lesions were not observed in rats in either the current 13-week or 2-year studies. However, ulcers and associated regenerative epithelial hyperplasia of the forestomach were observed in male and female rats in the 2-year studies. Similar lesions have been observed in other gavage studies and may be due to the irritant effects of the chemicals. Direct trauma to the forestomach associated with the gavage needle may also have contributed to the development of the ulcers.

In the current studies, the conventional histopathologic evaluation of the kidney (a single section each of the left and right kidney) identified a tubular cell carcinoma in a low dose male and tubular cell adenomas in three high dose males. Renal tubular cell hyperplasia was observed in three vehicle control, one low dose, and four high dose male rats. Although the number of dosed male rats with renal tubular cell neoplasms is low, renal tubular cell neoplasms are uncommon in historical corn oil vehicle control F344/N rats (male: 11/2,092; 0.5%). The highest number of tubular cell neoplasms observed in a corn oil vehicle control group in the current National Toxicology Program (NTP) historical data base is 1/48; however, three tubular cell adenomas have been reported in each of two recent untreated control groups. Thus, the low number of renal tubular cell neoplasms identified by the conventional histologic technique in male rats given phenylbutazone is difficult to interpret.

The NTP (Table 23) and other investigators (Kurokawa et al., 1983) have found that multiple sectioning of the kidney may enable a more precise evaluation of a potential chemical-related induction of renal tubular cell neoplasms compared with observations obtained from single-section sampling. With routine sections, the number of renal tubular cell neoplasms observed is often so low that statistical analyses are not helpful in the evaluation. Because the majority of renal tubular cell neoplasms in these and other studies shown in Table 23 are microscopic (i.e., not observed by macroscopic examination at necropsy), multiple sections might be expected to increase the number of neoplasms observed and therefore allow for a more rigorous statistical evaluation. Therefore, because of the marginal increases in renal neoplasms in rats of each sex (albeit of differing histogenesis; see below for discussion of transitional cell carcinomas in female rats), step-sections of the kidney were prepared and examined microscopically.

The data from the subsequent histopathologic review of the kidney (see Table 11) revealed no evidence of neoplasia in vehicle control rats but provided confirmatory evidence of tubular cell adenomas in all dosed groups of rats. This is the first NTP study in which the kidney of rats of each sex has been evaluated after step-sectioning; the NTP data base includes three other studies in which the kidney of male rats has been reevaluated. As shown in Table 23, the composite incidence of renal tubular cell adenomas or carcinomas (combined) numbered 11/210

TABLE 23. NUMBERS OF RENAL TUBULAR CELL LESIONS OBSERVED AFTER STEP-SECTIONING IN SELECTED CONTROL GROUPS OF MALE F344/N RATS IN NTP STUDIES

Lesion	Nitrofurantoin (a)		Furosemide (b)		Toluene (c)		Phenylbutazone (d)		Total	
	Single (e)	Step (f)	Single	Step	Single	Step	Single	Step	Single	Step
Number of animals	50	50	50	50	60	60	50	50	210	210
Hyperplasia	2	9	4	2	4	0	3	2	13	13
Cystic hyperplasia	0	1	0	1	0	0	0	2	0	4
Adenoma	0	3	1	(g) 2	0	5	0	0	1	(g) 10
Carcinoma	0	0	0	0	0	0	0	0	0	0
Oncocytic hyperplasia	0	1	0	0	0	0	0	0	0	1

(a) NTP, 1989a (feed study)
(b) NTP, 1989b (feed study)
(c) NTP, 1990 (inhalation study)
(d) Current study (corn oil gavage)
(e) Two kidney sections per rat were examined microscopically by single-sectioning.
(f) Six to eight kidney sections per rat were examined microscopically by step-sectioning.
(g) These adenomas occurred in animals other than the one in which an adenoma was diagnosed in the single section.

in corn oil vehicle control male F344/N rats, indicating that six to eight additional sections per animal resulted in an increased background (5.2% vs. 0.5%) over that observed with routine single-section (per kidney) histologic evaluation. However, by this method, the concurrent control incidence in these phenylbutazone studies remained at 0/50 for rats of each sex. The incidence for low dose male rats (4/49) obtained with step-sectioning was somewhat increased above the 5.2% control mean observed in other studies employing step-sectioning, and the high dose incidence of 2/50 was somewhat lower. As many as five adenomas have been observed in a control group after step-sectioning (see Table 23). Incidences in both dosed groups are above the concurrent control incidence of 0/50.

The composite incidences for renal tubular cell adenomas or carcinomas (combined) identified by both single- and step-section evaluation are shown in Table 12. Statistical analysis by logistic regression indicates that, in male rats, the composite low dose incidence (5/50) was significantly increased ($P = 0.019$) and the top dose incidence (4/50) was marginally increased ($P = 0.058$) compared with the vehicle control incidence. The result of the trend test was not significant. The composite incidence in either dosed group of female rats was not statistically different from that in vehicle controls. Nonetheless, the combined observations from the original evaluation and the step-section evaluation showed neoplasms in all four dosed groups.

The interpretation resulting from these studies regarding neoplastic responses in male rats exposed to phenylbutazone is based on the following considerations. The initial histopathologic review indicated a low incidence of tubular cell neoplasia (0, 1, 3). A review of additional sections indicated the presence of additional tubular cell adenomas in the dosed groups, bringing the composite observations to 0, 5, 4. Statistically, these indicated a marginally significant trend, and the P values of the pairwise comparisons between dosed and control groups fluctuated around significance. A comparison of these data with the limited historical data available for multiple sectioning revealed that the number of adenomas/carcinomas observed in the low dose phenylbutazone group (5) obtained by combining both single- and multiple-section sampling has been equaled in the control male group of another NTP study (toluene, NTP, 1990; see Table 23) in which multiple sections were reviewed. The data reported here also indicate that the kidney in male rats is a target organ

with respect to phenylbutazone-induced nonneoplastic lesions, as evidenced by the increased severity of nephropathy in dosed animals (see Table 9) and the dose-related increases in papillary necrosis and mineralization of the collecting tubules (see Table 10). Considered together, these observations provide equivocal evidence of phenylbutazone-induced carcinogenicity in male F344/N rats.

In the current studies, hyperplasia of the renal pelvis transitional epithelium occurred in female rats given phenylbutazone. The transitional cell hyperplasia often occurred near the fornices of the renal pelvis and was similar to that observed in male rats with severe nephropathy. In the current study, a dosed-related increased severity of nephropathy was seen in female rats (see Table 9), and the transitional cell hyperplasia likely reflects the increase in the number of female rats with marked nephropathy. Hyperplasia of the transitional epithelium occurred in the urinary bladder of one vehicle control and three top dose female rats, and a transitional cell papilloma occurred in one low dose female rat; the low incidences, however, preclude unequivocal association of these lesions with the administration of phenylbutazone.

Initial sampling revealed two transitional cell carcinomas in the renal pelvis in the top dose group of female rats, and the additional step-sections did not increase this number in any of the groups. This incidence, compared with the incidence of zero in the concurrent controls, is not statistically significant. However, these neoplasms have not been observed in nearly 2,100 corn oil vehicle control female F344/N rats or in over 1,600 historical untreated controls in the NTP data base. A statistical comparison between the two observed in these studies versus the historical data base (0/2,094 corn oil gavage) is highly significant ($P < 0.001$) and thereby unlikely to be due to chance alone. Although it was not possible to precisely determine the tissue of origin of the carcinoma observed in the low dose female rat, it displayed some characteristics of transitional cell morphology (see Figures 6-8) and was clearly malignant. The rarity of these neoplasms in the renal pelvic epithelium of control female F344/N rats, combined with the fact that this topography is a target for phenylbutazone-induced toxicity (hyperplasia), led to the conclusion that the three carcinomas observed in the dosed groups are probably related to the administration of phenylbutazone. It is noteworthy that transitional cell carcinomas may be associated with nonsterodial analgesic-induced nephropathy in humans (Burnett et al., 1980; Gonwa et al., 1980; Blohme and Johansson, 1981; McCredie et al., 1982).

Results of the step-sectioning identified the presence of an oncocytoma in the top dose group of female rats. Although the pathogenesis of this rare lesion is not known with certainty, some investigators (Bannasch et al., 1986; Nogueira and Bannasch, 1988) consider an oncocytoma to be a benign tumor that develops in the distal parts of the nephron (Tsuda et al., 1986), in contrast to tubular cell adenomas, which apparently originate in the proximal renal tubules and often progress to adenocarcinomas (Hiasa et al., 1979; Dees et al., 1980; Tsuda et al., 1983).

Mechanisms responsible for the observed kidney neoplasia in the tubular cells of dosed rats remain speculative. Although not mutagenic in bacterial cells, phenylbutazone is genotoxic and clastogenic in some mammalian assay systems (Kawachi et al., 1980; Pentiah et al., 1980; Ishidate et al., 1981). Investigators have demonstrated that phenylbutazone has a slight promoting effect on kidney neoplasms initiated by *N*-ethyl-*N*-nitrosourea or *N*-propyl-*N*-nitrosourea (Maekawa et al., 1987). There was no evidence of hyaline droplet formation or other aspects of the $\alpha_{2\mu}$-globulin nephrotoxic syndrome (Short et al., 1987) in these short-term or long-term studies.

Because survival of each sex of the dosed mice in the 2-year studies was similar to that of vehicle controls and because body weights were somewhat decreased only in the top dose groups (7%-11%), the doses chosen for mice are considered to have been appropriate. Results of these 2-year studies in mice showed a highly significant increase in the combined incidences of hepatocellular adenomas and carcinomas in male mice administered phenylbutazone (see Table 20).

The significance of this trend is due to increases in hepatocellular adenomas observed in the top dose group of male mice. The incidence of hepatocellular neoplasms observed in this group (62%) is nearly twice the mean incidence observed in corn oil vehicle controls at the study laboratory or in NTP studies (33%) and exceeds the highest incidence observed in historical controls (50%). Although there is no statistically significant increase in the combined incidences of adenomas and carcinomas in the low dose male mice, there is evidence of a dose-dependent increase in preneoplastic lesions in the liver (see Table 19). The high dose male mice had an increased incidence of clear cell foci, which are thought to be a preneoplastic change in the genesis of liver neoplasms (Maronpot and Boorman, 1982).

The hepatotoxicity and hepatocarcinogenicity of phenylbutazone have not been extensively reported. Another 2-year study with rats suggested a slight positive effect of phenylbutazone administration on the occurrence of neoplastic nodules in the liver, but the incidences were not statistically significant (Maekawa et al., 1987). Clinical investigations showed that phenylbutazone was associated with overt hepatic injury in about 2-3 persons per 1,000 given phenylbutazone therapeutically (Ishak et al., 1977).

The administration of phenylbutazone was also associated with decreased incidences of several neoplasms. There was a dramatic decrease in the incidence of mammary gland fibroadenomas in female rats. Although such a decrease has often been seen in dosed animals with substantially decreased body weights (Rao et al., 1987), it is noteworthy that, in this study, the decrease occurred in the absence of marked dose-dependent decreases in body weight. There was also a statistically significant decrease in the incidence of lymphomas in the top dose group of male mice. The biologic significance of this observation is uncertain.

The experimental and tabulated data for the NTP Technical Report on phenylbutazone were examined for accuracy, consistency, completeness, and compliance with Good Laboratory Practice regulations. As summarized in Appendix I, the audit revealed no major problems with the conduct of the studies or with collection and documentation of the experimental data. No discrepancies were found that influenced the final interpretation of the results of these studies.

Under the conditions of these 2-year gavage studies, there was *equivocal evidence of carcinogenic activity** of phenylbutazone for male F344/N rats, as shown by the occurrence of small numbers of renal tubular cell adenomas and carcinomas. There was *some evidence of carcinogenic activity* for female F344/N rats, as shown primarily by the occurrence of two rare transitional cell carcinomas in the top dose group; none has ever been seen in vehicle control or untreated control female rats. Tubular cell adenomas may have been associated with the administration of phenylbutazone to female rats. There was *some evidence of carcinogenic activity* for male $B6C3F_1$ mice, as shown by the increased incidence of hepatocellular adenomas or carcinomas (combined). There was *no evidence of carcinogenicity* for female $B6C3F_1$ mice administered phenylbutazone in corn oil by gavage at doses of 150 or 300 mg/kg.

Phenylbutazone was also nephrotoxic to rats, as shown by the dose-related increase in the severity of age-related nephropathy, necrosis of the renal papilla, and mineralization of the collecting ducts in the papilla.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 6.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 9-10.

V. REFERENCES

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APPENDIX A

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

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large, colon	(50)	*(50)	(49)
Serosa, mesothelioma malignant		1 (2%)	1 (2%)
Serosa, sarcoma, metastatic, spleen		1 (2%)	
Intestine small, duodenum	(50)	*(50)	(49)
Serosa, mesothelioma malignant	1 (2%)	1 (2%)	1 (2%)
Serosa, ileum, sarcoma, metastatic, spleen		1 (2%)	
Intestine small, ileum	(50)	*(50)	(49)
Lymphoid nodule, fibrosarcoma, metastatic, mammary gland	1 (2%)		
Liver	(50)	(50)	(50)
Leukemia mononuclear	2 (4%)	2 (4%)	2 (4%)
Lymphoma malignant lymphocytic	1 (2%)		
Neoplastic nodule		1 (2%)	1 (2%)
Osteosarcoma, metastatic, bone		1 (2%)	
Serosa, mesothelioma malignant	1 (2%)	1 (2%)	1 (2%)
Serosa, sarcoma, metastatic, spleen		1 (2%)	
Serosa, sarcoma, metastatic, uncertain primary site			1 (2%)
Mesentery	*(50)	*(50)	*(50)
Mesothelioma malignant	2 (4%)	2 (4%)	1 (2%)
Sarcoma, metastatic, spleen		1 (2%)	
Sarcoma, metastatic, uncertain primary site			1 (2%)
Pancreas	(50)	*(50)	(50)
Adenoma	3 (6%)	3 (6%)	4 (8%)
Lymphoma malignant lymphocytic	1 (2%)		
Sarcoma, metastatic, spleen		1 (2%)	
Serosa, mesothelioma malignant	2 (4%)	1 (2%)	1 (2%)
Salivary glands	(49)	*(50)	(49)
Lymphoma malignant lymphocytic	1 (2%)		
Stomach	(50)	(50)	(50)
Serosa, mesothelioma malignant		1 (2%)	
Stomach, forestomach	(50)	(50)	(50)
Serosa, sarcoma, metastatic, spleen		1 (2%)	
Serosa, glandular, sarcoma, metastatic, uncertain primary site			1 (2%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	*(50)	(50)
Leukemia mononuclear	1 (2%)		2 (4%)
Perivascular, mesothelioma malignant, metastatic			1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(49)	(50)
Capsule, mesothelioma malignant			1 (2%)
Adrenal gland, cortex	(50)	(49)	(50)
Leukemia mononuclear	2 (4%)		1 (2%)
Medulla, osteosarcoma, metastatic, bone		1 (2%)	
Adrenal gland, medulla	(50)	(48)	(49)
Leukemia mononuclear	2 (4%)		1 (2%)
Pheochromocytoma malignant	4 (8%)	2 (4%)	2 (4%)
Pheochromocytoma complex	1 (2%)		2 (4%)
Pheochromocytoma benign	9 (18%)	13 (27%)	12 (24%)
Pheochromocytoma benign, multiple	2 (4%)	1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
Adrenal gland, medulla (Continued)	(50)	(48)	(49)
Bilateral, pheochromocytoma, NOS		1 (2%)	
Bilateral, pheochromocytoma benign	5 (10%)	4 (8%)	7 (14%)
Islets, pancreatic	(50)	*(50)	(50)
Adenoma	2 (4%)	1 (2%)	
Carcinoma	2 (4%)		
Pituitary gland	(48)	*(50)	(47)
Pars distalis, adenoma	13 (27%)	9 (18%)	20 (43%)
Pars distalis, adenoma, multiple	3 (6%)	1 (2%)	1 (2%)
Pars intermedia, adenoma			1 (2%)
Thyroid gland	(49)	*(50)	(49)
C-cell, adenoma	6 (12%)	1 (2%)	2 (4%)
C-cell, carcinoma	1 (2%)	1 (2%)	
Follicular cell, adenoma	2 (4%)		1 (2%)
GENERAL BODY SYSTEM			
Tissue, NOS	*(50)	*(50)	*(50)
Lipoma	1 (2%)		
GENITAL SYSTEM			
Epididymis	(50)	(49)	(50)
Serosa, mesothelioma benign	1 (2%)		
Serosa, mesothelioma malignant	2 (4%)	3 (6%)	3 (6%)
Serosa, sarcoma, metastatic, spleen		1 (2%)	
Serosa, sarcoma, metastatic, uncertain primary site			1 (2%)
Preputial gland	(43)	*(50)	(47)
Adenocarcinoma		1 (2%)	1 (2%)
Adenoma	2 (5%)	4 (8%)	
Carcinoma			1 (2%)
Sarcoma	1 (2%)		
Prostate	(50)	*(50)	(46)
Lymphoma malignant lymphocytic	1 (2%)		
Seminal vesicle	(49)	*(50)	(47)
Serosa, mesothelioma malignant			1 (2%)
Serosa, sarcoma, metastatic, spleen		1 (2%)	
Testes	(50)	(49)	(50)
Leukemia mononuclear	1 (2%)		
Bilateral, interstitial cell, adenoma	35 (70%)	32 (65%)	38 (76%)
Interstitial cell, adenoma	11 (22%)	9 (18%)	10 (20%)
Tunic, mesothelioma malignant	3 (6%)	4 (8%)	3 (6%)
Tunic, sarcoma, metastatic, spleen		1 (2%)	
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	*(50)	(50)
Leukemia mononuclear	1 (2%)		
Lymphoma malignant lymphocytic	1 (2%)		
Lymph node	(50)	*(50)	(50)
Axillary, lymphoma malignant lymphocytic	1 (2%)		
Lumbar, lymphoma malignant lymphocytic	1 (2%)		
Mediastinal, leukemia mononuclear	1 (2%)		1 (2%)
Mediastinal, lymphoma malignant lymphocytic	1 (2%)		
Mediastinal, mesothelioma malignant, metastatic		1 (2%)	
Mediastinal, sarcoma, metastatic, spleen		1 (2%)	
Pancreatic, lymphoma malignant lymphocytic	1 (2%)		
Renal, lymphoma malignant lymphocytic	1 (2%)		
Lymph node, mandibular	(44)	*(50)	(41)
Fibrosarcoma, metastatic	1 (2%)		
Lymphoma malignant lymphocytic	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
Lymph node, mesenteric	(47)	*(50)	(49)
Lymphoma malignant lymphocytic	1 (2%)		
Serosa, mesothelioma malignant	1 (2%)		1 (2%)
Spleen	(50)	*(50)	(50)
Leukemia mononuclear	2 (4%)	1 (2%)	2 (4%)
Lymphoma malignant lymphocytic	1 (2%)		
Mesothelioma malignant	1 (2%)	2 (4%)	
Sarcoma		1 (2%)	1 (2%)
Sarcoma, metastatic, uncertain primary site			1 (2%)
Thymus	(42)	*(50)	(42)
Lymphoma malignant lymphocytic	1 (2%)		
INTEGUMENTARY SYSTEM			
Mammary gland	(21)	*(50)	(24)
Fibroadenoma	2 (10%)	5 (10%)	3 (13%)
Skin	(50)	*(50)	(49)
Basal cell carcinoma			1 (2%)
Basosquamous tumor malignant			1 (2%)
Keratoacanthoma	2 (4%)	1 (2%)	1 (2%)
Papilloma squamous		1 (2%)	
Sebaceous gland, adenoma		1 (2%)	
Subcutaneous tissue, fibroma	3 (6%)	3 (6%)	4 (8%)
Subcutaneous tissue, fibrosarcoma	2 (4%)		
Subcutaneous tissue, hemangiosarcoma			1 (2%)
Subcutaneous tissue, lipoma		1 (2%)	
Subcutaneous tissue, myxosarcoma	1 (2%)		
Subcutaneous tissue, schwannoma malignant	1 (2%)		
MUSCULOSKELETAL SYSTEM			
Bone	(50)	*(50)	(50)
Scapula, osteosarcoma		1 (2%)	
Skeletal muscle	*(50)	*(50)	*(50)
Osteosarcoma, extension, metastatic		1 (2%)	
Abdominal, mesothelioma malignant	1 (2%)	1 (2%)	
Diaphragm, sarcoma, metastatic, uncertain primary site			1 (2%)
NERVOUS SYSTEM			
Brain	(50)	*(50)	(50)
Astrocytoma malignant	1 (2%)	1 (2%)	1 (2%)
Granular cell tumor benign	1 (2%)		
Leukemia mononuclear	1 (2%)		
RESPIRATORY SYSTEM			
Lung	(50)	*(50)	(50)
Alveolar/bronchiolar adenoma		3 (6%)	
Alveolar/bronchiolar carcinoma	2 (4%)		
Fibrosarcoma, metastatic, ear	1 (2%)		
Leukemia mononuclear	2 (4%)		2 (4%)
Lymphoma malignant lymphocytic	1 (2%)		
Mesothelioma malignant, metastatic		1 (2%)	1 (2%)
Osteosarcoma, metastatic, bone		1 (2%)	
Pheochromocytoma malignant, metastatic		1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
SPECIAL SENSES SYSTEM			
Ear	*(50)	*(50)	*(50)
Pinna, fibrosarcoma	1 (2%)		
Eye	*(50)	*(50)	*(50)
Lids, fibroma	1 (2%)		
Harderian gland	*(50)	*(50)	*(50)
Adenoma	1 (2%)		
Zymbal gland	*(50)	*(50)	*(50)
Carcinoma	2 (4%)	1 (2%)	1 (2%)
URINARY SYSTEM			
Kidney	(50)	(49)	(50)
Leukemia mononuclear	2 (4%)		1 (2%)
Lymphoma malignant lymphocytic	1 (2%)		
Bilateral, renal tubule, adenoma			1 (2%)
Renal tubule, adenoma			2 (4%)
Renal tubule, carcinoma		1 (2%)	
Urinary bladder	(45)	(43)	(48)
Serosa, mesothelioma malignant	1 (2%)	1 (2%)	1 (2%)
Transitional epithelium, papilloma		2 (5%)	
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Mesothelioma malignant	3 (6%)	4 (8%)	3 (6%)
Mesothelioma benign	1 (2%)		
Lymphoma malignant lymphocytic	1 (2%)		
Leukemia mononuclear	2 (4%)	2 (4%)	2 (4%)
Hemangiosarcoma			1 (2%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Terminal sacrifice	32	20	27
Moribund sacrifice	11	13	16
Natural death	6	16	7
Terminal sacrifice	1		
Accident		1	
TUMOR SUMMARY			
Total animals with primary neoplasms **	50	48	50
Total primary neoplasms	130	112	125
Total animals with benign neoplasms	49	47	49
Total benign neoplasms	105	96	108
Total animals with malignant neoplasms	21	14	14
Total malignant neoplasms	25	15	17
Total animals with secondary neoplasms ***	2	5	2
Total secondary neoplasms	3	17	8
Total animals with malignant neoplasms--uncertain primary site			1
Total animals with neoplasms--uncertain benign or malignant		1	
Total uncertain neoplasms		1	

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

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

WEEKS ON STUDY	066	075	075	076	085	085	086	086	087	089	092	092	093	096	098	098	101	105	105	103	105	105	105	105	105	105
CARCASS ID	013	065	032	042	105	021	084	034	041	091	025	094	044	043	052	101	035	055	063	104	024	072	083	103	045
ALIMENTARY SYSTEM																										
Esophagus	M	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, mesothelioma malignant										X																
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoid nodule, fibrosarcoma, metastatic, mammary gland																										
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X												X									
Lymphoma malignant lymphocytic												X														
Serosa, mesothelioma malignant										X																
Mesentery										+										+						
Mesothelioma malignant										X																
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X					
Lymphoma malignant lymphocytic												X														
Serosa, mesothelioma malignant										X																
Salivary glands	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic												X														
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X																					
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X												X									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X												X									
Pheochromocytoma malignant										X		X						X								
Pheochromocytoma complex																										
Pheochromocytoma benign										X	X				X			X		X	X					
Pheochromocytoma benign, multiple																										
Bilateral, pheochromocytoma benign																						X			X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Carcinoma																										X
Parathyroid gland	+	M	+	M	M	M	M	M	+	M	+	+	+	+	M	M	M	M	M	+	M	M	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X			X		X											X		X		X	X	X	
Pars distalis, adenoma, multiple												X														
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
C-cell, adenoma														X												
C-cell, carcinoma																										
Follicular cell, adenoma																		X								
GENERAL BODY SYSTEM																										
Tissue, NOS																										
Lipoma																										
GENITAL SYSTEM																										
Coagulating gland																							+			
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, mesothelioma benign							X																			
Serosa, mesothelioma malignant										X																
Preputial gland	M	+	+	+	M	M	+	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X					
Sarcoma																								X		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic												X														
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X																					
Bilateral, interstitial cell, adenoma		X			X		X	X		X			X	X	X	X	X	X	X	X		X			X	X
Interstitial cell, adenoma	X		X			X			X		X	X									X		X			
Tunic, mesothelioma malignant							X			X																

+: Tissue examined microscopically
: Not examined
−: Present but not examined microscopically
I: Insufficient tissue

M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

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

WEEKS ON STUDY	105	105	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL:
CARCASS ID	0075	0093	0111	0112	0114	0222	0223	0231	0253	0254	0261	0262	0264	0271	0273	0274	0281	0292	0295	0302	0315	0333	0351	0382	0385		TISSUES TUMORS
ALIMENTARY SYSTEM																											
Esophagus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+		44
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+		47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+		49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Serosa, mesothelioma malignant																											1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymphoid nodule, fibrosarcoma, metastatic, mammary gland											X																1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear																											2
Lymphoma malignant lymphocytic																											1
Serosa, mesothelioma malignant																											1
Mesentery																	+					+					4
Mesothelioma malignant																	X										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adenoma									X										X								3
Lymphoma malignant lymphocytic																											1
Serosa, mesothelioma malignant																	X										2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Lymphoma malignant lymphocytic																											1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
CARDIOVASCULAR SYSTEM																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear																											1
ENDOCRINE SYSTEM																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear																											2
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear																											2
Pheochromocytoma malignant							X																				4
Pheochromocytoma complex		X																									1
Pheochromocytoma benign											X			X		X											9
Pheochromocytoma benign, multiple						X				X																	2
Bilateral, pheochromocytoma benign	X											X														X	5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X																X	2
Carcinoma																									X		2
Parathyroid gland	+	M	+	M	M	M	+	M	+	+	M	+	+	M	M	M	M	+	+	M	+	+	+	+	+		24
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+		48
Pars distalis, adenoma					X				X								X		X						X		13
Pars distalis, adenoma, multiple										X								X									3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
C-cell, adenoma							X	X				X							X						X		6
C-cell, carcinoma																		X									1
Follicular cell, adenoma																	X										2
GENERAL BODY SYSTEM																											
Tissue, NOS								+																			1
Lipoma								X																			1
GENITAL SYSTEM																											
Coagulating gland	+																										2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Serosa, mesothelioma benign																											1
Serosa, mesothelioma malignant																	X										2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+		48
Adenoma									X																		2
Sarcoma																											1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymphoma malignant lymphocytic																											1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear																											1
Bilateral, interstitial cell, adenoma	X	X		X		X	X	X	X	X	X		X	X	X			X	X	X	X	X	X		X			35
Interstitial cell, adenoma			X		X												X										11
Tunic, mesothelioma malignant																	X										3

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

WEEKS ON STUDY	06 6	07 5	07 5	07 6	08 5	08 5	08 6	08 6	08 7	08 9	09 2	09 2	09 3	09 6	09 8	09 8	10 1	10 5	10 5	10 5	10 5	10 5	10 5	10 5
CARCASS ID	01 3	06 5	03 2	04 2	10 5	02 1	08 4	03 4	04 1	09 1	02 5	09 4	04 4	04 3	05 2	10 1	03 5	05 5	06 3	10 4	02 4	07 2	08 3	10 3	04 5
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X																				
Lymphoma malignant lymphocytic												X													
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Axillary, lymphoma malignant lymphocytic												X													
Lumbar, lymphoma malignant lymphocytic												X													
Mediastinal, leukemia mononuclear					X																				
Mediastinal, lymphoma malignant lymphocytic												X													
Pancreatic, lymphoma malignant lymphocytic												X													
Renal, lymphoma malignant lymphocytic												X													
Lymph node, mandibular	M	+	M	+	+	+	M	M	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic																									
Lymphoma malignant lymphocytic												X													
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic												X													
Serosa, mesothelioma malignant										X															
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X											X									
Lymphoma malignant lymphocytic												X													
Mesothelioma malignant										X															
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Lymphoma malignant lymphocytic												X													
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	+	M	M	M	M	M	M	M	M	M	+	+	+	M	M	+	+	M	M	+	+	M
Fibroadenoma				X																					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma								X																	
Subcutaneous tissue, fibroma			X	X																					
Subcutaneous tissue, fibrosarcoma	X																								
Subcutaneous tissue, myxosarcoma														X											
Subcutaneous tissue, schwannoma malignant															X										
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Abdominal, mesothelioma malignant																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant													X												
Granular cell tumor benign															X										
Leukemia mononuclear					X																				
Spinal cord		+																							
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Fibrosarcoma, metastatic, ear																									
Leukemia mononuclear					X											X									
Lymphoma malignant lymphocytic												X													
Nose	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear							+							+											
Pinna, fibrosarcoma																									
Eye																									
Lids, fibroma																									
Harderian gland														+											
Adenoma														X											
Zymbal gland							+						+									+			
Carcinoma							X															X			
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X											X									
Lymphoma malignant lymphocytic												X													
Urethra																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Serosa, mesothelioma malignant										X															

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

WEEKS ON STUDY	105	105	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL:
CARCASS ID	075	093	011	012	014	022	023	031	053	054	061	062	064	071	073	074	081	092	095	102	115	133	151	182	185	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Lymphoma malignant lymphocytic																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Axillary, lymphoma malignant lymphocytic																										1
Lumbar, lymphoma malig. lymphocytic																										1
Mediastinal, leukemia mononuclear																										1
Mediastinal, lymphoma malignant lymphocytic																										1
Pancreatic, lymphoma malignant lymphocytic																										1
Renal, lymphoma malig. lymphocytic																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Fibrosarcoma, metastatic										X																1
Lymphoma malignant lymphocytic																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant lymphocytic																										1
Serosa, mesothelioma malignant																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Lymphoma malignant lymphocytic																										1
Mesothelioma malignant																										1
Thymus	+	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	M	+	M	+	42
Lymphoma malignant lymphocytic																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	M	M	+	M	+	M	M	+	+	+	M	+	M	M	M	M	+	+	M	M	+	+	+	21
Fibroadenoma																							X			2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																									X	2
Subcutaneous tissue, fibroma											X															3
Subcutaneous tissue, fibrosarcoma											X															2
Subcutaneous tissue, myxosarcoma																										1
Subcutaneous tissue, schwannoma malignant																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																	+									1
Abdominal, mesothelioma malignant																	X									1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Granular cell tumor benign																										1
Leukemia mononuclear																										1
Spinal cord																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma															X		X									2
Fibrosarcoma, metastatic, ear										X																1
Leukemia mononuclear																										2
Lymphoma malignant lymphocytic																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear										+																3
Pinna, fibrosarcoma										X																1
Eye																							+			1
Lids, fibroma																							X			1
Harderian gland																										1
Adenoma																										1
Zymbal gland																										3
Carcinoma																										2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Lymphoma malignant lymphocytic																										1
Urethra																				+						1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	M	M	+	+	+	+	+	45
Serosa, mesothelioma malignant																										1

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

WEEKS ON STUDY	041	055	064	068	075	077	078	083	084	085	086	087	087	088	089	099	099	099	099	091	092	093	094	096	098
CARCASS ID	192	133	181	203	122	165	153	151	141	142	124	135	185	131	143	193	163	183	202	195	134	114	182	172	154
ALIMENTARY SYSTEM																									
Esophagus	+	+	M	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M					
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Intestine large, cecum	M	+	M	+	M	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+					
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Serosa, mesothelioma malignant									X																
Serosa, sarcoma, metastatic, spleen																									
Intestine large, rectum	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Intestine small	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				+	
Intestine small, duodenum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				+	
Serosa, mesothelioma malignant									X																
Serosa, ileum, sarcoma, metastatic, spleen																									
Intestine small, ileum	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				+	
Intestine small, jejunum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				+	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																						X			
Neoplastic nodule														X											
Osteosarcoma, metastatic, bone																	X								
Serosa, mesothelioma malignant									X																
Serosa, sarcoma, metastatic, spleen																									
Mesentery									+																+
Mesothelioma malignant									X																
Sarcoma, metastatic, spleen																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+		+		+	
Adenoma							X																		
Sarcoma, metastatic, spleen																									
Serosa, mesothelioma malignant									X																
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+			
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, mesothelioma malignant									X																
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, sarcoma, metastatic, spleen																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Medulla, osteosarcoma, metastatic, bone																	X								
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	
Pheochromocytoma malignant																							X		
Pheochromocytoma benign						X		X													X			X	
Pheochromocytoma benign, multiple																									
Bilateral, pheochromocytoma, NOS																									
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Adenoma																									
Parathyroid gland	+	+	+	+	M	M	M	M	M	M	M	M	+	M	M	M	M	+	+	M					
Pituitary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+				+	+
Pars distalis, adenoma																	X		X						X
Pars distalis, adenoma, multiple																								X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
C-cell, adenoma																X									
C-cell, carcinoma								X																	
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, mesothelioma malignant									X																
Serosa, sarcoma, metastatic, spleen																									
Preputial gland	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+					
Adenocarcinoma																									
Adenoma						X																			
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+			
Serosa, sarcoma, metastatic, spleen																									
Testes	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma						X		X			X	X	X		X		X	X		X	X	X	X	X	
Interstitial cell, adenoma		X		X					X	X				X		X									
Tunic, mesothelioma malignant									X																
Tunic, sarcoma, metastatic, spleen																									

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

WEEKS ON STUDY	100	101	103	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	115	113	205	173	204	445	555	574	575	111	644	844	125	194	201	112	121	123	132	144	152	161	162	171	191	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus									+																	17
Intestine large								+																		21
Intestine large, cecum																										14
Intestine large, colon								+																		21
Serosa, mesothelioma malignant																										1
Serosa, sarcoma, metastatic, spleen								X																		1
Intestine large, rectum																										18
Intestine small							+	+								+										23
Intestine small, duodenum							+	+								+										23
Serosa, mesothelioma malignant																										1
Serosa, ileum, sarcoma, metastatic, spleen								X																		1
Intestine small, ileum																+										21
Intestine small, jejunum																+										21
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																	X									2
Neoplastic nodule																										1
Osteosarcoma, metastatic, bone																										1
Serosa, mesothelioma malignant																										1
Serosa, sarcoma, metastatic, spleen								X																		1
Mesentery								+			+							+								5
Mesothelioma malignant											X															2
Sarcoma, metastatic, spleen								X																		1
Pancreas							+	+			+			+			+									27
Adenoma							X										X									3
Sarcoma, metastatic, spleen								X																		1
Serosa, mesothelioma malignant																										1
Salivary glands					+					+																23
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Serosa, mesothelioma malignant																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Serosa, sarcoma, metastatic, spleen								X																		1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Heart																										20
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Medulla, osteosarcoma, metastatic, bone																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
Pheochromocytoma malignant										X																2
Pheochromocytoma benign				X			X				X			X	X		X	X	X	X						13
Pheochromocytoma benign, multiple								X																		1
Bilateral, pheochromocytoma, NOS									X																	1
Bilateral, pheochromocytoma benign		X			X											X									X	4
Islets, pancreatic														+			+									22
Adenoma																	X									1
Parathyroid gland									+																	8
Pituitary gland			+	+				+		+	+											+				26
Pars distalis, adenoma			X	X				X		X	X											X				9
Pars distalis, adenoma, multiple																										1
Thyroid gland									+																	21
C-cell, adenoma																										1
C-cell, carcinoma																										1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Serosa, mesothelioma malignant											X	X														3
Serosa, sarcoma, metastatic, spleen								X																		1
Preputial gland		+						+	+		+		+		+						+					25
Adenocarcinoma		X																								1
Adenoma								X	X				X													4
Prostate								+																		21
Seminal vesicle	+		+	+	M	+		+	+		+	A	+			+		+		+	+	+	+	+		36
Serosa, sarcoma, metastatic, spleen								X																		1
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		32
Interstitial cell, adenoma										X	X														X	9
Tunic, mesothelioma malignant							X				X	X														4
Tunic, sarcoma, metastatic, spleen								X																		1

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

WEEKS ON STUDY	041	055	064	068	075	077	078	083	084	085	086	087	087	088	089	089	089	090	090	091	092	093	094	096	098
CARCASS ID	192	133	181	203	122	165	153	151	141	142	124	135	185	131	143	193	163	183	202	195	134	114	182	172	154
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Lymph node	+	M	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+		+			
Mediastinal, mesothelioma malignant, metastatic									X																
Mediastinal, sarcoma, metastatic, spleen																									
Lymph node, mandibular	+	M	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	M	M		+			
Lymph node, mesenteric	+	M	+	+	M	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+					
Spleen	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+		+	+
Leukemia mononuclear																						X			
Mesothelioma malignant									X																
Sarcoma																									
Thymus	+	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					
Fibroadenoma																	X								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				+	
Keratoacanthoma																									
Papilloma squamous																	X								
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibroma						X						X												X	
Subcutaneous tissue, lipoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Scapula, osteosarcoma																		X							
Skeletal muscle								+	+									+							
Osteosarcoma, extension, metastatic																		X							
Abdominal, mesothelioma malignant									X																
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Astrocytoma malignant			X																						
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+
Alveolar/bronchiolar adenoma														X											
Mesothelioma malignant, metastatic																									
Osteosarcoma, metastatic, bone																		X							
Pheochromocytoma malignant, metastatic																							X		
Nose	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
SPECIAL SENSES SYSTEM																									
Ear													+												
Zymbal gland													+												
Carcinoma													X												
URINARY SYSTEM																									
Kidney	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, carcinoma																									
Ureter		+																							
Urethra								+																	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, mesothelioma malignant									X																
Transitional epithelium, papilloma											X														

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

WEEKS ON STUDY	100	101	103	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	115	113	205	173	204	445	555	574	575	111	164	184	255	194	201	112	121	123	132	144	152	161	162	171	191		TISSUES TUMORS
HEMATOPOIETIC SYSTEM																											
Bone marrow																											20
Lymph node				+	+			+		+	+	+			+				+								26
Mediastinal, mesothelioma malignant, metastatic																											1
Mediastinal, sarcoma, metastatic, spleen								X																			1
Lymph node, mandibular					+					+																	18
Lymph node, mesenteric										+					+					+							19
Spleen		+	+		+			+			+	+			+			+			+					+	32
Leukemia mononuclear																											1
Mesothelioma malignant												X															2
Sarcoma								X																			1
Thymus								+																			18
INTEGUMENTARY SYSTEM																											
Mammary gland	+			+				+									+			+						+	8
Fibroadenoma	X			X													X									X	5
Skin				+		+		+				+								+		+					27
Keratoacanthoma					X																						1
Papilloma squamous																											1
Sebaceous gland, adenoma							X																				1
Subcutaneous tissue, fibroma																											3
Subcutaneous tissue, lipoma												X															1
MUSCULOSKELETAL SYSTEM																											
Bone																						+					21
Scapula, osteosarcoma																											1
Skeletal muscle																											3
Osteosarcoma, extension, metastatic																											1
Abdominal, mesothelioma malignant																											1
NERVOUS SYSTEM																											
Brain																											20
Astrocytoma malignant																											1
RESPIRATORY SYSTEM																											
Lung			+					+	+	+	+	+	+						+				+	+			34
Alveolar/bronchiolar adenoma			X					X																			3
Mesothelioma malignant, metastatic											X																1
Osteosarcoma, metastatic, bone																											1
Pheochromocytoma malignant, metastatic																											1
Nose																											19
Trachea									+																		21
SPECIAL SENSES SYSTEM																											
Ear																											1
Zymbal gland																											1
Carcinoma																											1
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Renal tubule, carcinoma																							X				1
Ureter																											1
Urethra																											1
Urinary bladder	+		+	+	+	+	+	+	+		+		+	+		+	+		+		+	+	+		+		43
Serosa, mesothelioma malignant																											1
Transitional epithelium, papilloma						X																					2

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

WEEKS ON STUDY	071	073	074	075	079	081	081	083	083	086	091	092	094	099	099	100	101	101	102	103	103	103	103	105	105
CARCASS ID	282	244	211	274	252	265	222	305	261	273	284	254	272	292	241	303	224	213	233	293	214	263	275	223	225
ALIMENTARY SYSTEM																									
Esophagus	+	M	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	M	M	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Serosa, mesothelioma malignant	X																								
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Serosa, mesothelioma malignant	X																								
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X																							
Neoplastic nodule																									
Serosa, mesothelioma malignant	X																								
Serosa, sarcoma, metastatic, uncertain primary site																			X						
Mesentery	+																		+						
Mesothelioma malignant	X																								
Sarcoma, metastatic, uncertain primary site																			X						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Serosa, mesothelioma malignant	X																								
Salivary glands	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, glandular, sarcoma, metastatic, uncertain primary site																			X						
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X																							
Perivascular, mesothelioma malignant, metastatic	X																								
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, mesothelioma malignant	X																								
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X																							
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X																							
Pheochromocytoma malignant															X		X								
Pheochromocytoma complex							X																		
Pheochromocytoma benign														X	X		X						X		
Bilateral, pheochromocytoma benign													X			X		X		X					X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	M	M	M	+	+	+	+	M	M	M	M	M	M	M	+	M	+	M	M	+	+
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X		X	X		X					X	X	X				X	X		
Pars distalis, adenoma, multiple																									
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																								X	
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, mesothelioma malignant	X		X																						
Serosa, sarcoma, metastatic, uncertain primary site																			X						
Penis																	+								
Preputial gland	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma														X											
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, mesothelioma malignant	X																								
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma	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	
Tunic, mesothelioma malignant	X		X																						

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	232	234	235	242	294	304	215	221	243	245	251	253	255	262	264	271	212	231	281	283	285	291	295	301	302		TISSUES TUMORS
ALIMENTARY SYSTEM																											
Esophagus	+	+	+	+	M	M	+	+	M	M	+	M	+	M	+	M	+	+	+	+	+	+	M	M	M		32
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Serosa, mesothelioma malignant																											1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Serosa, mesothelioma malignant																											1
Intestine small, ileum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear									X																		2
Neoplastic nodule									X																		1
Serosa, mesothelioma malignant,																											1
Serosa, sarcoma, metastatic, uncertain primary site																											1
Mesentery															+												3
Mesothelioma malignant																											1
Sarcoma, metastatic, uncertain primary site																											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adenoma		X					X			X										X							4
Serosa, mesothelioma malignant																											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Serosa, glandular, sarcoma, metastatic, uncertain primary site																											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
CARDIOVASCULAR SYSTEM																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear									X																		2
Perivascular, mesothelioma malignant, metastatic																											1
ENDOCRINE SYSTEM																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Capsule, mesothelioma malignant																											1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear																											1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				49
Leukemia mononuclear																											1
Pheochromocytoma malignant																											2
Pheochromocytoma complex			X																								2
Pheochromocytoma benign		X		X		X						X		X				X			X		X			12
Bilateral, pheochromocytoma benign													X			X											7
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Parathyroid gland	M	+	M	M	M	+	M	M	+	M	+	+	+	M	M	M	M	M	M	M	+	M	M	+	M	M	19
Pituitary gland	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pars distalis, adenoma	X	X						X				X			X	X		X		X		X	X	X		20
Pars distalis, adenoma, multiple			X																								1
Pars intermedia, adenoma		X																									1
Thyroid gland	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
C-cell, adenoma						X																					2
Follicular cell, adenoma																				X							1
GENERAL BODY SYSTEM																											
None																											
GENITAL SYSTEM																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Serosa, mesothelioma malignant															X												3
Serosa, sarcoma, metastatic, uncertain primary site																											1
Penis																											1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Adenocarcinoma																											1
Carcinoma										X																	1
Prostate	+	M	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	M	+	+	+	+		46
Seminal vesicle	+	M	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+		47
Serosa, mesothelioma malignant																											1
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		38
Interstitial cell, adenoma					X							X			X						X			X	X		10
Tunic, mesothelioma malignant															X												3

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

WEEKS ON STUDY	071	073	074	075	079	081	081	083	083	086	091	092	094	099	099	100	101	101	102	103	103	103	103	105	105
CARCASS ID	282	244	211	274	252	265	222	305	261	273	284	254	272	292	241	303	224	213	233	293	214	263	275	223	225
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, leukemia mononuclear																									
Lymph node, mandibular	+	+	+	M	+	+	+	M	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, mesothelioma malignant	X																								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X																							
Sarcoma																									
Sarcoma, metastatic, uncertain primary site																			X						
Thymus	+	+	+	+	+	+	+	+	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
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma															X										
Basosquamous tumor malignant																									
Keratoacanthoma																	X								
Subcutaneous tissue, fibroma										X															
Subcutaneous tissue, hemangiosarcoma															X										
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																			+						
Diaphragm, sarcoma, metastatic, uncertain primary site																			X						
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant											X														
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X																							
Mesothelioma malignant, metastatic	X																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye											+					+			+						
Zymbal gland																									
Carcinoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X																							
Bilateral, renal tubule, adenoma																					X				
Renal tubule, adenoma																									
Urethra																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, mesothelioma malignant	X																								

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	232	234	235	242	294	304	215	221	243	245	251	253	255	262	264	271	212	231	281	283	285	291	295	301	302	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, leukemia mononuclear									X																	1
Lymph node, mandibular	+	+	+	+	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	41
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Serosa, mesothelioma malignant																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear									X																	2
Sarcoma																X										1
Sarcoma, metastatic, uncertain primary site																										1
Thymus	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	42
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	M	M	M	M	+	+	24
Fibroadenoma							X												X					X		3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Basal cell carcinoma																										1
Basosquamous tumor malignant																X										1
Keratoacanthoma																										1
Subcutaneous tissue, fibroma	X							X								X										4
Subcutaneous tissue, hemangiosarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Diaphragm, sarcoma, metastatic, uncertain primary site																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear									X																	2
Mesothelioma malignant, metastatic																										1
Nose	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye			I			I								I	I											3
Zymbal gland	+																									1
Carcinoma	X																									1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Bilateral, renal tubule, adenoma																										1
Renal tubule, adenoma			X	X																						2
Urethra			+																							1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	48
Serosa, mesothelioma malignant																										1

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

	Vehicle Control	50 mg/kg	100 mg/kg
Adrenal Medulla: Pheochromocytoma			
Overall Rates (a)	16/50 (32%)	18/49 (37%)	19/49 (39%)
Adjusted Rates (b)	42.9%	67.4%	55.0%
Terminal Rates (c)	12/33 (36%)	11/19 (58%)	11/26 (42%)
Day of First Observation	618	536	658
Life Table Tests (d)	P=0.132	P=0.035	P=0.168
Logistic Regression Tests (d)	P=0.228	P=0.146	P=0.264
Cochran-Armitage Trend Test (d)	P=0.275		
Fisher Exact Test (d)		P=0.388	P=0.310
Adrenal Medulla: Malignant Pheochromocytoma			
Overall Rates (a)	4/50 (8%)	2/49 (4%)	2/49 (4%)
Adjusted Rates (b)	10.5%	8.6%	5.8%
Terminal Rates (c)	1/33 (3%)	1/19 (5%)	0/26 (0%)
Day of First Observation	618	654	692
Life Table Tests (d)	P=0.296N	P=0.507N	P=0.365N
Logistic Regression Tests (d)	P=0.265N	P=0.367N	P=0.344N
Cochran-Armitage Trend Test (d)	P=0.260N		
Fisher Exact Test (d)		P=0.349N	P=0.349N
Adrenal Medulla: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	19/50 (38%)	20/49 (41%)	21/49 (43%)
Adjusted Rates (b)	49.6%	72.5%	59.0%
Terminal Rates (c)	14/33 (42%)	12/19 (63%)	12/26 (46%)
Day of First Observation	618	536	567
Life Table Tests (d)	P=0.168	P=0.040	P=0.210
Logistic Regression Tests (d)	P=0.298	P=0.186	P=0.342
Cochran-Armitage Trend Test (d)	P=0.348		
Fisher Exact Test (d)		P=0.468	P=0.387
Preputial Gland: Adenoma			
Overall Rates (a)	2/43 (5%)	(e) 4/25 (16%)	0/47 (0%)
Adjusted Rates (b)	6.3%		0.0%
Terminal Rates (c)	2/32 (6%)		0/27 (0%)
Day of First Observation	730		
Life Table Test (d)			P=0.276N
Logistic Regression Test (d)			P=0.276N
Fisher Exact Test (d)			P=0.225N
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	2/43 (5%)	(e) 4/25 (16%)	1/47 (2%)
Adjusted Rates (b)	6.3%		3.7%
Terminal Rates (c)	2/32 (6%)		1/27 (4%)
Day of First Observation	730		730
Life Table Test (d)			P=0.560N
Logistic Regression Test (d)			P=0.560N
Fisher Exact Test (d)			P=0.466N
Preputial Gland: Adenoma, Adenocarcinoma, or Carcinoma			
Overall Rates (a)	2/43 (5%)	(e) 5/25 (20%)	2/47 (4%)
Adjusted Rates (b)	6.3%		6.3%
Terminal Rates (c)	2/32 (6%)		1/27 (4%)
Day of First Observation	730		689
Life Table Test (d)			P=0.656
Logistic Regression Test (d)			P=0.685N
Fisher Exact Test (d)			P=0.657N

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

	Vehicle Control	50 mg/kg	100 mg/kg
Pancreatic Islets: Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	(e) 1/22 (5%)	0/50 (0%)
Adjusted Rates (b)	12.1%		0.0%
Terminal Rates (c)	4/33 (12%)		0/27 (0%)
Day of First Observation	730		
Life Table Test (d)			P=0.090N
Logistic Regression Test (d)			P=0.090N
Fisher Exact Test (d)			P=0.059N
Kidney: Renal Tubule Adenoma			
Overall Rates (a)	0/50 (0%)	0/49 (0%)	3/50 (6%)
Adjusted Rates (b)	0.0%	0.0%	10.5%
Terminal Rates (c)	0/33 (0%)	0/20 (0%)	2/27 (7%)
Day of First Observation			716
Life Table Tests (d)	P=0.035	(f)	P=0.095
Logistic Regression Tests (d)	P=0.040	(f)	P=0.111
Cochran-Armitage Trend Test (d)	P=0.038		
Fisher Exact Test (d)		(f)	P=0.121
Kidney: Renal Tubule Adenoma or Carcinoma			
Overall Rates (a)	0/50 (0%)	1/49 (2%)	3/50 (6%)
Adjusted Rates (b)	0.0%	5.0%	10.5%
Terminal Rates (c)	0/33 (0%)	1/20 (5%)	2/27 (7%)
Day of First Observation		730	716
Life Table Tests (d)	P=0.053	P=0.400	P=0.095
Logistic Regression Tests (d)	P=0.061	P=0.400	P=0.111
Cochran-Armitage Trend Test (d)	P=0.061		
Fisher Exact Test (d)		P=0.495	P=0.121
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	2/50 (4%)	(e) 3/34 (9%)	0/50 (0%)
Mammary Gland: Fibroadenoma			
Overall Rates (g)	2/50 (4%)	5/50 (10%)	3/50 (6%)
Adjusted Rates (b)	5.1%	20.0%	11.1%
Terminal Rates (c)	1/33 (3%)	2/20 (10%)	3/27 (11%)
Day of First Observation	526	623	730
Life Table Tests (d)	P=0.348	P=0.108	P=0.425
Logistic Regression Tests (d)	P=0.414	P=0.193	P=0.499
Cochran-Armitage Trend Test (d)	P=0.420		
Fisher Exact Test (d)		P=0.218	P=0.500
Pancreas: Adenoma			
Overall Rates (a)	3/50 (6%)	(e) 3/27 (11%)	4/50 (8%)
Adjusted Rates (b)	9.1%		14.8%
Terminal Rates (c)	3/33 (9%)		4/27 (15%)
Day of First Observation	730		730
Life Table Test (d)			P=0.390
Logistic Regression Test (d)			P=0.390
Fisher Exact Test (d)			P=0.500
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	16/48 (33%)	(e) 10/26 (38%)	21/47 (45%)
Adjusted Rates (b)	44.2%		59.7%
Terminal Rates (c)	12/31 (39%)		12/25 (48%)
Day of First Observation	521		564
Life Table Test (d)			P=0.092
Logistic Regression Test (d)			P=0.174
Fisher Exact Test (d)			P=0.178

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

	Vehicle Control	50 mg/kg	100 mg/kg
Subcutaneous Tissue: Fibroma			
Overall Rates (g)	3/50 (6%)	3/50 (6%)	4/50 (8%)
Adjusted Rates (b)	7.1%	8.3%	13.3%
Terminal Rates (c)	1/33 (3%)	0/20 (0%)	3/27 (11%)
Day of First Observation	521	536	598
Life Table Tests (d)	P=0.372	P=0.581	P=0.429
Logistic Regression Tests (d)	P=0.429	P=0.506N	P=0.515
Cochran-Armitage Trend Test (d)	P=0.421		
Fisher Exact Test (d)		P=0.661	P=0.500
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (g)	4/50 (8%)	3/50 (6%)	4/50 (8%)
Adjusted Rates (b)	8.9%	8.3%	13.3%
Terminal Rates (c)	1/33 (3%)	0/20 (0%)	3/27 (11%)
Day of First Observation	456	536	598
Life Table Tests (d)	P=0.520	P=0.581N	P=0.576
Logistic Regression Tests (d)	P=0.565N	P=0.268N	P=0.622N
Cochran-Armitage Trend Test (d)	P=0.576N		
Fisher Exact Test (d)		P=0.500N	P=0.643
Subcutaneous Tissue: Fibrosarcoma or Myxosarcoma			
Overall Rates (g)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	7.5%	0.0%	0.0%
Terminal Rates (c)	1/33 (3%)	0/20 (0%)	0/27 (0%)
Day of First Observation	456		
Life Table Tests (d)	P=0.049N	P=0.179N	P=0.136N
Logistic Regression Tests (d)	P=0.029N	P=0.074N	P=0.109N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.121N	P=0.121N
Subcutaneous Tissue: Fibroma, Fibrosarcoma, or Myxosarcoma			
Overall Rates (g)	5/50 (10%)	3/50 (6%)	4/50 (8%)
Adjusted Rates (b)	11.4%	8.3%	13.3%
Terminal Rates (c)	1/33 (3%)	0/20 (0%)	3/27 (11%)
Day of First Observation	456	536	598
Life Table Tests (d)	P=0.481N	P=0.456N	P=0.563N
Logistic Regression Tests (d)	P=0.408N	P=0.165N	P=0.472N
Cochran-Armitage Trend Test (d)	P=0.427N		
Fisher Exact Test (d)		P=0.357N	P=0.500N
Testis: Interstitial Cell Adenoma			
Overall Rates (a)	46/50 (92%)	41/49 (84%)	48/50 (96%)
Adjusted Rates (b)	93.9%	95.1%	100.0%
Terminal Rates (c)	30/33 (91%)	18/20 (90%)	27/27 (100%)
Day of First Observation	456	381	494
Life Table Tests (d)	P=0.127	P=0.077	P=0.129
Logistic Regression Tests (d)	P=0.275	P=0.270N	P=0.319
Cochran-Armitage Trend Test (d)	P=0.305		
Fisher Exact Test (d)		P=0.168N	P=0.339
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	6/49 (12%)	(e) 1/21 (5%)	2/49 (4%)
Adjusted Rates (b)	17.9%		7.7%
Terminal Rates (c)	5/32 (16%)		2/26 (8%)
Day of First Observation	672		730
Life Table Test (d)			P=0.198N
Logistic Regression Test (d)			P=0.143N
Fisher Exact Test (d)			P=0.134N

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

	Vehicle Control	50 mg/kg	100 mg/kg
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	7/49 (14%)	(e) 2/21 (10%)	2/49 (4%)
Adjusted Rates (b)	20.9%		7.7%
Terminal Rates (c)	6/32 (19%)		2/26 (8%)
Day of First Observation	672		730
Life Table Test (d)			P=0.130N
Logistic Regression Test (d)			P=0.087N
Fisher Exact Test (d)			P=0.080N
All Sites: Mesothelioma			
Overall Rates (g)	3/50 (6%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	7.5%	17.0%	7.6%
Terminal Rates (c)	1/33 (3%)	3/20 (15%)	1/27 (4%)
Day of First Observation	598	584	494
Life Table Tests (d)	P=0.508	P=0.326	P=0.621
Logistic Regression Tests (d)	P=0.574N	P=0.488	P=0.642N
Cochran-Armitage Trend Test (d)	P=0.579		
Fisher Exact Test (d)		P=0.500	P=0.661N

(a) Number of tumor-bearing animals/number of animals examined microscopically at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence in animals killed at the end of the study
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or a lower incidence in a dosed group than in vehicle controls is indicated by (N).
(e) Incomplete sampling of tissues
(f) No P value is reported because no tumors were observed in the 50 mg/kg and vehicle control groups.
(g) Number of tumor-bearing animals/number of animals examined grossly at the site

TABLE A4a. HISTORICAL INCIDENCE OF KIDNEY TUBULAR CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Adenomas or Adenocarcinomas in Vehicle Controls
Historical Incidence at EG&G Mason Research Institute	
Diglycidyl resorcinol ether	(b) 1/50
Diglycidyl resorcinol ether	0/50
1,2-Dichloropropane	0/50
Chlorodibromomethane	0/50
n-Butyl chloride	0/50
Bromodichloromethane	0/50
TOTAL	1/300 (0.3%)
SD (c)	0.82%
Range (d)	
High	1/50
Low	0/50
Overall Historical Incidence	
TOTAL	(e) 11/2,092 (0.5%)
SD (c)	0.89%
Range (d)	
High	1/48
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Tubular cell adenocarcinoma
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes four tubular cell adenomas, two adenocarcinomas, NOS, and five tubular cell adenocarcinomas

TABLE A4b. HISTORICAL INCIDENCE OF URINARY BLADDER TRANSITIONAL CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Papillomas or Carcinomas in Vehicle Controls
Historical Incidence at EG&G Mason Research Institute	
Diglycidyl resorcinol ether	0/50
Diglycidyl resorcinol ether	0/49
1,2-Dichloropropane	0/49
Chlorodibromomethane	0/50
n-Butyl chloride	0/50
Bromodichloromethane	(b) 1/49
TOTAL	1/297 (0.3%)
SD (c)	0.83%
Range (d)	
High	1/49
Low	0/50
Overall Historical Incidence	
TOTAL	(e) 5/2,034 (0.2%)
SD (c)	0.80%
Range (d)	
High	(f) 2/50
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Transitional cell papilloma
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes three transitional cell papillomas and two transitional cell carcinomas
(f) Both tumors were transitional cell carcinomas.

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Esophagus	(44)	(17)	(32)
Inflammation, necrotizing, acute			1 (3%)
Submucosa, hemorrhage	1 (2%)		
Intestine large, cecum	(47)	(14)	(50)
Inflammation, necrotizing, acute			1 (2%)
Parasite metazoan	1 (2%)		2 (4%)
Intestine large, colon	(50)	(21)	(49)
Angiectasis	1 (2%)		
Parasite metazoan	13 (26%)	3 (14%)	12 (24%)
Intestine large, rectum	(49)	(18)	(49)
Parasite metazoan	2 (4%)		2 (4%)
Intestine small, duodenum	(50)	(23)	(49)
Inflammation, chronic active			1 (2%)
Inflammation, necrotizing, acute			1 (2%)
Epithelium, hyperplasia			1 (2%)
Liver	(50)	(50)	(50)
Angiectasis		2 (4%)	2 (4%)
Basophilic focus	37 (74%)	27 (54%)	25 (50%)
Clear cell focus	15 (30%)	11 (22%)	19 (38%)
Congestion		1 (2%)	
Degeneration, cystic	4 (8%)	1 (2%)	4 (8%)
Eosinophilic focus	7 (14%)	9 (18%)	10 (20%)
Fatty change	41 (82%)	39 (78%)	49 (98%)
Fibrosis	1 (2%)		
Hemorrhage	1 (2%)	1 (2%)	
Hepatodiaphragmatic nodule		2 (4%)	1 (2%)
Hyperplasia			3 (6%)
Infarct		1 (2%)	
Inflammation, chronic active	28 (56%)	23 (46%)	17 (34%)
Mixed cell focus	3 (6%)	4 (8%)	7 (14%)
Necrosis, coagulative	6 (12%)	6 (12%)	5 (10%)
Bile duct, hyperplasia	35 (70%)	43 (86%)	32 (64%)
Centrilobular, cytomegaly			1 (2%)
Kupffer cell, hyperplasia		2 (4%)	
Mesentery	(4)	(5)	(3)
Inflammation, chronic active	1 (25%)	2 (40%)	
Necrosis, coagulative	1 (25%)	2 (40%)	1 (33%)
Pancreas	(50)	(27)	(50)
Atrophy	9 (18%)	2 (7%)	15 (30%)
Ectopic tissue	1 (2%)		
Hyperplasia	8 (16%)	3 (11%)	6 (12%)
Inflammation, chronic	8 (16%)	1 (4%)	6 (12%)
Inflammation, chronic active		1 (4%)	
Pigmentation	2 (4%)		
Acinus, hyperplasia	1 (2%)		
Duct, hyperplasia	1 (2%)		
Salivary glands	(49)	(23)	(49)
Atrophy			1 (2%)
Hemorrhage	2 (4%)		
Inflammation, chronic	2 (4%)	1 (4%)	1 (2%)
Parotid gland, atrophy			1 (2%)
Submandibular gland, atrophy			1 (2%)
Stomach	(50)	(50)	(50)
Hyperplasia, basal cell			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
ALIMENTARY SYSTEM (Continued)			
Stomach, forestomach	(50)	(50)	(50)
Acanthosis	4 (8%)	8 (16%)	7 (14%)
Hyperkeratosis	3 (6%)	8 (16%)	7 (14%)
Hyperplasia, basal cell	4 (8%)	9 (18%)	1 (2%)
Hyperplasia, pseudoepitheliomatous		1 (2%)	
Inflammation, chronic active		3 (6%)	2 (4%)
Ulcer		5 (10%)	6 (12%)
Muscularis, mineralization	1 (2%)		
Stomach, glandular	(50)	(50)	(49)
Erosion		1 (2%)	2 (4%)
Fibrosis	1 (2%)		
Inflammation, chronic		1 (2%)	
Inflammation, chronic active			6 (12%)
Mineralization	1 (2%)	1 (2%)	1 (2%)
Ulcer	1 (2%)		1 (2%)
Arteriole, mineralization	1 (2%)		
Epithelium, hyperplasia			1 (2%)
Mucosa, mineralization		1 (2%)	
Mucosa, necrosis		1 (2%)	
Muscularis, mineralization	2 (4%)	3 (6%)	
CARDIOVASCULAR SYSTEM			
Heart	(50)	(20)	(50)
Cardiomyopathy	48 (96%)	18 (90%)	48 (96%)
Atrioventricular valve, mineralization, focal	1 (2%)		
Atrium, congestion			1 (2%)
Atrium, thrombus	1 (2%)	1 (5%)	3 (6%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(49)	(50)
Angiectasis	29 (58%)	19 (39%)	18 (36%)
Atrophy	1 (2%)		
Congestion		1 (2%)	
Hyperplasia	7 (14%)	6 (12%)	9 (18%)
Vacuolization cytoplasmic	32 (64%)	26 (53%)	32 (64%)
Adrenal gland, medulla	(50)	(48)	(49)
Angiectasis	34 (68%)	23 (48%)	23 (47%)
Fibrosis	1 (2%)		
Hyperplasia	11 (22%)	15 (31%)	12 (24%)
Mineralization	1 (2%)		
Necrosis	1 (2%)		
Thrombus	2 (4%)		
Islets, pancreatic	(50)	(22)	(50)
Hyperplasia	2 (4%)		2 (4%)
Pituitary gland	(48)	(26)	(47)
Pars distalis, angiectasis	4 (8%)	1 (4%)	1 (2%)
Pars distalis, cyst	2 (4%)	1 (4%)	2 (4%)
Pars distalis, hemorrhage	1 (2%)		
Pars distalis, hyperplasia	22 (46%)	8 (31%)	26 (55%)
Pars distalis, necrosis, coagulative	1 (2%)		
Pars distalis, pigmentation		2 (8%)	
Pars intermedia, angiectasis	2 (4%)		1 (2%)
Pars intermedia, cyst	1 (2%)		1 (2%)
Pars intermedia, hyperplasia			1 (2%)
Pars intermedia, pigmentation		1 (4%)	

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
Thyroid gland	(49)	(21)	(49)
C-cell, hyperplasia	22 (45%)	3 (14%)	17 (35%)
Follicle, cyst	1 (2%)		1 (2%)
Follicle, mineralization	1 (2%)		
Follicular cell, hyperplasia	1 (2%)		2 (4%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Epididymis	(50)	(49)	(50)
Hyperplasia		1 (2%)	
Inflammation, chronic active	1 (2%)		
Epithelium, hyperplasia	16 (32%)	26 (53%)	26 (52%)
Preputial gland	(43)	(25)	(47)
Abscess		1 (4%)	
Fibrosis	1 (2%)		
Hyperplasia			1 (2%)
Inflammation, acute	1 (2%)		2 (4%)
Inflammation, chronic	16 (37%)	7 (28%)	7 (15%)
Inflammation, chronic active	22 (51%)	12 (48%)	36 (77%)
Prostate	(50)	(21)	(46)
Atrophy	1 (2%)		
Cyst			1 (2%)
Inflammation, acute	5 (10%)	3 (14%)	9 (20%)
Inflammation, chronic			4 (9%)
Inflammation, chronic active	19 (38%)	5 (24%)	10 (22%)
Epithelium, hyperplasia	4 (8%)		
Seminal vesicle	(49)	(36)	(47)
Atrophy	17 (35%)	14 (39%)	23 (49%)
Inflammation, acute		1 (3%)	
Testes	(50)	(49)	(50)
Hemorrhage			1 (2%)
Arteriole, inflammation, chronic active	2 (4%)		
Arteriole, necrosis, fibrinoid	1 (2%)		
Interstitial cell, hyperplasia	35 (70%)	14 (29%)	29 (58%)
Seminiferous tubule, atrophy	44 (88%)	41 (84%)	45 (90%)
Seminiferous tubule, mineralization	5 (10%)	26 (53%)	14 (28%)
Seminiferous tubule, necrosis, coagulative	1 (2%)		1 (2%)
HEMATOPOIETIC SYSTEM			
Lymph node	(50)	(26)	(50)
Mediastinal, angiectasis	2 (4%)		
Mediastinal, depletion lymphoid		1 (4%)	1 (2%)
Mediastinal, ectasia	1 (2%)	1 (4%)	
Mediastinal, hemorrhage	8 (16%)	1 (4%)	7 (14%)
Mediastinal, hyperplasia	1 (2%)		
Mediastinal, inflammation, chronic active		1 (4%)	
Mediastinal, pigmentation	3 (6%)	2 (8%)	3 (6%)
Pancreatic, angiectasis	1 (2%)		
Pancreatic, fibrosis	1 (2%)		
Pancreatic, hemorrhage		1 (4%)	
Pancreatic, infiltration cellular, histiocytic		1 (4%)	
Pancreatic, pigmentation	1 (2%)		
Renal, hemorrhage		1 (4%)	
Renal, pigmentation	1 (2%)	1 (4%)	

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
Lymph node, mandibular	(44)	(18)	(41)
Angiectasis	1 (2%)		
Congestion	1 (2%)		1 (2%)
Ectasia	10 (23%)	1 (6%)	2 (5%)
Hematocyst			1 (2%)
Hemorrhage	5 (11%)	3 (17%)	5 (12%)
Hyperplasia	7 (16%)	1 (6%)	2 (5%)
Infiltration cellular, histiocytic			3 (7%)
Pigmentation			2 (5%)
Lymph node, mesenteric	(47)	(19)	(49)
Angiectasis	1 (2%)		1 (2%)
Hemorrhage	1 (2%)	1 (5%)	5 (10%)
Infiltration cellular, histiocytic	30 (64%)	3 (16%)	35 (71%)
Pigmentation	34 (72%)	4 (21%)	32 (65%)
Spleen	(50)	(32)	(50)
Congestion	2 (4%)	1 (3%)	1 (2%)
Depletion lymphoid	6 (12%)	13 (41%)	9 (18%)
Fibrosis	2 (4%)	2 (6%)	
Hematopoietic cell proliferation	1 (2%)	1 (3%)	3 (6%)
Hyperplasia, reticulum cell			4 (8%)
Necrosis, coagulative, focal	1 (2%)		
Pigmentation		1 (3%)	
Capsule, inflammation, necrotizing, chronic active		1 (3%)	
Thymus	(42)	(18)	(42)
Congestion		1 (6%)	
Cyst	2 (5%)		1 (2%)
Depletion lymphoid	37 (88%)	13 (72%)	38 (90%)
Hemorrhage	1 (2%)	2 (11%)	1 (2%)
INTEGUMENTARY SYSTEM			
Mammary gland	(21)	(8)	(24)
Galactocele		1 (13%)	
Hyperplasia	10 (48%)	3 (38%)	19 (79%)
Pigmentation	1 (5%)		
Skin	(50)	(27)	(49)
Acanthosis	1 (2%)	2 (7%)	2 (4%)
Atrophy	1 (2%)		
Cyst epithelial inclusion	2 (4%)		1 (2%)
Hyperkeratosis	1 (2%)	1 (4%)	2 (4%)
Hyperplasia, basal cell	1 (2%)		2 (4%)
Hyperplasia, pseudoepitheliomatous		1 (4%)	
Inflammation, chronic active		1 (4%)	1 (2%)
Inflammation, hemorrhagic, acute		1 (4%)	
Inflammation, necrotizing, acute		1 (4%)	
Inflammation, necrotizing, chronic active	2 (4%)		
Ulcer			1 (2%)
Subcutaneous tissue, fibrosis	2 (4%)	1 (4%)	
Subcutaneous tissue, inflammation, chronic active		1 (4%)	
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(21)	(50)
Autolysis		1 (5%)	
Skeletal muscle	(1)	(3)	(1)
Hemorrhage		1 (33%)	

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

	Vehicle Control	Low Dose	High Dose
NERVOUS SYSTEM			
Brain	(50)	(20)	(50)
Mineralization, multifocal	1 (2%)		
Pigmentation	1 (2%)		
Meninges, hemorrhage	1 (2%)		1 (2%)
Thalamus, mineralization			1 (2%)
Third ventricle, hemorrhage		1 (5%)	
RESPIRATORY SYSTEM			
Lung	(50)	(34)	(50)
Congestion	2 (4%)	10 (29%)	4 (8%)
Crystals		1 (3%)	1 (2%)
Edema		2 (6%)	1 (2%)
Fibrosis	2 (4%)	1 (3%)	
Foreign body	1 (2%)		
Granuloma	1 (2%)	1 (3%)	2 (4%)
Hemorrhage	2 (4%)	2 (6%)	1 (2%)
Infiltration cellular, histiocytic	13 (26%)	13 (38%)	12 (24%)
Inflammation, chronic	11 (22%)	4 (12%)	2 (4%)
Inflammation, chronic active	7 (14%)	3 (9%)	6 (12%)
Metaplasia, osseous, focal			1 (2%)
Pigmentation			1 (2%)
Alveolar epithelium, hyperplasia	7 (14%)	3 (9%)	5 (10%)
Artery, hyperplasia	2 (4%)	1 (3%)	1 (2%)
Artery, mineralization	21 (42%)	16 (47%)	24 (48%)
Bronchiole, epithelium, hyperplasia	1 (2%)		1 (2%)
Bronchus, bronchiectasis		1 (3%)	
Nose	(49)	(19)	(49)
Edema		2 (11%)	
Hemorrhage	2 (4%)	1 (5%)	2 (4%)
Inflammation, acute	11 (22%)		5 (10%)
Inflammation, chronic	2 (4%)		1 (2%)
Inflammation, chronic active	4 (8%)	1 (5%)	2 (4%)
Nasolacrimal duct, inflammation, acute	1 (2%)		1 (2%)
Nasolacrimal duct, inflammation, chronic	1 (2%)	3 (16%)	2 (4%)
Nasolacrimal duct, inflammation, chronic active		1 (5%)	
Nasolacrimal duct, metaplasia, squamous		2 (11%)	4 (8%)
Nasopharyngeal duct, inflammation, chronic active	1 (2%)		
Trachea	(50)	(21)	(50)
Inflammation, necrotizing, acute			1 (2%)
Peritracheal tissue, hemorrhage	1 (2%)		
SPECIAL SENSES SYSTEM			
Ear	(3)	(1)	
Inflammation, chronic active	1 (33%)	1 (100%)	
Eye	(1)		(3)
Cataract			1 (33%)
Retina, degeneration			1 (33%)
URINARY SYSTEM			
Kidney	(50)	(49)	(50)
Congestion	3 (6%)		8 (16%)
Cyst	2 (4%)		2 (4%)
Metaplasia, osseous		1 (2%)	
Nephropathy	49 (98%)	49 (100%)	50 (100%)
Collecting tubule, mineralization	5 (10%)	10 (20%)	35 (70%)
Papilla, necrosis	1 (2%)	10 (20%)	24 (48%)
Papilla, necrosis, coagulative			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
Kidney (Continued)	(50)	(49)	(50)
Pelvis, dilatation	1 (2%)	1 (2%)	1 (2%)
Pelvis, mineralization	1 (2%)		
Pelvis, epithelium, hyperplasia	14 (28%)	7 (14%)	12 (24%)
Proximal convoluted renal tubule, inflammation, acute	6 (12%)	13 (27%)	27 (54%)
Proximal convoluted renal tubule, mineralization	1 (2%)	1 (2%)	
Proximal convoluted renal tubule, pigmentation	2 (4%)	1 (2%)	1 (2%)
Renal tubule, hyperplasia	3 (6%)	1 (2%)	3 (6%)
Renal tubule, hyperplasia, focal			1 (2%)
Urethra	(1)	(1)	(1)
Calculus, microscopic observation only	1 (100%)	1 (100%)	1 (100%)
Urinary bladder	(45)	(43)	(48)
Calculus, microscopic observation only		1 (2%)	
Hemorrhage	1 (2%)		
Inflammation, chronic	2 (4%)	1 (2%)	
Inflammation, chronic active	1 (2%)		1 (2%)

APPENDIX B

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

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine small, duodenum	(50)	*(50)	(50)
Adenocarcinoma			1 (2%)
Leiomyosarcoma		1 (2%)	
Liver	(50)	*(50)	(50)
Leukemia mononuclear	11 (22%)	3 (6%)	4 (8%)
Neoplastic nodule	1 (2%)	2 (4%)	
Mesentery	*(50)	*(50)	*(50)
Leukemia mononuclear		1 (2%)	
Sarcoma		1 (2%)	
Pancreas	(50)	*(50)	(50)
Adenoma	1 (2%)		
Leukemia mononuclear	3 (6%)	1 (2%)	
Salivary glands	(50)	*(50)	(50)
Leukemia mononuclear	1 (2%)		
Stomach, forestomach	(49)	(49)	(49)
Leukemia mononuclear	1 (2%)		
Papilloma squamous	1 (2%)		
Stomach, glandular	(50)	(49)	(50)
Leukemia mononuclear	2 (4%)	1 (2%)	
CARDIOVASCULAR SYSTEM			
Heart	(50)	*(50)	(50)
Leukemia mononuclear	7 (14%)		
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(50)	(50)
Adenoma	1 (2%)	1 (2%)	
Carcinoma		1 (2%)	
Leukemia mononuclear	9 (18%)	1 (2%)	1 (2%)
Adrenal gland, medulla	(50)	(50)	(50)
Leukemia mononuclear	9 (18%)	1 (2%)	
Pheochromocytoma, NOS			1 (2%)
Pheochromocytoma benign	3 (6%)	1 (2%)	2 (4%)
Pituitary gland	(48)	(49)	(50)
Pars distalis, adenoma	30 (63%)	24 (49%)	21 (42%)
Pars distalis, adenoma, multiple			1 (2%)
Pars distalis, leukemia mononuclear	3 (6%)	1 (2%)	
Pars intermedia, leukemia mononuclear		1 (2%)	
Pars nervosa, leukemia mononuclear		1 (2%)	
Thyroid gland	(50)	(49)	(50)
C-cell, adenoma	2 (4%)	4 (8%)	
C-cell, carcinoma	1 (2%)	1 (2%)	
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland	(36)	*(50)	(41)
Adenoma	5 (14%)	4 (8%)	
Carcinoma		2 (4%)	2 (5%)
Squamous cell carcinoma		1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
GENITAL SYSTEM (Continued)			
Ovary	(50)	*(50)	(50)
Granulosa cell tumor malignant		1 (2%)	
Granulosa cell tumor benign			1 (2%)
Leukemia mononuclear	7 (14%)		
Uterus	(50)	*(50)	(50)
Basosquamous tumor malignant		1 (2%)	
Leiomyosarcoma	1 (2%)		
Leukemia mononuclear	3 (6%)		
Polyp stromal	15 (30%)	7 (14%)	12 (24%)
Polyp stromal, multiple	1 (2%)		
Sarcoma stromal	2 (4%)	3 (6%)	
HEMATOPOIETIC SYSTEM			
Bone marrow	(49)	*(50)	(48)
Leukemia mononuclear	2 (4%)		
Lymph node	(50)	*(50)	(49)
Lumbar, leukemia mononuclear		1 (2%)	
Mediastinal, leukemia mononuclear	5 (10%)	1 (2%)	
Pancreatic, leukemia mononuclear	2 (4%)	1 (2%)	
Renal, leukemia mononuclear	1 (2%)		
Lymph node, mandibular	(42)	*(50)	(37)
Leukemia mononuclear	5 (12%)		
Squamous cell carcinoma, metastatic, Zymbal gland	1 (2%)		
Lymph node, mesenteric	(50)	*(50)	(46)
Leukemia mononuclear	4 (8%)	2 (4%)	
Spleen	(50)	(50)	(50)
Leukemia mononuclear	11 (22%)	6 (12%)	4 (8%)
Thymus	(42)	*(50)	(38)
Leukemia mononuclear	4 (10%)		
INTEGUMENTARY SYSTEM			
Mammary gland	(46)	*(50)	(40)
Adenocarcinoma	1 (2%)	1 (2%)	
Fibroadenoma	18 (39%)	8 (16%)	7 (18%)
Fibroadenoma, multiple	4 (9%)	7 (14%)	
Leukemia mononuclear	1 (2%)		
Skin	(50)	*(50)	(49)
Carcinosarcoma		1 (2%)	
Papilloma squamous		1 (2%)	
Subcutaneous tissue, fibroma	1 (2%)	1 (2%)	1 (2%)
Subcutaneous tissue, sarcoma	1 (2%)		
MUSCULOSKELETAL SYSTEM			
Skeletal muscle	*(50)	*(50)	*(50)
Leukemia mononuclear	1 (2%)		
Sarcoma		1 (2%)	
Abdominal, mesothelioma malignant	1 (2%)		
NERVOUS SYSTEM			
Brain	(50)	*(50)	(50)
Glioma benign		1 (2%)	
Leukemia mononuclear	3 (6%)		
Meninges, leukemia mononuclear		1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
RESPIRATORY SYSTEM			
Lung	(50)	*(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)		2 (4%)
Alveolar/bronchiolar carcinoma			1 (2%)
Carcinoma, metastatic, adrenal gland		1 (2%)	
Leukemia mononuclear	9 (18%)	3 (6%)	1 (2%)
Sarcoma stromal, metastatic, uterus	1 (2%)		
Squamous cell carcinoma, metastatic, Zymbal gland	1 (2%)		
Mediastinum, leukemia mononuclear	1 (2%)		
SPECIAL SENSES SYSTEM			
Zymbal gland	*(50)	*(50)	*(50)
Carcinoma			2 (4%)
Squamous cell carcinoma	1 (2%)		
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Carcinoma		1 (2%)	
Leukemia mononuclear	9 (18%)	2 (4%)	
Transitional epithelium, carcinoma			2 (4%)
Urinary bladder	(50)	(49)	(49)
Leukemia mononuclear	2 (4%)		
Transitional epithelium, papilloma		1 (2%)	
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	11 (22%)	6 (12%)	4 (8%)
Mesothelioma malignant	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Terminal sacrifice	30	35	21
Moribund sacrifice	14	9	14
Natural death	5	5	15
Terminal sacrifice	1		
Accident		1	
TUMOR SUMMARY			
Total animals with primary neoplasms **	46	46	36
Total primary neoplasms	103	84	60
Total animals with benign neoplasms	43	39	35
Total benign neoplasms	84	62	47
Total animals with malignant neoplasms	19	16	12
Total malignant neoplasms	19	22	12
Total animals with secondary neoplasms ***	2	1	
Total secondary neoplasms	3	1	
Total animals with neoplasms-- uncertain benign or malignant			1
Total uncertain neoplasms			1

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

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

WEEKS ON STUDY	0 3 1	0 6 1	0 7 0	0 7 2	0 7 3	0 7 7	0 7 9	0 8 5	0 8 9	0 9 1	0 9 1	0 9 3	0 9 6	0 9 7	0 9 8	1 0 0	1 0 1	1 0 2	1 0 4	1 0 5	1 0 5	1 0 5	1 0 5	1 0 6	1 0 6
CARCASS ID	4 0 3	4 0 4	3 9 1	3 8 5	3 5 1	3 8 2	3 5 5	3 9 4	3 9 5	3 2 3	3 7 2	3 2 4	3 4 4	3 2 5	3 6 2	3 1 3	3 8 1	3 9 3	3 7 1	3 4 5	3 1 1	3 3 1	3 6 3	3 3 4	3 3 5
ALIMENTARY SYSTEM																									
Esophagus	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	–	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X			X			X	X	X	X			X	X					
Neoplastic nodule																									
Mesentery																									+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							
Leukemia mononuclear							X							X					X						
Salivary glands	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X						
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																				X					
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X												X						
CARDIOVASCULAR SYSTEM																									
Blood vessel																						+			
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X			X					X				X	X					
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leukemia mononuclear				X			X			X			X	X	X				X	X					
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X			X			X	X	X				X	X					
Pheochromocytoma benign											X														
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	+	+	M	M	+	+	M	+	+	+	M	+	M	M	A	M	M	+	+	M	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X		X				X		X	X		X			X		X	X	X		X		
Pars distalis, leukemia mononuclear														X					X	X					
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma									X		X														
C-cell, carcinoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	–	+	+	+	M	+	+	+	+	+	M	+	+	+	M	+	M	M	M	M	M	M	+	+	+
Adenoma																									X
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X						X		X	X				X					
Oviduct																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																						X			
Leukemia mononuclear				X											X				X						
Polyp stromal				X						X	X				X	X			X		X			X	X
Polyp stromal, multiple			X																						
Sarcoma stromal												X						X							

+: Tissue examined microscopically
: Not examined
–: Present but not examined microscopically
I: Insufficient tissue

M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

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

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL:
CARCASS ID	352	332	333	341	365	374	401	312	314	315	321	322	342	343	353	354	361	364	373	375	383	384	392	402	405	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	44
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X			X																			11
Neoplastic nodule																		X								1
Mesentery			+																							2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Leukemia mononuclear																										3
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Papilloma squamous				X																						1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
CARDIOVASCULAR SYSTEM																										
Blood vessel						+																				2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear							X																			7
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X														1
Leukemia mononuclear							X																			9
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear							X																			9
Pheochromocytoma benign												X								X						3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	M	+	+	M	M	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	31
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma	X	X	X		X	X	X	X		X	X	X		X		X	X	X	X	X			X	X	X	30
Pars distalis, leukemia mononuclear																										3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																										2
C-cell, carcinoma																					X					1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	M	+	+	+	+	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	36
Adenoma		X		X						X											X					5
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear							X																			7
Oviduct																								+		1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Leukemia mononuclear																										3
Polyp stromal			X				X							X								X		X	X	15
Polyp stromal, multiple																										1
Sarcoma stromal																										2

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

WEEKS ON STUDY	031	061	070	072	073	077	079	085	089	091	091	093	096	097	098	100	101	102	104	105	105	105	105	106	106
CARCASS ID	403	404	391	385	351	382	355	394	395	323	372	324	344	325	362	313	381	393	371	345	311	331	363	334	335
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear															X					X					
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, leukemia mononuclear													X	X	X	X			X						
Pancreatic, leukemia mononuclear														X	X										
Renal, leukemia mononuclear																X									
Lymph node, mandibular	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+
Leukemia mononuclear														X	X	X			X	X					
Squamous cell carcinoma, metastatic, Zymbal gland											X														
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear														X	X				X	X					
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X			X			X	X	X	X			X	X					
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X			X			X	X					
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Adenocarcinoma																	X								
Fibroadenoma			X															X	X	X		X		X	
Fibroadenoma, multiple																X									
Leukemia mononuclear																			X						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, sarcoma		X																							
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																			+						+
Leukemia mononuclear																			X						
Abdominal, mesothelioma malignant																									X
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X															X	X					
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Leukemia mononuclear				X			X			X			X		X	X			X	X					
Sarcoma stromal, metastatic, uterus												X													
Squamous cell carcinoma, metastatic, Zymbal gland											X														
Mediastinum, leukemia mononuclear														X											
Nose	−	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye													I						+			+			
Harderian gland																									
Zymbal gland											+														
Squamous cell carcinoma											X														
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X			X			X	X	X				X	X					
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X												X						

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

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL:
CARCASS ID	352	332	333	341	365	374	401	312	314	315	321	322	342	343	353	354	361	364	373	375	383	384	392	402	405	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										2
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, leukemia mononuclear																										5
Pancreatic, leukemia mononuclear																										2
Renal, leukemia mononuclear																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	42
Leukemia mononuclear																										5
Squamous cell carcinoma, metastatic, Zymbal gland																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										4
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X			X																			11
Thymus	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	M	M	42
Leukemia mononuclear																										4
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenocarcinoma																										1
Fibroadenoma		X			X	X		X				X	X	X	X	X					X		X		X	18
Fibroadenoma, multiple	X		X														X									4
Leukemia mononuclear																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma	X																									1
Subcutaneous tissue, sarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle																										2
Leukemia mononuclear																										1
Abdominal, mesothelioma malignant																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X																			1
Leukemia mononuclear							X																			9
Sarcoma stromal, metastatic, uterus																										1
Squamous cell carcinoma, metastatic, Zymbal gland																										1
Mediastinum, leukemia mononuclear																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye			I		+																					3
Harderian gland					+									+												2
Zymbal gland																										1
Squamous cell carcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear							X																			9
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2

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

WEEKS ON STUDY	043	049	052	055	080	083	089	094	096	098	098	099	100	101	102	105	105	105	105	105	105	105	106	106	106
CARCASS ID	4944	4771	4434	4662	4664	4822	4115	4955	4355	4544	4552	5001	4114	4775	4663	4111	4113	4224	4255	4333	4442	4934	4112	4222	4223
ALIMENTARY SYSTEM																									
Esophagus	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+																		
Intestine large, cecum	–	A	+	+	+	+	+																		
Intestine large, colon	+	+	+	+	+	+	+																		
Intestine large, rectum	M	+	+	+	+	+	+																		
Intestine small	+	+	+	+	+	+	+					+													
Intestine small, duodenum	+	+	+	+	+	+	+					+													
Leiomyosarcoma																									
Intestine small, ileum	+	+	+	+	+	+	+					+													
Intestine small, jejunum	+	M	+	+	+	+	+					+													
Liver	+	+	+	+	+	+	+	+	+				+	+	+	+	+		+	+			+	+	
Leukemia mononuclear					X				X					X											
Neoplastic nodule								X								X									
Mesentery									+		+														
Leukemia mononuclear									X																
Sarcoma																									
Pancreas	+	+	+	+	+	+	+		+			+													
Leukemia mononuclear									X																
Salivary glands	+	+	+	+	+	+	+																		
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+
Leukemia mononuclear									X																
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+																		
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X		
Carcinoma																					X				
Leukemia mononuclear									X																
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X																
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+																		
Parathyroid gland	+	M	M	+	M	+	+	+	+	+		+		+	+			+				+			+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X						X			X	X	X				X		X	X	X	X
Pars distalis, leukemia mononuclear									X																
Pars intermedia, leukemia mononuclear									X																
Pars nervosa, leukemia mononuclear									X																
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma							X																		
C-cell, carcinoma																		X							
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	–	+	M	+	M	M	+				+		+												+
Adenoma											X														X
Carcinoma																									
Squamous cell carcinoma													X												
Ovary	+	+	+	+	+	+	+							+			+					+	+	+	
Granulosa cell tumor malignant																	X								
Uterus	+	+	+	+	+	+	+							+					+	+				+	
Basosquamous tumor malignant																									
Polyp stromal																		X	X					X	
Sarcoma stromal			X	X	X																				

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

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL:
CARCASS ID	432	441	444	445	451	453	455	461	465	472	473	474	481	483	484	485	491	492	502	503	504	505	421	431	443	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+		+	+	+	+	+	+	46
Intestine large																										7
Intestine large, cecum																										5
Intestine large, colon																										7
Intestine large, rectum																										6
Intestine small										+																9
Intestine small, duodenum										+																9
Leiomyosarcoma										X																1
Intestine small, ileum																										8
Intestine small, jejunum																										7
Liver						+			+					+	+				+		+		+	+	+	27
Leukemia mononuclear																										3
Neoplastic nodule																										2
Mesentery	+										+								+							5
Leukemia mononuclear																										1
Sarcoma											X															1
Pancreas																										9
Leukemia mononuclear																										1
Salivary glands																										7
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
CARDIOVASCULAR SYSTEM																										
Heart																										7
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma																										1
Leukemia mononuclear																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Pheochromocytoma benign																			X							1
Islets, pancreatic																										7
Parathyroid gland	+	+	+	+	+	+	+	+	+		+	+	+		+	+	+		+	+	+	+		+	+	34
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X	X		X		X			X	X				X		X			X	X	X	X	X	X	24
Pars distalis, leukemia mononuclear																										1
Pars intermedia, leukemia mononuclear																										1
Pars nervosa, leukemia mononuclear																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma								X	X									X								4
C-cell, carcinoma																										1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland								+						+	+				+						+	11
Adenoma														X												4
Carcinoma								X											X							2
Squamous cell carcinoma																										1
Ovary					+			+																		14
Granulosa cell tumor malignant																										1
Uterus	+	+									+	+								+				+		17
Basosquamous tumor malignant											X															1
Polyp stromal	X										X	X								X						7
Sarcoma stromal																										3

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

WEEKS ON STUDY	043	049	052	055	080	083	089	094	096	098	098	099	100	101	102	105	105	105	105	105	105	105	106	106	106
CARCASS ID	494	471	434	462	464	482	415	495	435	454	452	501	414	475	463	411	413	424	425	433	442	493	412	422	423
HEMATOPOIETIC SYSTEM																									
Blood														+											
Bone marrow	+	+	M	+	+	+	+																		
Lymph node	+	+	+	+	+	+	+		+					+	+						+				
Lumbar, leukemia mononuclear																									
Mediastinal, leukemia mononuclear																									
Pancreatic, leukemia mononuclear																									
Lymph node, mandibular	M	+	M	+	M	M	+														+				
Lymph node, mesenteric	+	+	+	+	+	+	+		+					+	+										
Leukemia mononuclear									X																
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X				X					X						X					
Thymus	+	+	+	+	+	+	+								+										
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	+	M	+	M	+		+	+	+		+									+	+	+
Adenocarcinoma																									
Fibroadenoma								X		X	X	X											X		
Fibroadenoma, multiple						X								X										X	
Skin	+	+	+	+	+	+	+			+															+
Carcinosarcoma																									
Papilloma squamous																									X
Subcutaneous tissue, fibroma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+																		
Skeletal muscle																									
Sarcoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+		+						+									+	
Glioma benign	X																								
Meninges, leukemia mononuclear									X																
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+				+					+	+		+				
Carcinoma, metastatic, adrenal gland																					X				
Leukemia mononuclear					X				X																
Nose	–	+	+	+	+	+	+																		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
None																						•			
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Leukemia mononuclear					X				X																
Urinary bladder	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																									

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

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL:
CARCASS ID	432	441	444	445	451	453	455	461	465	472	473	474	481	483	484	485	491	492	502	503	504	505	421	431	443	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										1
Bone marrow																										6
Lymph node											+									+				+	+	15
Lumbar, leukemia mononuclear											X															1
Mediastinal, leukemia mononuclear											X															1
Pancreatic, leukemia mononuclear											X															1
Lymph node, mandibular																									+	5
Lymph node, mesenteric											+									+				+		13
Leukemia mononuclear											X															2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear											X		X													6
Thymus																										8
INTEGUMENTARY SYSTEM																										
Mammary gland					+			+		+	+			+							+	+		+		18
Adenocarcinoma											X															1
Fibroadenoma								X		X												X				8
Fibroadenoma, multiple					X						X										X			X		7
Skin											+											+		+		12
Carcinosarcoma											X															1
Papilloma squamous																										1
Subcutaneous tissue, fibroma																								X		1
MUSCULOSKELETAL SYSTEM																										
Bone																										7
Skeletal muscle											+															1
Sarcoma											X															1
NERVOUS SYSTEM																										
Brain																										10
Glioma benign																										1
Meninges, leukemia mononuclear																										1
RESPIRATORY SYSTEM																										
Lung				+						+	+			+		+	+			+						20
Carcinoma, metastatic, adrenal gland																										1
Leukemia mononuclear											X															3
Nose																										6
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	48
SPECIAL SENSES SYSTEM																										
None																										
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma					X																					1
Leukemia mononuclear																										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional epithelium, papilloma																								X		1

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

WEEKS ON STUDY	017	060	070	072	072	073	073	075	076	080	081	083	084	084	085	089	089	089	094	095	095	097	097	101	102
CARCASS ID	602	593	595	521	514	573	604	551	512	603	524	533	564	581	542	601	523	561	583	513	534	582	591	535	515
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Mesentery			+		+										+	+	+								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma, NOS																									
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	M	+	+	+	+	+	M	M	M	M	M	M	+	+	M	M	M	+	M	+	+	M	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X			X				X			X		X	X	X		X		X		
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	−	+	+	+	+	+	+	+	+	M	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+
Carcinoma																							X	X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal						X	X						X								X	X			
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	M	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	M	+	M	M	+	+	M	+	+	M	+	+	+	M	M	+	+	+	M	M	+	+	M	+
Lymph node, mesenteric	+	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	+	M	+	+	+	+	+	M	+	+	+	M	+	+	M	+	M	+	+	+	+	+	+
Fibroadenoma															X	X									X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma									X																
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord						+																			
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								X	
Alveolar/bronchiolar carcinoma																									
Leukemia mononuclear																									
Nose	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear							+													+					
Eye																								I	I
Lacrimal gland																									
Zymbal gland						+	+																		
Carcinoma						X	X																		
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, carcinoma												X													
Ureter					+																				
Urinary bladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	103	103	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	106	106	106	106	106	106	TOTAL:
CARCASS ID	571	605	554	511	522	545	531	541	553	555	562	563	565	574	575	584	585	592	594	525	532	544	543	552	572	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	M	+	M	M	M	M	M	M	M	M	M	M	+	M	M	+	M	M	M	M	M	M	M	M	25
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma											X															1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear							X					X								X		X				4
Mesentery			+						+		+			+		+										10
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear							X																			1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma, NOS						X																				1
Pheochromocytoma benign							X	X																		2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	M	M	M	M	M	M	+	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	+	+	14
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X	X	X	X	X		X			X			X	X				X	X					21
Pars distalis, adenoma, multiple													X													1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	41
Carcinoma																										2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign												X														1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal	X	X							X				X			X						X		X		12
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	37
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear							X					X								X		X				4
Thymus	+	+	+	M	+	+	M	+	+	M	M	M	+	M	+	M	+	+	+	M	+	+	+	+	+	38
INTEGUMENTARY SYSTEM																										
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	40
Fibroadenoma	X			X					X					X												7
Skin	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcutaneous tissue, fibroma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X																							2
Alveolar/bronchiolar carcinoma		X																								1
Leukemia mononuclear												X														1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear																										2
Eye							I			I			I													1
Lacrimal gland																							+			1
Zymbal gland																										2
Carcinoma																										2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional epithelium, carcinoma																								X		2
Ureter																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

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

	Vehicle Control	50 mg/kg	100 mg/kg
Adrenal Medulla: Pheochromocytoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	8.8%	2.9%	13.6%
Terminal Rates (c)	2/31 (6%)	1/35 (3%)	3/22 (14%)
Day of First Observation	637	732	732
Life Table Tests (d)	P=0.464	P=0.269N	P=0.507
Logistic Regression Tests (d)	P=0.518	P=0.294N	P=0.572
Cochran-Armitage Trend Test (d)	P=0.593N		
Fisher Exact Test (d)		P=0.309N	P=0.661N
Clitoral Gland: Adenoma			
Overall Rates (a)	5/36 (14%)	(e) 4/11 (36%)	0/41 (0%)
Adjusted Rates (b)	20.8%		0.0%
Terminal Rates (c)	5/24 (21%)		0/18 (0%)
Day of First Observation	732		
Life Table Test (d)			P=0.059N
Logistic Regression Test (d)			P=0.059N
Fisher Exact Test (d)			P=0.019N
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	5/36 (14%)	(e,f) 7/11 (64%)	2/41 (5%)
Adjusted Rates (b)	20.8%		7.0%
Terminal Rates (c)	5/24 (21%)		0/18 (0%)
Day of First Observation	732		673
Life Table Test (d)			P=0.339N
Logistic Regression Test (d)			P=0.230N
Fisher Exact Test (d)			P=0.165N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	1/50 (2%)	(e) 0/20 (0%)	3/50 (6%)
Adjusted Rates (b)	3.2%		11.7%
Terminal Rates (c)	1/31 (3%)		0/22 (0%)
Day of First Observation	732		703
Life Table Test (d)			P=0.213
Logistic Regression Test (d)			P=0.228
Fisher Exact Test (d)			P=0.309
Mammary Gland: Fibroadenoma			
Overall Rates (g)	22/50 (44%)	15/50 (30%)	7/50 (14%)
Adjusted Rates (b)	62.5%	36.0%	24.7%
Terminal Rates (c)	18/31 (58%)	9/35 (26%)	3/22 (14%)
Day of First Observation	485	578	590
Life Table Tests (d)	P=0.010N	P=0.057N	P=0.017N
Logistic Regression Tests (d)	P=0.002N	P=0.076N	P=0.003N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.107N	P<0.001N
Mammary Gland: Fibroadenoma or Adenocarcinoma			
Overall Rates (g)	23/50 (46%)	15/50 (30%)	7/50 (14%)
Adjusted Rates (b)	63.6%	36.0%	24.7%
Terminal Rates (c)	18/31 (58%)	9/35 (26%)	3/22 (14%)
Day of First Observation	485	578	590
Life Table Tests (d)	P=0.007N	P=0.041N	P=0.012N
Logistic Regression Tests (d)	P<0.001N	P=0.051N	P=0.002N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.074N	P<0.001N

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

	Vehicle Control	50 mg/kg	100 mg/kg
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	30/48 (63%)	24/49 (49%)	22/50 (44%)
Adjusted Rates (b)	78.3%	61.3%	64.7%
Terminal Rates (c)	22/30 (73%)	20/35 (57%)	11/22 (50%)
Day of First Observation	485	557	504
Life Table Tests (d)	P=0.404N	P=0.048N	P=0.490N
Logistic Regression Tests (d)	P=0.087N	P=0.080N	P=0.099N
Cochran-Armitage Trend Test (d)	P=0.042N		
Fisher Exact Test (d)		P=0.128N	P=0.051N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	2/50 (4%)	4/49 (8%)	0/50 (0%)
Adjusted Rates (b)	4.8%	10.6%	0.0%
Terminal Rates (c)	0/31 (0%)	3/35 (9%)	0/22 (0%)
Day of First Observation	619	619	
Life Table Tests (d)	P=0.302N	P=0.381	P=0.289N
Logistic Regression Tests (d)	P=0.228N	P=0.327	P=0.220N
Cochran-Armitage Trend Test (d)	P=0.224N		
Fisher Exact Test (d)		P=0.329	P=0.247N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	5/49 (10%)	0/50 (0%)
Adjusted Rates (b)	7.9%	13.4%	0.0%
Terminal Rates (c)	1/31 (3%)	4/35 (11%)	0/22 (0%)
Day of First Observation	619	619	
Life Table Tests (d)	P=0.206N	P=0.412	P=0.174N
Logistic Regression Tests (d)	P=0.147N	P=0.349	P=0.118N
Cochran-Armitage Trend Test (d)	P=0.134N		
Fisher Exact Test (d)		P=0.346	P=0.121N
Uterus: Stromal Polyp			
Overall Rates (g)	16/50 (32%)	7/50 (14%)	12/50 (24%)
Adjusted Rates (b)	40.8%	20.0%	38.3%
Terminal Rates (c)	9/31 (29%)	7/35 (20%)	5/22 (23%)
Day of First Observation	485	732	508
Life Table Test (d)	P=0.446N	P=0.019N	P=0.552N
Logistic Regression Test (d)	P=0.241N	P=0.026N	P=0.290N
Fisher Exact Test (d)	P=0.203N	P=0.028N	P=0.252N
Uterus: Stromal Sarcoma			
Overall Rates (g)	2/50 (4%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	5.5%	6.3%	0.0%
Terminal Rates (c)	0/31 (0%)	0/35 (0%)	0/22 (0%)
Day of First Observation	651	359	
Life Table Test (d)	P=0.230N	P=0.514	P=0.293N
Logistic Regression Test (d)	P=0.141N	P=0.505	P=0.247N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test (d)		P=0.500	P=0.247N
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (g)	11/50 (22%)	6/50 (12%)	4/50 (8%)
Adjusted Rates (b)	26.9%	15.0%	18.2%
Terminal Rates (c)	3/31 (10%)	3/35 (9%)	4/22 (18%)
Day of First Observation	504	557	732
Life Table Tests (d)	P=0.086N	P=0.119N	P=0.147N
Logistic Regression Tests (d)	P=0.035N	P=0.146N	P=0.057N
Cochran-Armitage Trend Test (d)	P=0.030N		
Fisher Exact Test (d)		P=0.143N	P=0.045N

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

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

TABLE B4a. HISTORICAL INCIDENCE OF RENAL TRANSITIONAL CELL TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls
Historical Incidence at EG&G Mason Research Institute	0/300
Overall Historical Incidence	0/2,094

(a) Data as of May 12, 1988, for studies of at least 104 weeks

TABLE B4b. HISTORICAL INCIDENCE OF RENAL TUBULAR CELL TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence of Adenomas in Vehicle Controls
Historical Incidence at EG&G Mason Research Institute	0/300
Overall Historical Incidence	
TOTAL	(d) 2/2,094 (0.1%)
SD (b)	0.43%
Range (c)	
High	1/50
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks; no adenocarcinomas have been observed.
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes one adenoma, NOS

TABLE B4c. HISTORICAL INCIDENCE OF URINARY BLADDER TRANSITIONAL CELL TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence of Papillomas in Vehicle Controls
Historical Incidence at EG&G Mason Research Institute	0/295
Overall Historical Incidence	
TOTAL	(d) 4/2,026 (0.2%)
SD (b)	0.63%
Range (c)	
High	1/45
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks; no carcinomas have been observed.
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes one papilloma, NOS

TABLE B4d. HISTORICAL INCIDENCE OF MAMMARY GLAND TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Fibroadenomas	Adenocarcinomas	Fibroadenomas or Adenocarcinomas
Historical Incidence at EG&G Mason Research Institute			
Diglycidyl resorcinol ether	18/50	2/50	19/50
Diglycidyl resorcinol ether	17/50	0/50	17/50
1,2-Dichloropropane	15/50	1/50	15/50
Chlorodibromomethane	18/50	1/50	18/50
n-Butyl chloride	16/50	1/50	17/50
Bromodichloromethane	20/50	1/50	21/50
TOTAL	104/300 (34.7%)	6/300 (2.0%)	107/300 (35.7%)
SD (b)	3.50%	1.26%	4.08%
Range (c)			
High	20/50	2/50	21/50
Low	15/50	0/50	15/50
Overall Historical Incidence			
TOTAL	(d) 615/2,100 (29.3%)	(e) 48/2,100 (2.3%)	(d,e) 647/2,100 (30.8%)
SD (b)	9.21%	1.95%	9.87%
Range (c)			
High	26/50	5/50	28/50
Low	7/50	0/50	7/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes 17 adenomas, NOS, 1 papillary adenoma, 5 cystadenomas, NOS, and 1 papillary cystadenoma, NOS
(e) Includes two carcinomas, NOS, and one papillary cystadenocarcinoma, NOS

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large, cecum	(48)	(5)	(49)
Depletion lymphoid			1 (2%)
Parasite metazoan	1 (2%)	1 (20%)	1 (2%)
Intestine large, colon	(49)	(7)	(49)
Angiectasis			1 (2%)
Parasite metazoan	9 (18%)		6 (12%)
Mucosa, fibrosis			1 (2%)
Intestine large, rectum	(48)	(6)	(48)
Metaplasia, squamous, focal			1 (2%)
Parasite metazoan	1 (2%)		1 (2%)
Intestine small, duodenum	(50)	(9)	(50)
Abscess, chronic			1 (2%)
Inflammation, necrotizing, chronic active			2 (4%)
Epithelium, hyperplasia			1 (2%)
Muscularis, inflammation, acute			1 (2%)
Muscularis, mineralization			1 (2%)
Serosa, fibrosis			1 (2%)
Serosa, inflammation, chronic			1 (2%)
Intestine small, ileum	(49)	(8)	(50)
Lymphoid nodule, depletion			1 (2%)
Intestine small, jejunum	(49)	(7)	(49)
Hemorrhage	1 (2%)		
Inflammation, necrotizing, chronic active			1 (2%)
Ulcer			1 (2%)
Muscularis, inflammation, acute			1 (2%)
Muscularis, mineralization			1 (2%)
Liver	(50)	(27)	(50)
Angiectasis	1 (2%)	2 (7%)	1 (2%)
Basophilic focus	35 (70%)	14 (52%)	31 (62%)
Clear cell focus	4 (8%)	1 (4%)	3 (6%)
Eosinophilic focus		5 (19%)	2 (4%)
Fatty change	20 (40%)	11 (41%)	19 (38%)
Focal cellular change			1 (2%)
Hemorrhage	1 (2%)		1 (2%)
Hepatodiaphragmatic nodule	1 (2%)	3 (11%)	3 (6%)
Hyperplasia	2 (4%)	1 (4%)	2 (4%)
Inflammation, chronic active	17 (34%)	11 (41%)	10 (20%)
Mixed cell focus	2 (4%)		
Necrosis, coagulative	6 (12%)	3 (11%)	5 (10%)
Pigmentation	1 (2%)		
Bile duct, cyst	1 (2%)		
Bile duct, hyperplasia	28 (56%)	8 (30%)	23 (46%)
Centrilobular, cytomegaly			1 (2%)
Kupffer cell, hyperplasia, focal	1 (2%)		1 (2%)
Periportal, fibrosis	2 (4%)	1 (4%)	1 (2%)
Serosa, inflammation, chronic, focal		1 (4%)	
Serosa, inflammation, suppurative			1 (2%)
Subserosa, necrosis, coagulative			1 (2%)
Mesentery	(2)	(5)	(10)
Fibrosis	1 (50%)	3 (60%)	2 (20%)
Hemorrhage		1 (20%)	1 (10%)
Inflammation, chronic active	1 (50%)		5 (50%)
Mineralization		2 (40%)	4 (40%)
Necrosis, coagulative	1 (50%)	3 (60%)	5 (50%)

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

	Vehicle Control	Low Dose	High Dose
ALIMENTARY SYSTEM (Continued)			
Pancreas	(50)	(9)	(50)
Atrophy	11 (22%)	3 (33%)	11 (22%)
Fibrosis, focal	1 (2%)		
Hyperplasia	1 (2%)		
Inflammation, chronic	12 (24%)	2 (22%)	7 (14%)
Salivary glands	(50)	(7)	(50)
Inflammation, chronic, focal	1 (2%)		
Stomach, forestomach	(49)	(49)	(49)
Acanthosis	4 (8%)		12 (24%)
Edema			1 (2%)
Erosion			1 (2%)
Hyperkeratosis	3 (6%)		12 (24%)
Hyperplasia, basal cell	4 (8%)	1 (2%)	12 (24%)
Inflammation, chronic active			1 (2%)
Inflammation, granulomatous	1 (2%)		
Ulcer	1 (2%)	1 (2%)	12 (24%)
Ulcer, multiple	1 (2%)		
Muscularis, mineralization		1 (2%)	
Submucosa, foreign body	1 (2%)		
Stomach, glandular	(50)	(49)	(50)
Abscess			1 (2%)
Edema			1 (2%)
Erosion	2 (4%)	1 (2%)	2 (4%)
Fibrosis		1 (2%)	
Inflammation, chronic	1 (2%)		
Inflammation, chronic active			5 (10%)
Mineralization	1 (2%)		4 (8%)
Ulcer			3 (6%)
Muscularis, mineralization		2 (4%)	
CARDIOVASCULAR SYSTEM			
Blood vessel	(2)		
Aorta, inflammation, chronic active	1 (50%)		
Heart	(50)	(7)	(50)
Cardiomyopathy	35 (70%)	4 (57%)	43 (86%)
Mineralization			3 (6%)
Necrosis, focal			1 (2%)
Atrium, embolus	1 (2%)		
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(50)	(50)
Angiectasis	30 (60%)	26 (52%)	17 (34%)
Atrophy	1 (2%)	1 (2%)	
Autolysis	1 (2%)	1 (2%)	
Congestion	1 (2%)		
Degeneration	1 (2%)		
Degeneration, fatty			1 (2%)
Hyperplasia	7 (14%)	12 (24%)	9 (18%)
Mineralization	1 (2%)		
Necrosis, coagulative	1 (2%)	2 (4%)	2 (4%)
Pigmentation	1 (2%)		
Vacuolization cytoplasmic	24 (48%)	27 (54%)	31 (62%)
Adrenal gland, medulla	(50)	(50)	(50)
Angiectasis		1 (2%)	
Autolysis	1 (2%)	1 (2%)	
Hyperplasia	3 (6%)	6 (12%)	19 (38%)
Necrosis, coagulative		2 (4%)	
Thrombus			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
Islets, pancreatic	(50)	(7)	(50)
Angiectasis, focal	1 (2%)		
Hyperplasia	1 (2%)		
Parathyroid gland	(31)	(34)	(14)
Hyperplasia			3 (21%)
Pituitary gland	(48)	(49)	(50)
Pars distalis, angiectasis	36 (75%)	19 (39%)	30 (60%)
Pars distalis, cyst	23 (48%)	26 (53%)	23 (46%)
Pars distalis, hemorrhage		1 (2%)	
Pars distalis, hyperplasia	10 (21%)	6 (12%)	15 (30%)
Pars distalis, pigmentation	12 (25%)	2 (4%)	6 (12%)
Pars intermedia, angiectasis	2 (4%)	2 (4%)	1 (2%)
Pars intermedia, cyst		4 (8%)	
Pars intermedia, pigmentation	2 (4%)		
Pars nervosa, angiectasis	2 (4%)	1 (2%)	
Pars nervosa, cyst	1 (2%)		
Pars nervosa, pigmentation	1 (2%)		
Thyroid gland	(50)	(49)	(50)
Inflammation, chronic	1 (2%)		
C-cell, hyperplasia	24 (48%)	26 (53%)	24 (48%)
Follicular cell, cyst		1 (2%)	
Follicular cell, hyperplasia	1 (2%)		
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland	(36)	(11)	(41)
Inflammation, acute		1 (9%)	3 (7%)
Inflammation, chronic	8 (22%)		6 (15%)
Inflammation, chronic active	12 (33%)	1 (9%)	17 (41%)
Inflammation, necrotizing, chronic active		4 (36%)	
Ovary	(50)	(14)	(50)
Atrophy		1 (7%)	
Congestion	1 (2%)		
Cyst	3 (6%)	2 (14%)	2 (4%)
Hyperplasia			1 (2%)
Mineralization	2 (4%)		
Corpus luteum, cyst	1 (2%)		
Periovarian tissue, cyst	4 (8%)	4 (29%)	
Oviduct	(1)		
Inflammation, chronic	1 (100%)		
Uterus	(50)	(17)	(50)
Hydrometria	6 (12%)	1 (6%)	9 (18%)
Inflammation, acute	2 (4%)		1 (2%)
Thrombus	1 (2%)		
Endometrium, hyperplasia	9 (18%)	3 (18%)	7 (14%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(49)	(6)	(48)
Myelofibrosis	1 (2%)		1 (2%)
Lymph node	(50)	(15)	(49)
Mediastinal, depletion lymphoid		1 (7%)	1 (2%)
Mediastinal, ectasia		1 (7%)	
Mediastinal, hemorrhage	3 (6%)	3 (20%)	11 (22%)
Mediastinal, hyperplasia	2 (4%)		
Mediastinal, inflammation, chronic active			1 (2%)
Mediastinal, pigmentation	4 (8%)		

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
Lymph node (Continued)	(50)	(15)	(49)
Pancreatic, depletion lymphoid	1 (2%)		
Pancreatic, infiltration cellular, histiocytic	1 (2%)		
Pancreatic, pigmentation	3 (6%)		
Renal, angiectasis	1 (2%)		
Renal, ectasia			1 (2%)
Renal, hemorrhage	1 (2%)		
Renal, hyperplasia		1 (7%)	
Renal, infiltration cellular, histiocytic			1 (2%)
Renal, pigmentation			1 (2%)
Lymph node, mandibular	(42)	(5)	(37)
Angiectasis	1 (2%)		
Depletion lymphoid			1 (3%)
Ectasia	4 (10%)		1 (3%)
Hemorrhage	6 (14%)	2 (40%)	7 (19%)
Hyperplasia	1 (2%)		5 (14%)
Infiltration cellular, histiocytic			1 (3%)
Pigmentation	1 (2%)		1 (3%)
Lymph node, mesenteric	(50)	(13)	(46)
Depletion lymphoid		1 (8%)	2 (4%)
Ectasia			5 (11%)
Hemorrhage	2 (4%)		4 (9%)
Hyperplasia			1 (2%)
Infiltration cellular, histiocytic	35 (70%)	5 (38%)	28 (61%)
Pigmentation	34 (68%)	7 (54%)	29 (63%)
Spleen	(50)	(50)	(50)
Congestion	2 (4%)	1 (2%)	
Depletion lymphoid	14 (28%)	14 (28%)	19 (38%)
Hematopoietic cell proliferation	1 (2%)		4 (8%)
Pigmentation	4 (8%)	5 (10%)	1 (2%)
Capsule, fibrosis, focal	1 (2%)		
Subcapsular, necrosis, coagulative			1 (2%)
Thymus	(42)	(8)	(38)
Congestion		1 (13%)	2 (5%)
Cyst			2 (5%)
Depletion lymphoid	28 (67%)	6 (75%)	32 (84%)
Hemorrhage	2 (5%)	2 (25%)	
Necrosis	1 (2%)		
INTEGUMENTARY SYSTEM			
Mammary gland	(46)	(18)	(40)
Degeneration			1 (3%)
Galactocele	4 (9%)	1 (6%)	1 (3%)
Hyperplasia	41 (89%)	5 (28%)	32 (80%)
Inflammation, chronic active	1 (2%)		
Skin	(50)	(12)	(49)
Subcutaneous tissue, inflammation, granulomatous, chronic active		1 (8%)	
MUSCULOSKELETAL SYSTEM			
Bone	(49)	(7)	(50)
Fibrous osteodystrophy			1 (2%)
Hyperostosis			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
NERVOUS SYSTEM			
Brain	(50)	(10)	(50)
Congestion			1 (2%)
Hemorrhage	2 (4%)		
Hydrocephalus	1 (2%)		
Cerebellum, infarct	2 (4%)		
Medulla, infarct	1 (2%)		
RESPIRATORY SYSTEM			
Lung	(50)	(20)	(50)
Congestion	1 (2%)	3 (15%)	2 (4%)
Edema			2 (4%)
Foreign body			4 (8%)
Granuloma			1 (2%)
Hemorrhage	4 (8%)	1 (5%)	
Infiltration cellular, histiocytic	9 (18%)	6 (30%)	22 (44%)
Inflammation, acute			3 (6%)
Inflammation, chronic	11 (22%)		8 (16%)
Inflammation, chronic active	9 (18%)	4 (20%)	6 (12%)
Inflammation, necrotizing, acute	1 (2%)		1 (2%)
Thrombus, multiple			1 (2%)
Alveolar epithelium, hyperplasia	9 (18%)	1 (5%)	2 (4%)
Artery, hyperplasia	1 (2%)		
Artery, mineralization	18 (36%)	4 (20%)	19 (38%)
Bronchus, mineralization			1 (2%)
Nose	(48)	(6)	(49)
Inflammation, acute	4 (8%)		3 (6%)
Inflammation, chronic			1 (2%)
Inflammation, chronic active	5 (10%)		1 (2%)
Inflammation, necrotizing, acute			1 (2%)
Inflammation, necrotizing, chronic active	1 (2%)		
Nasolacrimal duct, inflammation, chronic	1 (2%)	1 (17%)	3 (6%)
Nasolacrimal duct, inflammation, chronic active	1 (2%)		1 (2%)
Nasolacrimal duct, metaplasia, squamous		1 (17%)	1 (2%)
Trachea	(50)	(48)	(50)
Inflammation, necrotizing, acute			1 (2%)
SPECIAL SENSES SYSTEM			
Eye	(3)		
Cataract	1 (33%)		
Retina, degeneration	1 (33%)		
Sclera, metaplasia, osseous	1 (33%)		
Harderian gland	(2)		
Hyperplasia	1 (50%)		
Inflammation, chronic	1 (50%)		
Lacrimal gland			(1)
Hyperplasia			1 (100%)
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Atrophy	1 (2%)		
Bacterium			3 (6%)
Cyst	1 (2%)	2 (4%)	16 (32%)
Inflammation, chronic active			1 (2%)
Inflammation, necrotizing, acute		1 (2%)	2 (4%)
Inflammation, necrotizing, chronic active			2 (4%)
Nephropathy	38 (76%)	46 (92%)	47 (94%)
Pigmentation	2 (4%)		1 (2%)
Collecting tubule, mineralization	3 (6%)	31 (62%)	46 (92%)
Distal convoluted renal tubule, mineralization	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
Kidney (Continued)	(50)	(50)	(50)
Papilla, angiectasis			4 (8%)
Papilla, inflammation, acute			2 (4%)
Papilla, mineralization		1 (2%)	
Papilla, necrosis		18 (36%)	35 (70%)
Papilla, necrosis, coagulative			6 (12%)
Pelvis, calculus gross observation			1 (2%)
Pelvis, dilatation	1 (2%)		22 (44%)
Pelvis, epithelium, hyperplasia	7 (14%)	20 (40%)	37 (74%)
Pelvis, epithelium, mineralization	13 (26%)	11 (22%)	6 (12%)
Proximal convoluted renal tubule, hyperplasia			1 (2%)
Proximal convoluted renal tubule, inflammation, acute	2 (4%)	4 (8%)	26 (52%)
Proximal convoluted renal tubule, mineralization	1 (2%)		4 (8%)
Proximal convoluted renal tubule, pigmentation	4 (8%)	1 (2%)	1 (2%)
Renal tubule, hyperplasia	1 (2%)	1 (2%)	1 (2%)
Ureter			(1)
Dilatation			1 (100%)
Urinary bladder	(50)	(49)	(49)
Calculus, gross observation	1 (2%)		
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic active	1 (2%)		1 (2%)
Inflammation, necrotizing, acute		1 (2%)	
Inflammation, necrotizing, acute, focal			1 (2%)
Metaplasia, squamous	1 (2%)		
Transitional epithelium, hyperplasia	1 (2%)		3 (6%)

APPENDIX C

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

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine small, duodenum	(49)	*(50)	(50)
Lymphoma malignant undifferentiated cell type	1 (2%)	1 (2%)	
Intestine small, ileum	(49)	*(50)	(50)
Lymphoma malignant mixed		3 (6%)	1 (2%)
Lymphoma malignant undifferentiated cell type	2 (4%)		
Intestine small, jejunum	(49)	*(50)	(49)
Lymphoma malignant mixed			1 (2%)
Lymphoma malignant undifferentiated cell type	1 (2%)		
Liver	(50)	(50)	(50)
Adenoma, multiple			1 (2%)
Hemangiosarcoma		2 (4%)	
Hepatocellular carcinoma	8 (16%)	3 (6%)	11 (22%)
Hepatocellular carcinoma, multiple		1 (2%)	
Hepatocellular adenoma	6 (12%)	9 (18%)	15 (30%)
Hepatocellular adenoma, multiple	2 (4%)	3 (6%)	8 (16%)
Lymphoma malignant histiocytic	1 (2%)	1 (2%)	
Lymphoma malignant	1 (2%)		
Lymphoma malignant undifferentiated cell type	1 (2%)		
Salivary glands	(50)	*(50)	(50)
Hepatocellular carcinoma, metastatic			1 (2%)
Stomach, forestomach	(48)	*(50)	(50)
Papilloma squamous	1 (2%)		
Squamous cell carcinoma			1 (2%)
Stomach, glandular	(48)	*(50)	(50)
Lymphoma malignant undifferentiated cell type		1 (2%)	
CARDIOVASCULAR SYSTEM			
Heart	(50)	*(50)	(50)
Hepatocellular carcinoma, metastatic			1 (2%)
Lymphoma malignant undifferentiated cell type	1 (2%)		
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(49)	*(50)	(48)
Adenoma			1 (2%)
Pituitary gland	(47)	*(50)	(45)
Lymphoma malignant undifferentiated cell type		1 (2%)	
Pars distalis, adenoma	1 (2%)		1 (2%)
Pars intermedia, adenoma			1 (2%)
Thyroid gland	(48)	*(50)	(49)
Follicular cell, adenoma			1 (2%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Coagulating gland	*(50)	*(50)	*(50)
Adenocarcinoma	1 (2%)		
Preputial gland	*(50)	*(50)	*(50)
Basosquamous tumor, NOS	1 (2%)		
Squamous cell carcinoma		1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
Lymph node	(50)	*(50)	(50)
Bronchial, lymphoma malignant histiocytic	1 (2%)		
Bronchial, lymphoma malignant undifferentiated cell type	1 (2%)		
Lumbar, lymphoma malignant histiocytic		1 (2%)	
Mediastinal, lymphoma malignant histiocytic	1 (2%)	1 (2%)	
Mediastinal, lymphoma malignant	1 (2%)		
Mediastinal, lymphoma malignant mixed		3 (6%)	
Pancreatic, lymphoma malignant histiocytic		1 (2%)	
Pancreatic, lymphoma malignant mixed		1 (2%)	
Pancreatic, lymphoma malignant undifferentiated cell type	1 (2%)	1 (2%)	
Renal, lymphoma malignant histiocytic		1 (2%)	
Renal, lymphoma malignant mixed	1 (2%)	3 (6%)	
Lymph node, mandibular	(27)	*(50)	(23)
Lymphoma malignant histiocytic	1 (4%)		
Lymph node, mesenteric	(45)	*(50)	(47)
Lymphoma malignant histiocytic	2 (4%)		
Lymphoma malignant mixed	1 (2%)	2 (4%)	
Lymphoma malignant undifferentiated cell type	1 (2%)		
Spleen	(50)	*(50)	(50)
Hemangiosarcoma		1 (2%)	
Lymphoma malignant histiocytic	1 (2%)	1 (2%)	
Lymphoma malignant	1 (2%)		
Lymphoma malignant mixed	1 (2%)	3 (6%)	
Lymphoma malignant undifferentiated cell type	3 (6%)	3 (6%)	
Thymus	(41)	*(50)	(34)
Lymphoma malignant histiocytic	1 (2%)		
INTEGUMENTARY SYSTEM			
Skin	(50)	*(50)	(49)
Squamous cell carcinoma		1 (2%)	
Subcutaneous tissue, fibroma	1 (2%)	1 (2%)	2 (4%)
Subcutaneous tissue, fibrosarcoma	3 (6%)	2 (4%)	7 (14%)
Subcutaneous tissue, lipoma	1 (2%)		
Subcutaneous tissue, sarcoma			1 (2%)
MUSCULOSKELETAL SYSTEM			
Bone	(50)	*(50)	(50)
Scapula, osteosarcoma	1 (2%)		
Skeletal muscle	*(50)	*(50)	*(50)
Thoracic, lymphoma malignant	1 (2%)		
NERVOUS SYSTEM			
Brain	(50)	*(50)	(50)
Lymphoma malignant undifferentiated cell type		1 (2%)	
RESPIRATORY SYSTEM			
Lung	(50)	*(50)	(50)
Alveolar/bronchiolar adenoma	5 (10%)	5 (10%)	4 (8%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)	1 (2%)	
Alveolar/bronchiolar carcinoma			1 (2%)
Hepatocellular carcinoma, metastatic	4 (8%)		4 (8%)
Lymphoma malignant histiocytic	1 (2%)	1 (2%)	
Lymphoma malignant	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
SPECIAL SENSES SYSTEM			
Ear	*(50)	*(50)	*(50)
Fibrosarcoma	1 (2%)		
Eye	*(50)	*(50)	*(50)
Lids, fibrosarcoma, metastatic, ear	1 (2%)		
Harderian gland	*(50)	*(50)	*(50)
Adenoma	2 (4%)	1 (2%)	1 (2%)
URINARY SYSTEM			
Kidney	(49)	(50)	(50)
Lymphoma malignant histiocytic	1 (2%)		
Lymphoma malignant mixed		1 (2%)	
Lymphoma malignant undifferentiated cell type	1 (2%)		
Renal tubule, hepatocellular carcinoma, metastatic			1 (2%)
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Lymphoma malignant	1 (2%)		
Lymphoma malignant histiocytic	2 (4%)	1 (2%)	
Lymphoma malignant undifferentiated cell	3 (6%)	3 (6%)	
Lymphoma malignant mixed	1 (2%)	4 (8%)	1 (2%)
Hemangiosarcoma		3 (6%)	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Moribund sacrifice	12	6	11
Terminal sacrifice	35	40	36
Natural death	3	2	3
Accident		2	
TUMOR SUMMARY			
Total animals with primary neoplasms **	30	28	40
Total primary neoplasms	42	39	57
Total animals with benign neoplasms	17	17	30
Total benign neoplasms	20	20	35
Total animals with malignant neoplasms	18	17	21
Total malignant neoplasms	21	19	22
Total animals with secondary neoplasms ***	5		4
Total secondary neoplasms	5		7
Total animals with neoplasms--uncertain benign or malignant	1		
Total uncertain neoplasms	1		

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

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

WEEKS ON STUDY	063	080	084	085	087	090	092	095	096	100	100	101	102	102	106	106	106	106	106	106	106	106	106	106	106
CARCASS ID	033	065	095	054	094	024	034	051	063	075	111	155	052	082	012	133	141	021	022	023	025	031	032	035	041
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	M	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, cecum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, rectum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma	X				X		X	X					X												
Hepatocellular adenoma										X		X							X						
Hepatocellular adenoma, multiple						X																			
Lymphoma malignant histiocytic		X																							
Lymphoma malignant																		X							
Lymphoma malignant undifferentiated cell type																									
Mesentery					+																				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+
Tooth									+	+	+					+	+		+	+	+	+	+		
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Parathyroid gland	M	M	M	+	M	M	M	M	+	M	+	+	M	+	M	+	+	+	+	M	+	+	+	M	+
Pituitary gland	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Pars distalis, adenoma														X											
Thyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
GENERAL BODY SYSTEM																									
Tissue, NOS	+						+																		
GENITAL SYSTEM																									
Coagulating gland																									
Adenocarcinoma																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland								+			+			+	+						+				
Basosquamous tumor, NOS								X																	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+: Tissue examined microscopically
: Not examined
−: Present but not examined microscopically
I: Insufficient tissue

M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

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

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	
CARCASS ID	042	043	044	045	053	055	061	062	064	071	072	073	083	085	074	081	084	091	092	093	101	102	103	104	105	TOTAL: TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+		46
Gallbladder	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		45
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Lymphoma malignant undifferentiated cell type														X												1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Lymphoma malignant undifferentiated cell type													X							X						2
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Lymphoma malignant undifferentiated cell type													X													1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hepatocellular carcinoma							X										X			X						8
Hepatocellular adenoma	X																				X			X		6
Hepatocellular adenoma, multiple											X															2
Lymphoma malignant histiocytic																										1
Lymphoma malignant																										1
Lymphoma malignant undifferentiated cell type																				X						1
Mesentery	+												+									+				4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Papilloma squamous														X												1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Tooth	+		+				+	+	+											+		+				17
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymphoma malignant undifferentiated cell type														X												1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+		48
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Parathyroid gland	M	+	+	+	+	M	M	+	+	+	M	+	M	+	M	M	M	+	+	M	+	M	+	+	M	27
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Pars distalis, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
GENERAL BODY SYSTEM																										
Tissue, NOS																										2
GENITAL SYSTEM																										
Coagulating gland																							+			1
Adenocarcinoma																							X			1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland										+							+	+				+	+			10
Basosquamous tumor, NOS																										1
Prostate	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

WEEKS ON STUDY	063	080	084	085	087	090	092	095	096	100	100	101	102	102	106	106	106	106	106	106	106	106	106	106	106
CARCASS ID	033	065	095	054	094	024	034	051	063	075	111	115	052	082	112	113	114	021	022	023	025	031	032	035	041
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bronchial, lymphoma malignant histiocytic		X																							
Bronchial, lymphoma malignant undifferentiated cell type																									
Mediastinal, lymphoma malignant histiocytic		X																							
Mediastinal, lymphoma malignant																		X							
Pancreatic, lymphoma malignant undifferentiated cell type																									
Renal, lymphoma malignant mixed					X																				
Lymph node, mandibular	M	+	M	M	M	+	M	M	M	+	+	+	M	M	M	+	+	M	+	+	+	M	+	M	+
Lymphoma malignant histiocytic		X																							
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+	+	+
Lymphoma malignant histiocytic		X																							
Lymphoma malignant mixed					X																				
Lymphoma malignant undifferentiated cell type																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic		X																							
Lymphoma malignant																		X							
Lymphoma malignant mixed					X																				
Lymphoma malignant undifferentiated cell type																									
Thymus	+	+	M	+	M	M	M	+	+	+	+	M	+	+	+	+	+	A	+	M	M	+	+	+	+
Lymphoma malignant histiocytic		X																							
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma				X		X								X											
Subcutaneous tissue, lipoma												X													
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Scapula, osteosarcoma										X															
Skeletal muscle																		+							
Thoracic, lymphoma malignant																		X							
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								X	
Alveolar/bronchiolar adenoma, multiple																									
Hepatocellular carcinoma, metastatic							X	X					X												
Lymphoma malignant histiocytic		X																							
Lymphoma malignant																		X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear									+																
Fibrosarcoma									X																
Eye									+								I								
Lids, fibrosarcoma, metastatic, ear									X																
Harderian gland									+								+								
Adenoma																	X								
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Lymphoma malignant histiocytic		X																							
Lymphoma malignant undifferentiated cell type																									
Urethra																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	
CARCASS ID	042	043	044	045	053	055	061	062	064	071	072	073	083	085	074	081	084	091	092	093	101	102	103	104	105	TOTAL: TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bronchial, lymphoma malignant histiocytic																										1
Bronchial, lymphoma malignant undifferentiated cell type														X												1
Mediastinal, lymphoma malignant histiocytic																										1
Mediastinal, lymphoma malignant																										1
Pancreatic, lymphoma malignant undifferentiated cell type													X													1
Renal, lymphoma malignant mixed																										1
Lymph node, mandibular	+	+	+	M	+	M	M	+	+	+	M	+	M	M	M	+	M	+	M	M	+	+	+	+	+	27
Lymphoma malignant histiocytic																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	45
Lymphoma malignant histiocytic							X																			2
Lymphoma malignant mixed																										1
Lymphoma malignant undifferentiated cell type													X													1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Lymphoma malignant																										1
Lymphoma malignant mixed																										1
Lymphoma malignant undifferentiated cell type													X	X						X						3
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	41
Lymphoma malignant histiocytic																										1
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma								X																		1
Subcutaneous tissue, fibrosarcoma																										3
Subcutaneous tissue, lipoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Scapula, osteosarcoma																										1
Skeletal muscle									+																	2
Thoracic, lymphoma malignant																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X			X															X		X				5
Alveolar/bronchiolar adenoma, multiple																					X					1
Hepatocellular carcinoma, metastatic																	X									4
Lymphoma malignant histiocytic																										1
Lymphoma malignant																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Ear																										1
Fibrosarcoma																										1
Eye																					+					2
Lids, fibrosarcoma, metastatic, ear																										1
Harderian gland																					+					3
Adenoma																					X					2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant histiocytic																										1
Lymphoma malignant undifferentiated cell type																				X						1
Urethra																+			+					+	+	4
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

WEEKS ON STUDY	0 0 1	0 0 1	0 8 8	0 9 0	0 9 1	0 9 3	0 9 5	1 0 0	1 0 0	1 0 1	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5
CARCASS ID	1 4 2	1 8 3	1 8 1	1 2 1	1 2 5	1 9 4	1 8 2	1 9 2	2 0 5	1 3 3	1 1 1	1 1 2	1 1 3	1 1 4	1 1 5	1 2 2	1 2 3	1 2 4	1 3 1	1 3 2	1 3 4	1 3 5	1 4 1	1 4 3	1 4 4
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	M																				
Gallbladder	+	+	+	+	+					+	+	+		+	+	+	+				+		+	+	
Intestine large	+	+	+	+	+															+					
Intestine large, cecum	–	–	+	+	+																				
Intestine large, colon	+	+	+	+	+																				
Intestine large, rectum	M	M	+	+	+																				
Intestine small	+	+	+	+	+															+					
Intestine small, duodenum	+	+	+	+	+																				
Lymphoma malignant undifferentiated cell type			X																						
Intestine small, ileum	+	+	+	+	+															+					
Lymphoma malignant mixed																				X					
Intestine small, jejunum	M	M	+	+	+																				
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X																					X
Hepatocellular carcinoma																									
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma														X						X					
Hepatocellular adenoma, multiple						X																			
Lymphoma malignant histiocytic							X																		
Mesentery				+																					
Pancreas	+	+	+	+	+																				
Salivary glands	M	+	+	+	+																				
Stomach	+	+	+	+	+																				
Stomach, forestomach	+	+	+	+	+																				
Stomach, glandular	+	+	+	+	+																				
Lymphoma malignant undifferentiated cell type			X																						
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+																				
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+		+	+	+																
Adrenal gland, cortex	+	+	+	+	+		+	+	+																
Adrenal gland, medulla	+	+	+	+	+		+	+	+																
Islets, pancreatic	+	+	+	+	+																				
Parathyroid gland	+	M	+	+	M																				
Pituitary gland	+	+	+	+	+																				
Lymphoma malignant undifferentiated cell type			X																						
Thyroid gland	+	+	+	+	+																				
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Coagulating gland																									
Epididymis	–	–	+	+	+																				+
Preputial gland										+	+						+				+				
Squamous cell carcinoma																					X				
Prostate	+	+	+	+	+																				
Seminal vesicle	+	+	+	+	+																				
Testes	+	+	+	+	+																				+

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	145	151	152	153	154	155	161	164	165	171	162	163	172	173	174	175	184	185	191	193	195	201	202	203	204	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus																										4
Gallbladder		+		+				+	+													+				20
Intestine large																										6
Intestine large, cecum																										3
Intestine large, colon																										5
Intestine large, rectum																										3
Intestine small		+					+										+									9
Intestine small, duodenum																										5
Lymphoma malignant undifferentiated cell type																										1
Intestine small, ileum		+					+										+									9
Lymphoma malignant mixed							X										X									3
Intestine small, jejunum																										3
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										2
Hepatocellular carcinoma					X								X											X		3
Hepatocellular carcinoma, multiple																			X							1
Hepatocellular adenoma			X	X	X					X						X						X			X	9
Hepatocellular adenoma, multiple																	X		X							3
Lymphoma malignant histiocytic																										1
Mesentery		+																								2
Pancreas		+			+																			+		8
Salivary glands																										4
Stomach																										5
Stomach, forestomach																										5
Stomach, glandular																										5
Lymphoma malignant undifferentiated cell type																										1
CARDIOVASCULAR SYSTEM																										
Heart																										5
ENDOCRINE SYSTEM																										
Adrenal gland																										8
Adrenal gland, cortex																										8
Adrenal gland, medulla																										8
Islets, pancreatic																										5
Parathyroid gland																										3
Pituitary gland																										5
Lymphoma malignant undifferentiated cell type																										1
Thyroid gland																										5
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Coagulating gland																									+	1
Epididymis																										4
Preputial gland		+		+	+			+		+		+	+			+		+		+						14
Squamous cell carcinoma																										1
Prostate																										5
Seminal vesicle																			+							6
Testes															+											7

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

WEEKS ON STUDY	001	001	088	090	091	093	095	100	100	101	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	142	183	181	121	125	194	182	192	205	133	111	112	113	114	115	122	123	124	131	132	134	135	141	143	144
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+																					
Lymph node	M	+	+	+	+		+	+	+			+						+		+	+		+			
Lumbar, lymphoma malignant histiocytic							X																			
Mediastinal, lymphoma malignant histiocytic							X																			
Mediastinal, lymphoma malignant mixed																				X						
Pancreatic, lymphoma malignant histiocytic							X																			
Pancreatic, lymphoma malignant mixed																										
Pancreatic, lymphoma malignant undifferentiated cell type								X																		
Renal, lymphoma malignant histiocytic							X																			
Renal, lymphoma malignant mixed																				X						
Lymph node, mandibular	M	M	M	+	M																					
Lymph node, mesenteric	M	+	+	M	+							+						+		+	+		+			
Lymphoma malignant mixed																				X						
Spleen	+	+	+	+	+		+	+	+				+							+			+			
Hemangiosarcoma																							X			
Lymphoma malignant histiocytic							X																			
Lymphoma malignant mixed																				X						
Lymphoma malignant undifferentiated cell type			X					X																		
Thymus	M	+	+	+	+																					
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	M	M																					
Skin	+	+	+	+	+				+	+									+				+			
Squamous cell carcinoma																										
Subcutaneous tissue, fibroma																			X							
Subcutaneous tissue, fibrosarcoma			X																				X			
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+		+	+	+			+	+	+					+	+	+	+	+	+	+	
NERVOUS SYSTEM																										
Brain	+	+	+	+	+																					
Lymphoma malignant undifferentiated cell type			X																							
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+		+				+				+			+								
Alveolar/bronchiolar adenoma			X								X							X								
Alveolar/bronchiolar adenoma, multiple																										
Lymphoma malignant histiocytic							X																			
Nose	–	–	+	+	+																					
Trachea	+	+	+	+	+																					
SPECIAL SENSES SYSTEM																										
Ear						+																				
Harderian gland																		+		M			+			
Adenoma																		X								
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymphoma malignant mixed																										
Urinary bladder	+	+	+	+	+																					

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	145	151	152	153	154	155	161	164	165	171	162	163	172	173	174	175	184	185	191	193	195	201	202	203	204	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow																										5
Lymph node			+	+	+		+	+		+	+			+	+	+	+			+		+		+	+	27
Lumbar, lymphoma malignant histiocyt.																										1
Mediastinal, lymphoma malignant histiocytic																										1
Mediastinal, lymphoma malignant mixed			X				X																			3
Pancreatic, lymphoma malignant histiocytic																										1
Pancreatic, lymphoma malignant mixed			X																							1
Pancreatic, lymphoma malignant undifferentiated cell type																										1
Renal, lymphoma malignant histiocytic																										1
Renal, lymphoma malignant mixed			X				X																			3
Lymph node, mandibular																										1
Lymph node, mesenteric				+			+	+		+	+			+		+	+			+		+		+	+	20
Lymphoma malignant mixed							X																			2
Spleen			+				+	+	+					+	+	+			+					+		20
Hemangiosarcoma																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed			X				X																			3
Lymphoma malignant undifferentiated cell type									X																	3
Thymus																										4
INTEGUMENTARY SYSTEM																										
Mammary gland																										11
Skin														+	+											1
Squamous cell carcinoma															X											1
Subcutaneous tissue, fibroma																										2
Subcutaneous tissue, fibrosarcoma																										
MUSCULOSKELETAL SYSTEM																										
Bone	+	+				+	+	+	+		+	+		+	+		+	+	+	+		+				33
NERVOUS SYSTEM																										
Brain																										5
Lymphoma malignant undifferentiated cell type																										1
RESPIRATORY SYSTEM																										
Lung										+								+			+	+	+			14
Alveolar/bronchiolar adenoma										X												X				5
Alveolar/bronchiolar adenoma, multiple																		X								1
Lymphoma malignant histiocytic																										1
Nose																										1
Trachea																										3
																										5
SPECIAL SENSES SYSTEM																										
Ear																										1
Harderian gland																										2
Adenoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed							X																			1
Urinary bladder																		+								6

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

WEEKS ON STUDY	060	060	072	077	086	086	089	092	095	100	100	100	101	102	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	264	265	224	304	211	221	263	231	303	272	295	302	225	244	212	213	214	234	215	222	223	232	233	235	241
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	M	M	M	+	+	+	+	+	+
Gallbladder	+	M	M	M	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed														X											
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Lymphoma malignant mixed														X											
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, multiple			X																						
Hepatocellular carcinoma			X			X		X			X	X	X	X											
Hepatocellular adenoma								X	X																
Hepatocellular adenoma, multiple															X	X			X					X	
Mesentery																									+
Pancreas	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic														X											
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth							+						+						+						
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic														X											
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	M	M	+	+	+	M	+	+	M	M	M	+	+	+	+	M	+	+	+
Pituitary gland	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+
Pars distalis, adenoma																									
Pars intermedia, adenoma																						X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																							X		
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Coagulating gland															+			+	+					+	
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland				+															+						
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	24 2	24 3	24 5	25 1	25 2	25 3	25 4	25 5	26 1	26 2	27 1	27 3	27 4	27 5	28 1	28 2	28 3	28 4	28 5	29 1	29 2	29 3	29 4	30 1	30 5	TOTAL: TISSUES TUMORS	
ALIMENTARY SYSTEM																											
Esophagus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	43	
Gallbladder	M	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	M	M	+	+	39	
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	46	
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Lymphoma malignant mixed																										1	
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Lymphoma malignant mixed																										1	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Adenoma, multiple																										1	
Hepatocellular carcinoma													X						X	X			X			11	
Hepatocellular adenoma				X		X			X		X			X	X	X	X	X	X			X				15	
Hepatocellular adenoma, multiple							X	X					X												X	8	
Mesentery													+													2	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Hepatocellular carcinoma, metastatic																										1	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Squamous cell carcinoma								X																		1	
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Tooth									+										+							5	
CARDIOVASCULAR SYSTEM																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Hepatocellular carcinoma, metastatic																										1	
ENDOCRINE SYSTEM																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48	
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48	
Adenoma																						X				1	
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Parathyroid gland	M	+	M	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	M	+	M	M	+	34	
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	45	
Pars distalis, adenoma					X																					1	
Pars intermedia, adenoma																										1	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49	
Follicular cell, adenoma																										1	
GENERAL BODY SYSTEM																											
None																											
GENITAL SYSTEM																											
Coagulating gland	+	+		+	+										+	+			+							11	
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Preputial gland			+		+								+	+					+					+		8	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	

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

WEEKS ON STUDY	060	060	072	077	086	086	089	092	095	100	100	100	101	102	105	105	105	105	105	105	105	105	105	105
CARCASS ID	264	265	224	304	211	221	263	231	303	272	295	302	225	244	212	213	214	234	215	222	223	232	233	235	241
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	M	+	M	+	M	M	M	+	M	M	+	+	+	M	M	M	M	+	M	M	M	M	+	M	+
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	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	M	M
Skin	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																		X							
Subcutaneous tissue, fibrosarcoma							X		X	X	X														
Subcutaneous tissue, sarcoma					X																				
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																X									
Hepatocellular carcinoma, metastatic						X								X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland																		+							
Adenoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, hepatocellular carcinoma, metastatic														X											
Ureter																									
Urethra								+	+												+				
Urinary bladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	242	243	245	251	252	253	254	255	261	262	271	273	274	275	281	282	283	284	285	291	292	293	294	301	305	TOTAL: TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	M	M	+	M	+	M	M	M	+	M	+	+	+	+	+	M	+	+	M	+	M	M	+	+	+	23
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	34
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcutaneous tissue, fibroma										X																2
Subcutaneous tissue, fibrosarcoma										X				X												7
Subcutaneous tissue, sarcoma																									X	1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X											X				X		X								4
Alveolar/bronchiolar carcinoma																										1
Hepatocellular carcinoma, metastatic																			X				X			4
Nose	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Harderian gland					+																		+			3
Adenoma					X																					1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, hepatocellular carcinoma, metastatic																										1
Ureter							+																			1
Urethra			+			+							+	+												7
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	48

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

	Vehicle Control	150 mg/kg	300 mg/kg
Liver: Hepatocellular Adenoma			
Overall Rates (a)	8/50 (16%)	12/50 (24%)	24/50 (48%)
Adjusted Rates (b)	20.0%	29.1%	61.1%
Terminal Rates (c)	5/36 (14%)	11/40 (28%)	21/36 (58%)
Day of First Observation	627	647	500
Life Table Tests (d)	P<0.001	P=0.306	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.231	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.227	P<0.001
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	8/50 (16%)	4/50 (8%)	11/50 (22%)
Adjusted Rates (b)	18.3%	10.0%	25.1%
Terminal Rates (c)	3/36 (8%)	4/40 (10%)	4/36 (11%)
Day of First Observation	440	730	500
Life Table Tests (d)	P=0.248	P=0.157N	P=0.310
Logistic Regression Tests (d)	P=0.252	P=0.165N	P=0.355
Cochran-Armitage Trend Test (d)	P=0.245		
Fisher Exact Test (d)		P=0.178N	P=0.306
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	16/50 (32%)	14/50 (28%)	31/50 (62%)
Adjusted Rates (b)	35.6%	34.0%	70.3%
Terminal Rates (c)	8/36 (22%)	13/40 (33%)	23/36 (64%)
Day of First Observation	440	647	500
Life Table Tests (d)	P=0.003	P=0.326N	P=0.007
Logistic Regression Tests (d)	P=0.001	P=0.421N	P=0.002
Cochran-Armitage Trend Test (d)	P=0.002		
Fisher Exact Test (d)		P=0.414N	P=0.002
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	6/50 (12%)	(e) 6/14 (43%)	4/50 (8%)
Adjusted Rates (b)	16.7%		11.1%
Terminal Rates (c)	6/36 (17%)		4/36 (11%)
Day of First Observation	730		730
Life Table Test (d)			P=0.368N
Logistic Regression Test (d)			P=0.368N
Fisher Exact Test (d)			P=0.370N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	(e) 6/14 (43%)	5/50 (10%)
Adjusted Rates (b)	16.7%		13.9%
Terminal Rates (c)	6/36 (17%)		5/36 (14%)
Day of First Observation	730		730
Life Table Test (d)			P=0.500N
Logistic Regression Test (d)			P=0.500N
Fisher Exact Test (d)			P=0.500N
Subcutaneous Tissue: *Fibrosarcoma*			
Overall Rates (f)	3/50 (6%)	2/50 (4%)	7/50 (14%)
Adjusted Rates (b)	6.8%	4.5%	16.8%
Terminal Rates (c)	0/36 (0%)	1/40 (3%)	3/36 (8%)
Day of First Observation	593	612	618
Life Table Tests (d)	P=0.101	P=0.475N	P=0.164
Logistic Regression Tests (d)	P=0.101	P=0.442N	P=0.174
Cochran-Armitage Trend Test (d)	P=0.099		
Fisher Exact Test (d)		P=0.500N	P=0.159

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

	Vehicle Control	150 mg/kg	300 mg/kg
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (f)	4/50 (8%)	3/50 (6%)	8/50 (16%)
Adjusted Rates (b)	9.4%	7.0%	19.3%
Terminal Rates (c)	1/36 (3%)	2/40 (5%)	4/36 (11%)
Day of First Observation	593	612	618
Life Table Tests (d)	P=0.125	P=0.462N	P=0.185
Logistic Regression Tests (d)	P=0.124	P=0.482N	P=0.188
Cochran-Armitage Trend Test (d)	P=0.122		
Fisher Exact Test (d)		P=0.500N	P=0.178
Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Overall Rates (f)	3/50 (6%)	2/50 (4%)	8/50 (16%)
Adjusted Rates (b)	6.8%	4.5%	18.6%
Terminal Rates (c)	0/36 (0%)	1/40 (3%)	3/36 (8%)
Day of First Observation	593	612	598
Life Table Tests (d)	P=0.058	P=0.475N	P=0.109
Logistic Regression Tests (d)	P=0.057	P=0.442N	P=0.116
Cochran-Armitage Trend Test (d)	P=0.055		
Fisher Exact Test (d)		P=0.500N	P=0.100
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (f)	4/50 (8%)	3/50 (6%)	9/50 (18%)
Adjusted Rates (b)	9.4%	7.0%	21.1%
Terminal Rates (c)	1/36 (3%)	2/40 (5%)	4/36 (11%)
Day of First Observation	593	612	598
Life Table Tests (d)	P=0.077	P=0.462N	P=0.127
Logistic Regression Tests (d)	P=0.074	P=0.482N	P=0.130
Cochran-Armitage Trend Test (d)	P=0.073		
Fisher Exact Test (d)		P=0.500N	P=0.117
Circulatory System: Hemangiosarcoma			
Overall Rates (f)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	0.0%	7.0%	0.0%
Terminal Rates (c)	0/36 (0%)	2/40 (5%)	0/36 (0%)
Day of First Observation		627	
Life Table Tests (d)	P=0.636	P=0.138	(g)
Logistic Regression Tests (d)	P=0.639	P=0.120	(g)
Cochran-Armitage Trend Test (d)	P=0.638		
Fisher Exact Test (d)		P=0.121	(g)
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (f)	7/50 (14%)	(h) 8/50 (16%)	1/50 (2%)
Adjusted Rates (b)	17.5%	18.2%	2.8%
Terminal Rates (c)	5/36 (14%)	5/40 (13%)	1/36 (3%)
Day of First Observation	558	612	730
Life Table Tests (d)	P=0.040N	P=0.565	P=0.036N
Logistic Regression Tests (d)	P=0.038N	P=0.501	P=0.031N
Cochran-Armitage Trend Test (d)	P=0.038N		
Fisher Exact Test (d)		P=0.500	P=0.030N

(a) Number of tumor-bearing animals/number of animals examined microscopically at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence in animals killed at the end of the study
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or a lower incidence in a dosed group than in vehicle controls is indicated by (N).
(e) Incomplete sampling of tissues
(f) Number of tumor-bearing animals/number of animals examined grossly at the site
(g) No P value is reported because no tumors were observed in the 300 mg/kg and vehicle control groups.
(h) Twenty spleens were examined microscopically.

TABLE C4a. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
Diglycidyl resorcinol ether	7/49	7/49	13/49
1,2-Dichloropropane	7/50	11/50	18/50
Chlorodibromomethane	14/50	10/50	23/50
n-Butyl chloride	5/50	10/50	15/50
Bromodichloromethane	10/49	8/49	17/49
Bis(2-chloro-1-methylethyl) ether	8/50	5/50	13/50
n-Butyl chloride	4/50	9/50	12/50
TOTAL	55/348 (15.8%)	60/348 (17.2%)	111/348 (31.9%)
SD (b)	6.71%	4.09%	7.67%
Range (c)			
High	14/50	11/50	23/50
Low	4/50	5/50	12/50
Overall Historical Incidence			
TOTAL	325/2,084 (15.6%)	404/2,084 (19.4%)	688/2,084 (33.0%)
SD (b)	7.07%	7.46%	8.59%
Range (c)			
High	16/50	19/50	25/50
Low	0/50	3/49	7/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE C4b. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls	
	Lymphoma	Lymphoma or Leukemia
Historical Incidence at EG&G Mason Research Institute		
Diglycidyl resorcinol ether	6/50	6/50
1,2-Dichloropropane	8/50	8/50
Chlorodibromomethane	9/50	9/50
n-Butyl chloride	7/50	7/50
Bromodichloromethane	6/49	6/49
Bis(2-chloro-1-methylethyl) ether	6/50	6/50
n-Butyl chloride	9/50	9/50
TOTAL	51/349 (14.6%)	51/349 (14.6%)
SD (b)	2.72%	2.72%
Range (c)		
High	9/50	9/50
Low	6/50	6/50
Overall Historical Incidence		
TOTAL	249/2,091 (11.9%)	253/2,091 (12.1%)
SD (b)	4.56%	4.43%
Range (c)		
High	11/50	11/50
Low	2/50	2/49

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Esophagus	(46)	(4)	(43)
Necrosis		1 (25%)	
Adventitia, inflammation, acute		1 (25%)	
Gallbladder	(45)	(20)	(39)
Calculus, micro observation only		1 (5%)	
Fibrosis		1 (5%)	
Inflammation, chronic	5 (11%)		6 (15%)
Inflammation, chronic active		1 (5%)	
Epithelium, hyperplasia			1 (3%)
Intestine large, cecum	(48)	(3)	(46)
Hyperplasia, lymphoid	5 (10%)		1 (2%)
Epithelium, hyperplasia			1 (2%)
Intestine large, colon	(49)	(5)	(50)
Hyperplasia, lymphoid			1 (2%)
Intestine large, rectum	(48)	(3)	(50)
Hyperplasia, lymphoid	1 (2%)		
Intestine small, duodenum	(49)	(5)	(50)
Epithelium, hyperplasia		2 (40%)	
Intestine small, ileum	(49)	(9)	(50)
Hyperplasia, lymphoid	4 (8%)	1 (11%)	1 (2%)
Lymphoid tissue, necrosis			1 (2%)
Intestine small, jejunum	(49)	(3)	(49)
Hyperplasia, lymphoid	1 (2%)		1 (2%)
Peyer's patch, inflammation, chronic active			1 (2%)
Liver	(50)	(50)	(50)
Abscess		1 (2%)	
Angiectasis	1 (2%)		
Basophilic focus	1 (2%)	1 (2%)	2 (4%)
Clear cell focus			5 (10%)
Cyst			1 (2%)
Degeneration		22 (44%)	38 (76%)
Eosinophilic focus		2 (4%)	2 (4%)
Fatty change	11 (22%)	7 (14%)	20 (40%)
Fibrosis	1 (2%)		
Hematopoietic cell proliferation	1 (2%)	4 (8%)	
Hemorrhage	1 (2%)	16 (32%)	27 (54%)
Infarct	1 (2%)		
Inflammation, acute		1 (2%)	
Inflammation, chronic	8 (16%)	6 (12%)	8 (16%)
Inflammation, chronic active	2 (4%)	5 (10%)	8 (16%)
Karyomegaly			1 (2%)
Mineralization	1 (2%)		1 (2%)
Mixed cell focus		2 (4%)	2 (4%)
Necrosis, coagulative	4 (8%)	11 (22%)	36 (72%)
Pigmentation	1 (2%)	1 (2%)	26 (52%)
Regeneration		1 (2%)	
Centrilobular, cytomegaly		34 (68%)	45 (90%)
Centrilobular, karyomegaly		34 (68%)	44 (88%)
Periportal, inflammation, chronic	16 (32%)	2 (4%)	2 (4%)
Mesentery	(4)	(2)	(2)
Fibrosis	4 (100%)	1 (50%)	1 (50%)
Inflammation, chronic	1 (25%)	1 (50%)	1 (50%)
Inflammation, chronic active		1 (50%)	1 (50%)
Mineralization	3 (75%)		
Necrosis, coagulative	3 (75%)	2 (100%)	
Pigmentation			1 (50%)
Artery, thrombus	1 (25%)		

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

	Vehicle Control	Low Dose	High Dose
ALIMENTARY SYSTEM (Continued)			
Pancreas	(49)	(8)	(49)
Atrophy	1 (2%)		1 (2%)
Ectopic tissue	1 (2%)		
Hyperplasia	1 (2%)		
Inflammation, chronic	17 (35%)		11 (22%)
Inflammation, chronic active		2 (25%)	1 (2%)
Necrosis, coagulative	1 (2%)	1 (13%)	
Vacuolization cytoplasmic	1 (2%)		
Artery, mineralization	5 (10%)		2 (4%)
Duct, dilatation	1 (2%)		
Salivary glands	(50)	(4)	(50)
Parotid gland, inflammation, chronic	1 (2%)		1 (2%)
Parotid gland, mineralization	2 (4%)		
Sublingual gland, inflammation, chronic			1 (2%)
Submandibular gland, inflammation, chronic	42 (84%)	1 (25%)	40 (80%)
Stomach, forestomach	(48)	(5)	(50)
Acanthosis	4 (8%)		4 (8%)
Hyperkeratosis	5 (10%)		6 (12%)
Hyperplasia, basal cell	4 (8%)		3 (6%)
Inflammation, acute	1 (2%)		
Inflammation, chronic	1 (2%)		2 (4%)
Inflammation, chronic active	3 (6%)		4 (8%)
Inflammation, necrotizing, acute			1 (2%)
Inflammation, necrotizing, chronic active			1 (2%)
Karyomegaly, chronic active	1 (2%)		
Ulcer	1 (2%)		
Epithelium, mineralization	1 (2%)		
Muscularis, mineralization			1 (2%)
Stomach, glandular	(48)	(5)	(50)
Cyst	2 (4%)		
Inflammation, acute	1 (2%)		1 (2%)
Inflammation, chronic	12 (25%)	1 (20%)	8 (16%)
Inflammation, chronic active	2 (4%)		5 (10%)
Pigmentation			1 (2%)
Muscularis, mineralization			1 (2%)
Tooth	(17)		(5)
Incisor, abscess	8 (47%)		4 (80%)
Incisor, bacterium			1 (20%)
Incisor, dysplasia	9 (53%)		2 (40%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(5)	(50)
Fibrosis			1 (2%)
Inflammation, chronic	10 (20%)		3 (6%)
Inflammation, chronic active			1 (2%)
Coronary artery, mineralization	1 (2%)		
ENDOCRINE SYSTEM			
Adrenal gland	(49)	(8)	(48)
Capsule, inflammation, chronic	1 (2%)		
Adrenal gland, cortex	(49)	(8)	(48)
Cyst	1 (2%)		
Hyperplasia	5 (10%)		2 (4%)
Pigmentation	1 (2%)		2 (4%)
Adrenal gland, medulla	(48)	(8)	(48)
Angiectasis	1 (2%)		
Hyperplasia			3 (6%)
Islets, pancreatic	(49)	(5)	(50)
Hyperplasia			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
Parathyroid gland	(27)	(3)	(34)
Vacuolization cytoplasmic			1 (3%)
Pituitary gland	(47)	(5)	(45)
Pars distalis, cyst	7 (15%)	1 (20%)	1 (2%)
Pars distalis, hyperplasia	3 (6%)	1 (20%)	6 (13%)
Thyroid gland	(48)	(5)	(49)
Hemorrhage	1 (2%)		
Inflammation, chronic	1 (2%)		1 (2%)
Inflammation, chronic active	1 (2%)		
Follicle, cyst	1 (2%)		2 (4%)
Follicular cell, hyperplasia, focal	1 (2%)		
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Coagulating gland	(1)	(1)	(11)
Inflammation, chronic			1 (9%)
Perivascular, inflammation, chronic			1 (9%)
Epididymis	(49)	(4)	(50)
Inflammation, chronic	20 (41%)		20 (40%)
Inflammation, chronic active	1 (2%)		
Preputial gland	(10)	(14)	(8)
Abscess	6 (60%)	4 (29%)	
Cyst		1 (7%)	
Hemorrhage			1 (13%)
Inflammation, chronic	2 (20%)	2 (14%)	1 (13%)
Inflammation, chronic active	2 (20%)	4 (29%)	5 (63%)
Inflammation, necrotizing, chronic active		2 (14%)	
Duct, dilatation	2 (20%)	1 (7%)	
Prostate	(49)	(5)	(50)
Hemorrhage			1 (2%)
Inflammation, acute			1 (2%)
Inflammation, chronic	36 (73%)	1 (20%)	33 (66%)
Inflammation, necrotizing, acute	1 (2%)		
Epithelium, hyperplasia	1 (2%)		
Seminal vesicle	(50)	(6)	(50)
Atrophy		1 (17%)	
Fibrosis	1 (2%)		1 (2%)
Inflammation, chronic	22 (44%)		8 (16%)
Inflammation, chronic active			1 (2%)
Testes	(50)	(7)	(50)
Hemorrhage	1 (2%)		
Inflammation, chronic	1 (2%)		2 (4%)
Inflammation, chronic active		1 (14%)	
Seminiferous tubule, atrophy	2 (4%)	1 (14%)	3 (6%)
Seminiferous tubule, giant cell			1 (2%)
Seminiferous tubule, mineralization	1 (2%)		1 (2%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(49)	(5)	(50)
Congestion		1 (20%)	2 (4%)
Infarct		1 (20%)	
Myeloid cell, hyperplasia	1 (2%)	1 (20%)	
Lymph node	(50)	(27)	(50)
Axillary, hyperplasia, lymphoid		1 (4%)	
Axillary, hyperplasia, plasma cell			1 (2%)
Bronchial, hyperplasia, lymphoid			1 (2%)
Inguinal, angiectasis	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
Lymph node (Continued)	(50)	(27)	(50)
Inguinal, ectasia	1 (2%)		
Inguinal, hyperplasia, plasma cell			1 (2%)
Inguinal, inflammation, acute			1 (2%)
Inguinal, pigmentation			2 (4%)
Lumbar, hyperplasia, lymphoid	2 (4%)	1 (4%)	
Lumbar, hyperplasia, plasma cell	1 (2%)	1 (4%)	
Lumbar, pigmentation	1 (2%)		
Mediastinal, angiectasis			1 (2%)
Mediastinal, depletion lymphoid			1 (2%)
Mediastinal, hyperplasia, lymphoid			1 (2%)
Mediastinal, pigmentation			1 (2%)
Pancreatic, angiectasis			1 (2%)
Pancreatic, depletion lymphoid			1 (2%)
Pancreatic, ectasia			1 (2%)
Pancreatic, hematopoietic cell proliferation			1 (2%)
Pancreatic, hemorrhage		1 (4%)	
Renal, hemorrhage		1 (4%)	
Renal, hyperplasia, lymphoid	2 (4%)	1 (4%)	
Lymph node, mandibular	(27)	(1)	(23)
Depletion lymphoid	1 (4%)		
Hyperplasia, lymphoid			1 (4%)
Hyperplasia, plasma cell	2 (7%)		
Pigmentation			2 (9%)
Lymph node, mesenteric	(45)	(20)	(47)
Angiectasis	28 (62%)	3 (15%)	30 (64%)
Depletion lymphoid	1 (2%)		2 (4%)
Ectasia	2 (4%)		
Fibrosis			1 (2%)
Hematopoietic cell proliferation	1 (2%)	1 (5%)	
Hemorrhage	3 (7%)	14 (70%)	3 (6%)
Hyperplasia, lymphoid	3 (7%)	1 (5%)	5 (11%)
Infiltration cellular, histiocytic		1 (5%)	1 (2%)
Inflammation, acute	2 (4%)		
Pigmentation		1 (5%)	
Thrombus	2 (4%)		
Spleen	(50)	(20)	(50)
Depletion lymphoid	1 (2%)		5 (10%)
Hematopoietic cell proliferation	7 (14%)	5 (25%)	7 (14%)
Hyperplasia, lymphoid	4 (8%)	3 (15%)	6 (12%)
Necrosis, coagulative	1 (2%)		
Artery, endothelium, hyperplasia	1 (2%)		
Thymus	(41)	(4)	(34)
Cyst	12 (29%)		7 (21%)
Depletion lymphoid	4 (10%)	4 (100%)	4 (12%)
Hemorrhage	4 (10%)		2 (6%)
Necrosis	1 (2%)		1 (3%)
INTEGUMENTARY SYSTEM			
Skin	(50)	(11)	(49)
Acanthosis			1 (2%)
Cyst			1 (2%)
Hemorrhage			3 (6%)
Inflammation, acute	2 (4%)		6 (12%)
Inflammation, chronic	1 (2%)		1 (2%)
Inflammation, chronic active	2 (4%)		1 (2%)
Inflammation, hemorrhagic, acute			1 (2%)
Inflammation, necrotizing, acute	2 (4%)	1 (9%)	4 (8%)
Inflammation, necrotizing, chronic active		2 (18%)	
Epidermis, inflammation, acute		1 (9%)	

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

	Vehicle Control	Low Dose	High Dose
INTEGUMENTARY SYSTEM			
Skin (Continued)	(50)	(11)	(49)
Subcutaneous tissue, abscess	1 (2%)	1 (9%)	
Subcutaneous tissue, fibrosis	2 (4%)		1 (2%)
Subcutaneous tissue, granuloma			1 (2%)
Subcutaneous tissue, inflammation, chronic		1 (9%)	
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(33)	(50)
Joint, tarsal, hyperostosis	33 (66%)	28 (85%)	35 (70%)
Skeletal muscle	(2)		
Abdominal, regeneration	1 (50%)		
NERVOUS SYSTEM			
Brain	(50)	(5)	(50)
Hemorrhage		1 (20%)	
Thalamus, mineralization	39 (78%)	1 (20%)	40 (80%)
RESPIRATORY SYSTEM			
Lung	(50)	(14)	(50)
Congestion		3 (21%)	
Embolus tumor			1 (2%)
Hemorrhage	5 (10%)	4 (29%)	5 (10%)
Infiltration cellular, histiocytic	3 (6%)		5 (10%)
Inflammation, acute			1 (2%)
Inflammation, chronic			1 (2%)
Inflammation, chronic active	1 (2%)		4 (8%)
Alveolar epithelium, hyperplasia	3 (6%)		3 (6%)
Bronchiole, epithelium, hyperplasia	1 (2%)		
Fat, mediastinum, necrosis, liquifactive		1 (7%)	
Mediastinum, inflammation, chronic active	1 (2%)		
Peribronchial, inflammation, chronic	1 (2%)		
Peribronchiolar, inflammation, chronic		1 (7%)	
Perivascular, inflammation, chronic	2 (4%)	1 (7%)	1 (2%)
Pleura, inflammation, acute	1 (2%)		
Nose	(50)	(3)	(47)
Glands, inflammation, acute		1 (33%)	
Lumen, inflammation, acute	2 (4%)		2 (4%)
Mucosa, inflammation, acute	26 (52%)		18 (38%)
Mucosa, inflammation, chronic			1 (2%)
Mucosa, inflammation, chronic active	2 (4%)		1 (2%)
Nasolacrimal duct, inflammation, acute	1 (2%)		
Nasolacrimal duct, inflammation, chronic active	1 (2%)		3 (6%)
Nasolacrimal duct, metaplasia, squamous	1 (2%)		1 (2%)
Nasopharyngeal duct, inflammation, chronic active	1 (2%)		
SPECIAL SENSES SYSTEM			
Ear	(1)	(1)	
Inflammation, chronic active	1 (100%)		
Eye	(2)		
Cornea, inflammation, necrotizing, chronic active	1 (50%)		
Lids, inflammation, necrotizing, chronic active	1 (50%)		
Harderian gland	(3)	(2)	(3)
Hyperplasia		1 (50%)	1 (33%)
Inflammation, chronic	1 (33%)		1 (33%)

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

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
Kidney	(49)	(50)	(50)
Abscess	1 (2%)		
Bacterium	1 (2%)		
Cyst	1 (2%)		
Glomerulosclerosis	4 (8%)	6 (12%)	6 (12%)
Hydronephrosis	1 (2%)		
Infarct			1 (2%)
Inflammation, chronic	44 (90%)	42 (84%)	47 (94%)
Inflammation, chronic active		1 (2%)	1 (2%)
Metaplasia, osseous	2 (4%)		
Medulla, mineralization			1 (2%)
Papilla, necrosis, coagulative	1 (2%)		
Proximal convoluted renal tubule, atrophy	2 (4%)		
Proximal convoluted renal tubule, degeneration		1 (2%)	
Proximal convoluted renal tubule, mineralization	1 (2%)		
Proximal convoluted renal tubule, regeneration	36 (73%)	3 (6%)	36 (72%)
Proximal convoluted renal tubule, vacuolization cytoplasmic	1 (2%)		
Transitional epithelium, hyperplasia		1 (2%)	
Ureter			(1)
Inflammation, chronic			1 (100%)
Urethra	(4)		(7)
Calculus, micro observation only	4 (100%)		6 (86%)
Inflammation, chronic			1 (14%)
Urinary bladder	(50)	(6)	(48)
Calculus, gross observation	1 (2%)		1 (2%)
Calculus, microscopic observation only	3 (6%)		3 (6%)
Inflammation, chronic	35 (70%)	2 (33%)	30 (63%)
Inflammation, chronic active	1 (2%)		1 (2%)
Mineralization		1 (17%)	

APPENDIX D

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

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Gallbladder	(44)	*(50)	(47)
Lymphoma malignant mixed			1 (2%)
Intestine large, cecum	(50)	*(50)	(40)
Lymphoma malignant mixed			1 (3%)
Intestine small, ileum	(46)	*(50)	(44)
Lymphoma malignant undifferentiated cell type			1 (2%)
Intestine small, jejunum	(49)	*(50)	(45)
Leukemia granulocytic			1 (2%)
Liver	(50)	(49)	(50)
Hepatocellular carcinoma	1 (2%)		
Hepatocellular adenoma	3 (6%)	4 (8%)	4 (8%)
Hepatocellular adenoma, multiple	1 (2%)	1 (2%)	3 (6%)
Leukemia, poorly differentiated		1 (2%)	
Leukemia granulocytic			1 (2%)
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant mixed		1 (2%)	4 (8%)
Lymphoma malignant undifferentiated cell type	5 (10%)	1 (2%)	1 (2%)
Mesentery	*(50)	*(50)	*(50)
Fibrosarcoma, metastatic, skin			1 (2%)
Lymphoma malignant undifferentiated cell type	1 (2%)		
Sarcoma, metastatic, skin	1 (2%)		
Pancreas	(50)	*(50)	(49)
Leukemia granulocytic			1 (2%)
Lymphoma malignant mixed		1 (2%)	
Lymphoma malignant undifferentiated cell type	2 (4%)	1 (2%)	
Pharynx	*(50)	*(50)	*(50)
Palate, lymphoma malignant histiocytic			1 (2%)
Salivary glands	(48)	*(50)	(49)
Submandibular gland, lymphoma malignant mixed			1 (2%)
Submandibular gland, lymphoma malignant undifferentiated cell type	1 (2%)	1 (2%)	
Stomach, forestomach	(50)	*(50)	(48)
Papilloma squamous	3 (6%)		2 (4%)
Squamous cell carcinoma, early invasion	2 (4%)		
Stomach, glandular	(49)	*(50)	(48)
Lymphoma malignant undifferentiated cell type	1 (2%)	1 (2%)	
CARDIOVASCULAR SYSTEM			
Heart	(50)	*(50)	(50)
Carcinoma, metastatic, lung		1 (2%)	
Lymphoma malignant lymphocytic	1 (2%)		
Lymphoma malignant undifferentiated cell type	1 (2%)		
ENDOCRINE SYSTEM			
Adrenal gland	(48)	*(50)	(49)
Leukemia granulocytic			1 (2%)
Capsule, lymphoma malignant histiocytic			1 (2%)
Capsule, lymphoma malignant undifferentiated cell type	1 (2%)		
Adrenal gland, cortex	(48)	*(50)	(49)
Lymphoma malignant undifferentiated cell type	1 (2%)	1 (2%)	
Adrenal gland, medulla	(47)	*(50)	(48)
Lymphoma malignant undifferentiated cell type		1 (2%)	
Pheochromocytoma benign			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
Pituitary gland	(44)	*(50)	(47)
Pars distalis, adenoma	8 (18%)	5 (10%)	3 (6%)
Pars distalis, carcinoma			1 (2%)
Thyroid gland	(48)	*(50)	(50)
Follicular cell, adenoma	2 (4%)		
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Ovary	(50)	(47)	(47)
Cystadenoma		1 (2%)	
Granulosa cell tumor benign		1 (2%)	1 (2%)
Leukemia granulocytic			1 (2%)
Luteoma	1 (2%)		
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant lymphocytic		1 (2%)	
Lymphoma malignant mixed			1 (2%)
Lymphoma malignant undifferentiated cell type	1 (2%)		
Periovarian tissue, lymphoma malignant lymphocytic	1 (2%)		
Periovarian tissue, lymphoma malignant undifferentiated cell type	3 (6%)		1 (2%)
Uterus	(50)	(49)	(48)
Adenocarcinoma		2 (4%)	
Hemangioma			1 (2%)
Leiomyoma	1 (2%)		1 (2%)
Lymphoma malignant lymphocytic		1 (2%)	
Lymphoma malignant undifferentiated cell type		1 (2%)	
Polyp stromal		1 (2%)	
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	*(50)	(50)
Leukemia, poorly differentiated		1 (2%)	
Leukemia granulocytic			1 (2%)
Lymphoma malignant histiocytic			1 (2%)
Sternal, sarcoma, metastatic, skin	1 (2%)		
Lymph node	(47)	*(50)	(48)
Axillary, lymphoma malignant lymphocytic		1 (2%)	
Axillary, lymphoma malignant mixed		1 (2%)	
Axillary, lymphoma malignant undifferentiated cell type	2 (4%)		
Inguinal, carcinoma, metastatic, lung		1 (2%)	
Inguinal, lymphoma malignant lymphocytic		1 (2%)	
Inguinal, lymphoma malignant mixed		1 (2%)	
Inguinal, lymphoma malignant undifferentiated cell type	1 (2%)		
Lumbar, adenocarcinoma, metastatic, uterus		1 (2%)	
Lumbar, lymphoma malignant histiocytic			1 (2%)
Lumbar, lymphoma malignant lymphocytic		1 (2%)	
Lumbar, lymphoma malignant mixed	1 (2%)	2 (4%)	1 (2%)
Lumbar, lymphoma malignant undifferentiated cell type	3 (6%)	2 (4%)	1 (2%)
Mediastinal, leukemia granulocytic			1 (2%)
Mediastinal, lymphoma malignant lymphocytic	1 (2%)	1 (2%)	
Mediastinal, lymphoma malignant mixed		1 (2%)	2 (4%)
Mediastinal, lymphoma malignant undifferentiated cell type	3 (6%)		1 (2%)
Mediastinal, sarcoma, metastatic, skin	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
Lymph node (Continued)	(47)	*(50)	(48)
Pancreatic, lymphoma malignant	1 (2%)		
Pancreatic, lymphoma malignant mixed		2 (4%)	1 (2%)
Pancreatic, lymphoma malignant undifferentiated cell type	3 (6%)	1 (2%)	
Renal, lymphoma malignant histiocytic			1 (2%)
Renal, lymphoma malignant lymphocytic		1 (2%)	
Renal, lymphoma malignant	1 (2%)		
Renal, lymphoma malignant mixed		2 (4%)	2 (4%)
Renal, lymphoma malignant undifferentiated cell type	3 (6%)	2 (4%)	1 (2%)
Lymph node, mandibular	(34)	*(50)	(30)
Lymphoma malignant histiocytic			1 (3%)
Lymphoma malignant lymphocytic	1 (3%)	1 (2%)	
Lymphoma malignant mixed	1 (3%)	1 (2%)	1 (3%)
Lymphoma malignant undifferentiated cell type	3 (9%)	1 (2%)	
Lymph node, mesenteric	(42)	*(50)	(41)
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant lymphocytic		1 (2%)	
Lymphoma malignant mixed	1 (2%)	1 (2%)	3 (7%)
Lymphoma malignant undifferentiated cell type	4 (10%)	2 (4%)	1 (2%)
Spleen	(50)	*(50)	(49)
Hemangiosarcoma		1 (2%)	
Leukemia, poorly differentiated		1 (2%)	
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant lymphocytic		1 (2%)	
Lymphoma malignant mixed	1 (2%)	4 (8%)	2 (4%)
Lymphoma malignant undifferentiated cell type	6 (12%)	2 (4%)	1 (2%)
Thymus	(37)	*(50)	(39)
Lymphoma malignant lymphocytic	1 (3%)		
Lymphoma malignant mixed			1 (3%)
INTEGUMENTARY SYSTEM			
Mammary gland	(31)	*(50)	(23)
Adenocarcinoma			1 (4%)
Skin	(49)	*(50)	(48)
Hemangioma	1 (2%)		
Subcutaneous tissue, fibrosarcoma		1 (2%)	1 (2%)
Subcutaneous tissue, sarcoma	2 (4%)		
MUSCULOSKELETAL SYSTEM			
Bone	(50)	*(50)	(50)
Carcinoma, metastatic, lung		1 (2%)	
Sternum, fibrosarcoma, deep invasion		1 (2%)	
Skeletal muscle	*(50)	*(50)	*(50)
Sarcoma, extension	1 (2%)		
Hindlimb, carcinoma, metastatic, lung		1 (2%)	
Intercostal, lymphoma malignant histiocytic			1 (2%)
Intercostal, lymphoma malignant lymphocytic	1 (2%)		
Intercostal, lymphoma malignant undifferentiated cell type		1 (2%)	
NERVOUS SYSTEM			
Brain	(50)	*(50)	(50)
Lymphoma malignant undifferentiated cell type	1 (2%)		
Meninges, lymphoma malignant mixed	1 (2%)		
Meninges, lymphoma malignant undifferentiated cell type		1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
RESPIRATORY SYSTEM			
Lung	(50)	*(50)	(50)
Alveolar/bronchiolar adenoma	3 (6%)	2 (4%)	3 (6%)
Alveolar/bronchiolar carcinoma		1 (2%)	
Leukemia, poorly differentiated		1 (2%)	
Leukemia granulocytic			1 (2%)
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant lymphocytic	1 (2%)		
Lymphoma malignant mixed			1 (2%)
Lymphoma malignant undifferentiated cell type	5 (10%)	1 (2%)	
Sarcoma, metastatic, skin	1 (2%)		
Mediastinum, lymphoma malignant mixed			1 (2%)
Nose	(50)	*(50)	(41)
Nasolacrimal duct, lymphoma malignant histiocytic			1 (2%)
SPECIAL SENSES SYSTEM			
Harderian gland	*(50)	*(50)	*(50)
Adenoma	1 (2%)		
Lacrimal gland	*(50)	*(50)	*(50)
Carcinoma	1 (2%)		
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Carcinoma, metastatic, lung		1 (2%)	
Fibrosarcoma, metastatic, skin			1 (2%)
Leukemia, poorly differentiated		1 (2%)	
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant lymphocytic	1 (2%)	1 (2%)	
Lymphoma malignant mixed	1 (2%)	1 (2%)	1 (2%)
Lymphoma malignant undifferentiated cell type	3 (6%)	1 (2%)	1 (2%)
Ureter	*(50)	*(50)	*(50)
Lymphoma malignant undifferentiated cell type		1 (2%)	
Urinary bladder	(50)	*(50)	(48)
Fibrosarcoma, metastatic, skin			1 (2%)
Lymphoma malignant undifferentiated cell type	2 (4%)	1 (2%)	1 (2%)
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Lymphoma malignant	1 (2%)		
Lymphoma malignant lymphocytic	2 (4%)	1 (2%)	
Lymphoma malignant mixed	2 (4%)	5 (10%)	4 (8%)
Lymphoma malignant undifferentiated cell	7 (14%)	2 (4%)	3 (6%)
Leukemia		1 (2%)	
Hemangioma	1 (2%)		1 (2%)
Hemangiosarcoma		1 (2%)	
Leukemia granulocytic			1 (2%)
Lymphoma malignant histiocytic			1 (2%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Moribund sacrifice	20	11	5
Terminal sacrifice	22	29	32
Natural death	8	9	12
Dead		1	
Accident			1

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

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary neoplasms **	31	20	25
Total primary neoplasms	43	30	31
Total animals with benign neoplasms	20	13	15
Total benign neoplasms	24	15	19
Total animals with malignant neoplasms	17	12	12
Total malignant neoplasms	19	15	12
Total animals with secondary neoplasms ***	1	2	1
Total secondary neoplasms	4	6	3

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

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

WEEKS ON STUDY	072	082	082	085	086	086	087	088	088	089	091	091	092	094	095	095	096	096	098	099	099	101	102	103	103
CARCASS ID	323	372	361	343	334	355	332	313	333	385	395	321	314	394	382	335	535	375	392	365	403	312	315	411	362
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	M	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+
Intestine small, ileum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	A
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Hepatocellular adenoma																				X					
Hepatocellular adenoma, multiple																									
Lymphoma malignant undifferentiated cell type						X	X					X											X		
Mesentery				+			+								+				+	+					+
Lymphoma malignant undifferentiated cell type																									
Sarcoma, metastatic, skin															X										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type						X	X																		
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Submandibular gland, lymphoma malignant undifferentiated cell type							X																		
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																	X		X						
Squamous cell carcinoma, early invasion																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type							X																		
Tooth									+				+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic										X															
Lymphoma malignant undifferentiated cell type												X													
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, lymphoma malignant undifferentiated cell type																									
Adrenal gland, cortex	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																									
Adrenal gland, medulla	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	M	M	+	+	+	+	+	+	M	M	M	+	M	M	+	M	M	M	+	M	+
Pituitary gland	M	+	M	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+
Pars distalis, adenoma														X											
Thyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																X									
GENERAL BODY SYSTEM																									
Tissue, NOS																				+					
GENITAL SYSTEM																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Luteoma																									
Lymphoma malignant undifferentiated cell type																									
Periovarian tissue, lymphoma malignant lymphocytic										X															
Periovarian tissue, lymphoma malignant undifferentiated cell type						X	X					X													
Oviduct		+																+		+		+			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									

+: Tissue examined microscopically
: Not examined
−: Present but not examined microscopically
I: Insufficient tissue

M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

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

WEEKS ON STUDY	104	104	105	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL:
CARCASS ID	363	364	341	324	325	331	351	381	393	322	342	344	345	352	354	384	371	373	374	383	391	401	402	404	405	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	47
Gallbladder	+	A	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma											X															1
Hepatocellular adenoma						X									X											3
Hepatocellular adenoma, multiple																	X									1
Lymphoma malignant undifferentiated cell type				X																						5
Mesentery	+	+		+																						9
Lymphoma malignant undifferentiated cell type				X																						1
Sarcoma, metastatic, skin																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant undifferentiated cell type																										2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Submandibular gland, lymphoma malignant undifferentiated cell type																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous												X														3
Squamous cell carcinoma, early invasion															X			X								2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant undifferentiated cell type																										1
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+			+		+	+	+	+	+	35
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Lymphoma malignant undifferentiated cell type																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	48
Capsule, lymphoma malignant undifferentiated cell type				X																						1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant undifferentiated cell type				X																						1
Adrenal gland, medulla	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	47
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	M	+	M	M	+	M	M	+	+	+	+	+	M	+	M	+	+	+	+	+	+	31
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Pars distalis, adenoma					X		X					X					X			X	X	X				8
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell, adenoma								X																		2
GENERAL BODY SYSTEM																										
Tissue, NOS																										1
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Luteoma									X																	1
Lymphoma malignant undifferentiated cell type				X																						1
Periovarian tissue, lymphoma malignant lymphocytic																										1
Periovarian tissue, lymphoma malignant undifferentiated cell type																										3
Oviduct	+	+												+								+				8
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																						X				1

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

WEEKS ON STUDY	072	082	082	085	086	086	087	088	088	089	091	091	092	094	095	095	096	096	098	099	099	101	102	103	103
CARCASS ID	323	372	361	343	334	355	332	313	333	385	395	321	314	394	382	335	337	353	392	365	403	312	315	311	362
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sternal, sarcoma, metastatic, skin															X										
Lymph node	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Axillary, lymphoma malignant undifferentiated cell type						X						X													
Inguinal, lymphoma malignant undifferentiated cell type												X													
Lumbar, lymphoma malignant mixed																									
Lumbar, lymphoma malignant undifferentiated cell type						X	X					X													
Mediastinal, lymphoma malignant lymphocytic										X															
Mediastinal, lymphoma malignant undifferentiated cell type						X	X					X													
Mediastinal, sarcoma, metastatic, skin															X										
Pancreatic, lymphoma malignant																									
Pancreatic, lymphoma malignant undifferentiated cell type						X	X					X													
Renal, lymphoma malignant																									
Renal, lymphoma malignant undifferentiated cell type						X	X					X													
Lymph node, mandibular	M	M	M	+	+	+	+	+	+	M	+	+	M	M	+	+	M	+	+	+	M	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																									
Lymphoma malignant undifferentiated cell type						X	X					X													
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	M	M	+	M
Lymphoma malignant mixed																									
Lymphoma malignant undifferentiated cell type						X	X					X													
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Lymphoma malignant undifferentiated cell type						X	X					X				X							X		
Thymus	M	M	M	+	+	+	+	M	+	+	M	M	M	+	+	+	+	+	M	+	+	+	M	M	+
Lymphoma malignant lymphocytic										X															
INTEGUMENTARY SYSTEM																									
Mammary gland	+	M	M	M	M	+	M	M	M	M	+	M	M	+	+	M	+	+	+	+	M	M	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Hemangioma			X																						
Subcutaneous tissue, sarcoma														X	X										
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle										+					+										
Sarcoma, extension															X										
Intercostal, lymphoma malignant lymphocytic										X															
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																									
Meninges, lymphoma malignant mixed																									
Spinal cord			+																						
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X														
Lymphoma malignant lymphocytic										X															
Lymphoma malignant undifferentiated cell type						X	X					X											X		
Sarcoma, metastatic, skin															X										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear										+															
Harderian gland																		+					+		
Adenoma																							X		
Lacrimal gland					+																				
Carcinoma					X																				
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic										X															
Lymphoma malignant mixed																									
Lymphoma malignant undifferentiated cell type						X	X					X													
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type							X					X													

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

WEEKS ON STUDY	104	104	105	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	
CARCASS ID	363	364	341	324	325	331	351	381	393	322	342	344	345	352	354	384	371	373	374	383	391	401	402	404	405	TOTAL: TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sternal, sarcoma, metastatic, skin																										1
Lymph node	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Axillary, lymphoma malignant undifferentiated cell type																										2
Inguinal, lymphoma malignant undifferentiated cell type																										1
Lumbar, lymphoma malignant mixed																X										1
Lumbar, lymphoma malignant undifferentiated cell type																										3
Mediastinal, lymphoma malignant lymphocytic																										1
Mediastinal, lymphoma malignant undifferentiated cell type																										3
Mediastinal, sarcoma, metastatic, skin																										1
Pancreatic, lymphoma malignant																X										1
Pancreatic, lymphoma malignant undifferentiated cell type																										3
Renal, lymphoma malignant																X										1
Renal, lymphoma malignant undifferentiated cell type																										3
Lymph node, mandibular	M	+	+	+	+	M	+	+	M	+	+	M	M	+	+	+	+	+	+	M	+	+	M	+	M	34
Lymphoma malignant lymphocytic							X																			1
Lymphoma malignant mixed																X										1
Lymphoma malignant undifferentiated cell type																										3
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	42
Lymphoma malignant mixed																X										1
Lymphoma malignant undifferentiated cell type																								X		4
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																X										1
Lymphoma malignant undifferentiated cell type				X																						6
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	37
Lymphoma malignant lymphocytic																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	M	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M	M	M	+	+	+	+	+	+	31
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																										1
Subcutaneous tissue, sarcoma																										2
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Sarcoma, extension																										1
Intercostal, lymphoma malignant lymphocytic																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant undifferentiated cell type				X																						1
Meninges, lymphoma malignant mixed																			X							1
Spinal cord																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X								X										3
Lymphoma malignant lymphocytic																										1
Lymphoma malignant undifferentiated cell type				X																						5
Sarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Ear											+															2
Harderian gland																										2
Adenoma																										1
Lacrimal gland																										1
Carcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																			X							1
Lymphoma malignant undifferentiated cell type																										3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant undifferentiated cell type																										2

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

WEEKS ON STUDY	0 0 5	0 2 9	0 3 5	0 3 5	0 6 2	0 6 4	0 6 8	0 7 3	0 8 0	0 8 1	0 8 2	0 8 3	0 8 7	0 8 8	0 8 8	0 9 0	0 9 3	0 9 3	0 9 9	1 0 1	1 0 2	1 0 5	1 0 5	1 0 5	1 0 5
CARCASS ID	4 9 1	4 1 1	4 8 4	4 8 1	4 2 2	4 9 4	4 8 2	4 6 2	5 0 5	4 3 3	4 5 2	4 5 3	4 3 1	4 1 2	4 6 1	4 4 2	4 2 5	4 4 4	4 3 5	4 9 2	4 7 5	4 1 3	4 1 4	4 1 5	4 2 1
ALIMENTARY SYSTEM																									
Esophagus	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+									
Gallbladder	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+			+		+			+	
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+				
Intestine large, cecum	–	–	–	–	+	M	M	A	M	–	+	+	+	+	+	+					+				
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Intestine large, rectum	M	M	M	M	+	+	+	+	+	M	+	+	+	+	+	+									
Intestine small	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+									
Intestine small, duodenum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+									
Intestine small, ileum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+									
Intestine small, jejunum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+									
Liver	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																								X	
Hepatocellular adenoma, multiple																									
Leukemia, poorly differentiated					X																				
Lymphoma malignant mixed																X									
Lymphoma malignant undifferentiated cell type														X											
Mesentery		+					+	+	+		+	+			+								+		
Pancreas	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				M				+
Lymphoma malignant mixed																									
Lymphoma malignant undifferentiated cell type														X											
Salivary glands	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Submandibular gland, lymphoma malignant undifferentiated cell type														X											
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Lymphoma malignant undifferentiated cell type														X											
CARDIOVASCULAR SYSTEM																									
Heart	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Carcinoma, metastatic, lung											X														
ENDOCRINE SYSTEM																									
Adrenal gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Adrenal gland, cortex	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Lymphoma malignant undifferentiated cell type														X											
Adrenal gland, medulla	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Lymphoma malignant undifferentiated cell type														X											
Islets, pancreatic	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Parathyroid gland	M	+	M	+	M	+	+	+	+	M	M	+	M	+	M	M									
Pituitary gland	M	M	+	+	+	+	+	M	+	+	M	+	+	+	+	+					+				M
Pars distalis, adenoma																X					X				
Thyroid gland	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland		+																							
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	M	+	+	+	+	+	+	+
Cystadenoma																									
Granulosa cell tumor benign											X														
Lymphoma malignant lymphocytic																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									X
Lymphoma malignant lymphocytic																									
Lymphoma malignant undifferentiated cell type														X											
Polyp stromal																						X			

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL:
CARCASS ID	423	424	432	434	441	443	445	451	454	455	463	464	465	471	472	473	474	483	485	493	495	501	502	503	504	TISSUES / TUMORS
ALIMENTARY SYSTEM																										
Esophagus																										14
Gallbladder		+		+	+	M	+	+	+			M		+		+		+			+		+	+		28
Intestine large																										17
Intestine large, cecum																										8
Intestine large, colon																										16
Intestine large, rectum																										11
Intestine small																										15
Intestine small, duodenum																										15
Intestine small, ileum																										15
Intestine small, jejunum																										15
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma														X								X		X		4
Hepatocellular adenoma, multiple										X																1
Leukemia, poorly differentiated																										1
Lymphoma malignant mixed																										1
Lymphoma malignant undifferentiated cell type																										1
Mesentery																										8
Pancreas																					+				+	19
Lymphoma malignant mixed																					X					1
Lymphoma malignant undifferentiated cell type																										1
Salivary glands																									+	16
Submandibular gland, lymphoma malignant undifferentiated cell type																										1
Stomach																										16
Stomach, forestomach																										16
Stomach, glandular																										16
Lymphoma malignant undifferentiated cell type																										1
CARDIOVASCULAR SYSTEM																										
Heart												+														16
Carcinoma, metastatic, lung																										1
ENDOCRINE SYSTEM																										
Adrenal gland																										15
Adrenal gland, cortex																										15
Lymphoma malignant undifferentiated cell type																										1
Adrenal gland, medulla																										15
Lymphoma malignant undifferentiated cell type																										1
Islets, pancreatic																										15
Parathyroid gland																										8
Pituitary gland							+													+				+	+	17
Pars distalis, adenoma																				X				X	X	5
Thyroid gland																										14
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland																									+	2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Cystadenoma																					X					1
Granulosa cell tumor benign																										1
Lymphoma malignant lymphocytic										X																1
Uterus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma																X										2
Lymphoma malignant lymphocytic										X																1
Lymphoma malignant undifferentiated cell type																										1
Polyp stromal																										1

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

WEEKS ON STUDY	0 2 9	0 3 5	0 3 5	0 6 2	0 6 4	0 6 8	0 7 3	0 8 0	0 8 1	0 8 2	0 8 3	0 8 7	0 8 8	0 8 8	0 9 0	0 9 3	0 9 3	0 9 9	1 0 1	1 0 2	1 0 5	1 0 5	1 0 5	1 0 5
CARCASS ID	4 1 1	4 8 4	4 8 1	4 2 2	4 9 4	4 8 2	4 6 2	5 0 5	4 3 3	4 5 2	4 5 3	4 3 1	4 1 2	4 6 1	4 4 2	4 2 5	4 4 4	4 3 5	4 9 2	4 7 5	4 1 3	4 1 4	4 1 5	4 2 1
HEMATOPOIETIC SYSTEM																								
Bone marrow	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+									
Leukemia, poorly differentiated				X																				
Lymph node	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+		+	+				+
Axillary, lymphoma malignant lymphocytic																								
Axillary, lymphoma malignant mixed															X									
Inguinal, carcinoma, metastatic, lung										X														
Inguinal, lymphoma malignant lymphocytic																								
Inguinal, lymphoma malignant mixed															X									
Lumbar, adenocarcinoma, metastatic, uterus																								
Lumbar, lymphoma malignant lymphocytic																								
Lumbar, lymphoma malignant mixed															X									
Lumbar, lymphoma malignant undifferentiated cell type													X											X
Mediastinal, lymphoma malignant lymphocytic																								
Mediastinal, lymphoma malignant mixed															X									
Pancreatic, lymphoma malignant mixed															X									
Pancreatic, lymphoma malignant undifferentiated cell type													X											
Renal, lymphoma malignant lymphocytic																								
Renal, lymphoma malignant mixed															X									
Renal, lymphoma malignant undifferentiated cell type													X											X
Lymph node, mandibular	M	M	+	+	+	M	+	M	+	+	+	M	+	+	+									
Lymphoma malignant lymphocytic																								
Lymphoma malignant mixed															X									
Lymphoma malignant undifferentiated cell type													X											
Lymph node, mesenteric	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+			+					+
Lymphoma malignant lymphocytic																								
Lymphoma malignant mixed															X									
Lymphoma malignant undifferentiated cell type													X											X
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+						+
Hemangiosarcoma																								
Leukemia, poorly differentiated					X																			
Lymphoma malignant lymphocytic																								
Lymphoma malignant mixed															X									
Lymphoma malignant undifferentiated cell type													X											X
Thymus	M	+	+	+	+	+	+	+	M	+	+	+	+	M	M	M								
INTEGUMENTARY SYSTEM																								
Mammary gland	M	+	M	+	M	M	M	M	M	+	+	M	M	M	M	+								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Subcutaneous tissue, fibrosarcoma												X												
MUSCULOSKELETAL SYSTEM																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Carcinoma, metastatic, lung										X														
Sternum, fibrosarcoma, deep invasion												X												
Skeletal muscle						+				+	+		+											
Hindlimb, carcinoma, metastatic, lung										X														
Intercostal, lymphoma malignant undifferentiated cell type													X											
NERVOUS SYSTEM																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Meninges, lymphoma malignant undifferentiated cell type													X											
Spinal cord										+														
RESPIRATORY SYSTEM																								
Lung	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+		
Alveolar/bronchiolar adenoma																								
Alveolar/bronchiolar carcinoma										X														
Leukemia, poorly differentiated				X																				
Lymphoma malignant undifferentiated cell type													X											
Nose	–	+	–	–	+	+	+	+	+	–	+	+	+	+	+									
Trachea	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
SPECIAL SENSES SYSTEM																								
Harderian gland																							+	
URINARY SYSTEM																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, lung										X														
Leukemia, poorly differentiated				X																				
Lymphoma malignant lymphocytic																								
Lymphoma malignant mixed																								
Lymphoma malignant undifferentiated cell type													X											
Ureter													+											
Lymphoma malignant undifferentiated cell type													X											
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+								
Lymphoma malignant undifferentiated cell type													X											

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL:
CARCASS ID	423	424	432	434	441	443	445	451	454	455	463	464	465	471	472	473	474	483	485	493	495	501	502	503	504	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow																										15
Leukemia, poorly differentiated																										1
Lymph node		+				+				+							+				+					24
Axillary, lymphoma malig. lymphocytic										X																1
Axillary, lymphoma malignant mixed																										1
Inguinal, carcinoma, metastatic, lung																										1
Inguinal, lymphoma malig. lymphocytic										X																1
Inguinal, lymphoma malignant mixed																										1
Lumbar, adenocarcinoma, metastatic, uterus																X										1
Lumbar, lymphoma malig. lymphocytic										X																1
Lumbar, lymphoma malignant mixed																					X					2
Lumbar, lymphoma malignant undifferentiated cell type																										2
Mediastinal, lymphoma malignant lymphocytic										X																1
Mediastinal, lymphoma malig. mixed																										1
Pancreatic, lymphoma malignant mixed																X										2
Pancreatic, lymphoma malignant undifferentiated cell type																										1
Renal, lymphoma malignant lymphocytic										X																1
Renal, lymphoma malignant mixed																					X					2
Renal, lymphoma malignant undifferentiated cell type																										2
Lymph node, mandibular										+																12
Lymphoma malignant lymphocytic										X																1
Lymphoma malignant mixed																										1
Lymphoma malignant undifferentiated cell type																										1
Lymph node, mesenteric		+								+																18
Lymphoma malignant lymphocytic										X																1
Lymphoma malignant mixed																										1
Lymphoma malignant undifferentiated cell type																										2
Spleen		+				+			+	+	+	+	+	+							+				+	29
Hemangiosarcoma									X																	1
Leukemia, poorly differentiated																										1
Lymphoma malignant lymphocytic										X																1
Lymphoma malignant mixed													X	X							X					4
Lymphoma malignant undifferentiated cell type																										2
Thymus																										11
INTEGUMENTARY SYSTEM																										
Mammary gland																										5
Skin																										16
Subcutaneous tissue, fibrosarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone																										16
Carcinoma, metastatic, lung																										1
Sternum, fibrosarcoma, deep invasion																										1
Skeletal muscle																										4
Hindlimb, carcinoma, metastatic, lung																										1
Intercostal, lymphoma malignant undifferentiated cell type																										1
NERVOUS SYSTEM																										
Brain																										16
Meninges, lymphoma malignant undifferentiated cell type																										1
Spinal cord																										1
RESPIRATORY SYSTEM																										
Lung	+						+		+	+			+													21
Alveolar/bronchiolar adenoma							X			X																2
Alveolar/bronchiolar carcinoma																										1
Leukemia, poorly differentiated																										1
Lymphoma malignant undifferentiated cell type																										1
Nose																										12
Trachea																										15
SPECIAL SENSES SYSTEM																										
Harderian gland																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, lung																										1
Leukemia, poorly differentiated																										1
Lymphoma malignant lymphocytic										X																1
Lymphoma malignant mixed																					X					1
Lymphoma malignant undifferentiated cell type																										1
Ureter																										1
Lymphoma malignant undifferentiated cell type																										1
Urinary bladder																										16
Lymphoma malignant undifferentiated cell type																										1

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

WEEKS ON STUDY	0 0 1	0 0 9	0 0 9	0 0 9	0 5 4	0 6 7	0 7 1	0 7 1	0 7 1	0 7 4	0 8 2	0 8 7	0 9 2	0 9 3	1 0 0	1 0 1	1 0 2	1 0 2	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5
CARCASS ID	5 1 5	5 5 2	5 5 1	5 5 3	5 3 1	5 8 3	5 4 2	6 0 3	6 0 5	5 4 4	6 0 2	5 4 5	5 7 1	5 3 3	6 0 1	5 2 4	5 7 2	5 2 5	5 1 1	5 1 2	5 1 4	5 1 3	5 2 1	5 2 2	5 2 3
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+
Gallbladder	+	+	+	+	+	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Intestine large	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, cecum	–	–	–	–	M	M	+	M	+	+	+	+	M	–	+	+	+	A	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Intestine large, colon	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, rectum	M	M	A	M	M	+	+	+	+	+	+	+	+	M	+	+	+	A	+	+	+	+	+	+	+
Intestine small	+	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	A	+	+	+	M	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, ileum	+	A	A	+	+	+	+	M	+	+	M	+	+	M	+	+	+	A	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																									
Intestine small, jejunum	+	M	A	+	+	+	+	M	+	+	M	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Leukemia granulocytic					X																				
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																						X			
Hepatocellular adenoma, multiple																									
Leukemia granulocytic					X																				
Lymphoma malignant histiocytic								X																	
Lymphoma malignant mixed																				X					
Lymphoma malignant undifferentiated cell type															X										
Mesentery						+			+							+	+								
Fibrosarcoma, metastatic, skin									X																
Pancreas	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia granulocytic					X																				
Pharynx								+																	
Palate, lymphoma malignant histiocytic								X																	
Salivary glands	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Submandibular gland, lymphoma malignant mixed																									
Stomach	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Papilloma squamous																						X			
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Tooth															+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Leukemia granulocytic					X																				
Capsule, lymphoma malignant histiocytic								X																	
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	M	M	+	+	+	M	M	M	+	M	M	M	M	+	+	M	M	+	M	+	+	+
Pituitary gland	M	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Pars distalis, carcinoma												X													
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Granulosa cell tumor benign																									
Leukemia granulocytic					X																				
Lymphoma malignant histiocytic								X																	
Lymphoma malignant mixed																									
Periovarian tissue, lymphoma malignant undifferentiated cell type															X										
Uterus	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Leiomyoma												X													

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	532	534	535	541	543	554	555	561	562	563	565	564	573	574	575	581	582	584	585	591	592	593	594	595	604	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	44
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant mixed																									X	1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Lymphoma malignant mixed																									X	1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Lymphoma malignant undifferentiated cell type															X											1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Leukemia granulocytic																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma					X	X												X								4
Hepatocellular adenoma, multiple								X														X	X			3
Leukemia granulocytic																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed																X					X				X	4
Lymphoma malignant undifferentiated cell type																										1
Mesentery																										4
Fibrosarcoma, metastatic, skin																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia granulocytic																										1
Pharynx																										1
Palate, lymphoma malignant histiocytic																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Submandibular gland, lymphoma malignant mixed																									X	1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Papilloma squamous				X																						2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth	+	+	+	+	+	+	+	+	+	+	+			+				+	+		+	+			+	28
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia granulocytic																										1
Capsule, lymphoma malignant histiocytic																										1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign								X																		1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	M	M	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	30
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pars distalis, adenoma	X			X									X													3
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	47
Granulosa cell tumor benign																X										1
Leukemia granulocytic																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed																X										1
Periovarian tissue, lymphoma malignant undifferentiated cell type																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangioma		X																								1
Leiomyoma																										1

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

WEEKS ON STUDY	001	009	009	009	054	067	071	071	071	074	082	087	092	093	100	101	102	102	105	105	105	105	105	105	105
CARCASS ID	515	552	551	553	531	583	542	603	605	544	602	545	571	533	601	524	572	525	511	512	514	513	521	522	523
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia granulocytic					X																				
Lymphoma malignant histiocytic								X																	
Lymph node	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lumbar, lymphoma malignant histiocytic								X																	
Lumbar, lymphoma malignant mixed																									
Lumbar, lymphoma malignant undifferentiated cell type															X										
Mediastinal, leukemia granulocytic					X																				
Mediastinal, lymphoma malignant mixed																									
Mediastinal, lymphoma malignant undifferentiated cell type															X										
Pancreatic, lymphoma malignant mixed																									
Renal, lymphoma malignant histiocytic								X																	
Renal, lymphoma malignant mixed																									
Renal, lymphoma malignant undifferentiated cell type															X										
Lymph node, mandibular	M	+	+	+	M	M	+	+	+	+	+	+	M	M	+	+	+	+	M	M	M	M	M	+	M
Lymphoma malignant histiocytic								X																	
Lymphoma malignant mixed																									
Lymph node, mesenteric	M	+	M	M	M	+	+	+	M	+	+	+	M	+	+	+	M	M	+	+	+	+	+	+	+
Lymphoma malignant histiocytic								X																	
Lymphoma malignant mixed																									
Lymphoma malignant undifferentiated cell type																									
Spleen	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic								X																	
Lymphoma malignant mixed																									
Lymphoma malignant undifferentiated cell type																									
Thymus	M	+	M	+	M	+	+	M	M	+	+	M	M	M	+	+	+	+	M	+	+	+	+	+	+
Lymphoma malignant mixed																									
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	+	M	M	+	M	M	+	M	+	+	+	+	+	+
Adenocarcinoma																									
Skin	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma									X																
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle						+		+		+	+														
Intercostal, lymphoma malignant histiocytic								X																	
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X							X							
Leukemia granulocytic					X																				
Lymphoma malignant histiocytic								X																	
Lymphoma malignant mixed																									
Mediastinum, lymphoma malignant mixed																									
Nose	−	−	−	−	+	+	+	+	+	+	M	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Nasolacrimal duct, lymphoma malignant histiocytic								X																	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear												+													
Harderian gland																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin									X																
Lymphoma malignant histiocytic								X																	
Lymphoma malignant mixed																									
Lymphoma malignant undifferentiated cell type															X										
Urinary bladder	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin									X																
Lymphoma malignant undifferentiated cell type															X										

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	532	534	535	541	543	554	555	561	562	563	565	564	573	574	575	581	582	584	585	591	592	593	594	595	604	TOTAL: TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia granulocytic																										1
Lymphoma malignant histiocytic																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lumbar, lymphoma malig. histiocytic																										1
Lumbar, lymphoma malignant mixed																					X					1
Lumbar, lymphoma malignant undifferentiated cell type																										1
Mediastinal, leukemia granulocytic																										1
Mediastinal, lymphoma malig. mixed																					X				X	2
Mediastinal, lymphoma malignant undifferentiated cell type																										1
Pancreatic, lymphoma malignant mixed																X										1
Renal, lymphoma malignant histiocytic																										1
Renal, lymphoma malignant mixed																X					X					2
Renal, lymphoma malignant undifferentiated cell type																										1
Lymph node, mandibular	+	+	+	M	M	+	M	+	+	+	M	M	+	+	M	M	+	M	+	+	+	M	+	+	+	30
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed																									X	1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed																X					X				X	3
Lymphoma malignant undifferentiated cell type															X											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed																X					X					2
Lymphoma malignant undifferentiated cell type									X																	1
Thymus	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Lymphoma malignant mixed																									X	1
INTEGUMENTARY SYSTEM																										
Mammary gland	M	+	M	M	M	+	+	+	+	+	+	M	M	+	M	+	M	M	M	+	+	+	M	+	+	23
Adenocarcinoma											X															1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Subcutaneous tissue, fibrosarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										4
Intercostal, lymphoma malignant histiocytic																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma													X													3
Leukemia granulocytic																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed																X										1
Mediastinum, lymphoma malig. mixed																X										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+	+	+	+	41
Nasolacrimal duct, lymphoma malignant histiocytic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear																										1
Harderian gland		+																								1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed																					X					1
Lymphoma malignant undifferentiated cell type																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrosarcoma, metastatic, skin																										1
Lymphoma malignant undifferentiated cell type																										1

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

	Vehicle Control	150 mg/kg	300 mg/kg
Liver: Hepatocellular Adenoma			
Overall Rates (a)	4/50 (8%)	5/49 (10%)	7/50 (14%)
Adjusted Rates (b)	16.4%	17.2%	21.9%
Terminal Rates (c)	3/22 (14%)	5/29 (17%)	7/32 (22%)
Day of First Observation	688	731	731
Life Table Tests (d)	P=0.413	P=0.625N	P=0.490
Logistic Regression Tests (d)	P=0.355	P=0.532	P=0.413
Cochran-Armitage Trend Test (d)	P=0.211		
Fisher Exact Test (d)		P=0.487	P=0.262
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	5/49 (10%)	7/50 (14%)
Adjusted Rates (b)	20.8%	17.2%	21.9%
Terminal Rates (c)	4/22 (18%)	5/29 (17%)	7/32 (22%)
Day of First Observation	688	731	731
Life Table Tests (d)	P=0.563	P=0.466N	P=0.613N
Logistic Regression Tests (d)	P=0.504	P=0.599N	P=0.570
Cochran-Armitage Trend Test (d)	P=0.319		
Fisher Exact Test (d)		P=0.617	P=0.380
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	3/50 (6%)	(e,f) 2/21 (10%)	3/50 (6%)
Adjusted Rates (b)	11.4%		8.4%
Terminal Rates (c)	2/22 (9%)		1/32 (3%)
Day of First Observation	631		568
Life Table Test (d)			P=0.578N
Logistic Regression Test (d)			P=0.641
Fisher Exact Test (d)			P=0.661N
Anterior Pituitary Gland: Adenoma			
Overall Rates (a)	8/44 (18%)	(e) 5/17 (29%)	3/47 (6%)
Adjusted Rates (b)	35.1%		9.4%
Terminal Rates (c)	7/21 (33%)		3/32 (9%)
Day of First Observation	652		731
Life Table Test (d)			P=0.021N
Logistic Regression Test (d)			P=0.053N
Fisher Exact Test (d)			P=0.080N
Anterior Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	8/44 (18%)	(e) 5/17 (29%)	4/47 (9%)
Adjusted Rates (b)	35.1%		11.7%
Terminal Rates (c)	7/21 (33%)		3/32 (9%)
Day of First Observation	652		605
Life Table Test (d)			P=0.056N
Logistic Regression Test (d)			P=0.143N
Fisher Exact Test (d)			P=0.146N
Forestomach: Squamous Papilloma			
Overall Rates (g)	3/50 (6%)	0/50 (0%)	2/50 (4%)
Adjusted Rates (b)	10.2%	0.0%	6.3%
Terminal Rates (c)	1/22 (5%)	0/29 (0%)	2/32 (6%)
Day of First Observation	669		731
Life Table Tests (d)	P=0.304N	P=0.111N	P=0.384N
Logistic Regression Tests (d)	P=0.399N	P=0.134N	P=0.512N
Cochran-Armitage Trend Test (d)	P=0.391N		
Fisher Exact Test (d)		P=0.121N	P=0.500N

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

	Vehicle Control	150 mg/kg	300 mg/kg
Forestomach: Squamous Papilloma or Squamous Cell Carcinoma			
Overall Rates (g)	5/50 (10%)	0/50 (0%)	2/50 (4%)
Adjusted Rates (b)	18.8%	0.0%	6.3%
Terminal Rates (c)	3/22 (14%)	0/29 (0%)	2/32 (6%)
Day of First Observation	669		731
Life Table Tests (d)	P=0.066N	P=0.023N	P=0.118N
Logistic Regression Tests (d)	P=0.114N	P=0.038N	P=0.206N
Cochran-Armitage Trend Test (d)	P=0.119N		
Fisher Exact Test (d)		P=0.028N	P=0.218N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (g)	11/50 (22%)	(h) 8/50 (16%)	8/50 (16%)
Adjusted Rates (b)	34.3%	25.0%	22.8%
Terminal Rates (c)	5/22 (23%)	6/29 (21%)	6/32 (19%)
Day of First Observation	599	612	492
Life Table Tests (d)	P=0.129N	P=0.226N	P=0.163N
Logistic Regression Tests (d)	P=0.305N	P=0.368N	P=0.352N
Cochran-Armitage Trend Test (d)	P=0.257N		
Fisher Exact Test (d)		P=0.306N	P=0.306N

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

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

Study	Incidence of Adenomas or Adenocarcinomas in Vehicle Controls
Historical Incidence at EG&G Mason Research Institute	
Diglycidyl resorcinol ether	0/49
1,2-Dichloropropane	0/50
Chlorodibromomethane	0/48
n-Butyl chloride	0/50
Bromodichloromethane	(b) 1/50
Bis(2-chloro-1-methylethyl) ether	0/49
n-Butyl chloride	0/50
TOTAL	1/346 (0.3%)
SD (c)	0.76%
Range (d)	
High	1/50
Low	0/50
Overall Historical Incidence	
TOTAL	(e) 7/2,077 (0.3%)
SD (c)	1.09%
Range (d)	
High	3/49
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Adenocarcinoma, NOS
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes two adenomas, NOS, four adenocarcinomas, NOS, and one carcinoma, NOS; one squamous cell carcinoma was also observed.

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Esophagus	(47)	(14)	(44)
Inflammation, acute			1 (2%)
Necrosis			1 (2%)
Gallbladder	(44)	(28)	(47)
Inflammation, acute	4 (9%)		3 (6%)
Inflammation, chronic	7 (16%)		7 (15%)
Inflammation, chronic active	2 (5%)		
Intestine large, cecum	(50)	(8)	(40)
Mesothelium, hyperplasia			1 (3%)
Serosa, inflammation, chronic active	2 (4%)		
Intestine large, colon	(50)	(16)	(48)
Inflammation, acute			1 (2%)
Epithelium, hyperplasia			1 (2%)
Mesothelium, hyperplasia	1 (2%)		1 (2%)
Muscularis, inflammation, chronic active	1 (2%)		
Serosa, inflammation, acute	1 (2%)		
Intestine large, rectum	(48)	(11)	(43)
Mesothelium, hyperplasia			1 (2%)
Serosa, inflammation, acute	1 (2%)		
Intestine small, duodenum	(48)	(15)	(46)
Mesothelium, hyperplasia	1 (2%)		1 (2%)
Serosa, fibrosis	1 (2%)		
Serosa, inflammation, chronic active	2 (4%)		
Intestine small, ileum	(46)	(15)	(44)
Lymphoid nodule, hyperplasia	3 (7%)		
Mesothelium, hyperplasia	2 (4%)		1 (2%)
Mucosa, vacuolization cytoplasmic	1 (2%)		
Serosa, inflammation, acute		2 (13%)	
Intestine small, jejunum	(49)	(15)	(45)
Hemorrhage			1 (2%)
Mesothelium, hyperplasia	3 (6%)		1 (2%)
Serosa, inflammation, chronic active	2 (4%)		1 (2%)
Liver	(50)	(49)	(50)
Basophilic focus	1 (2%)		1 (2%)
Clear cell focus			1 (2%)
Congestion	2 (4%)		1 (2%)
Degeneration		1 (2%)	
Eosinophilic focus	1 (2%)	1 (2%)	
Fatty change	5 (10%)	6 (12%)	
Hematopoietic cell proliferation	19 (38%)	3 (6%)	7 (14%)
Hemorrhage		6 (12%)	1 (2%)
Inflammation, acute	3 (6%)		
Inflammation, chronic	12 (24%)	7 (14%)	3 (6%)
Inflammation, chronic active	1 (2%)	7 (14%)	
Mixed cell focus		3 (6%)	
Necrosis, coagulative	8 (16%)	14 (29%)	12 (24%)
Pigmentation		2 (4%)	
Vacuolization cytoplasmic, diffuse	1 (2%)	2 (4%)	
Periportal, inflammation, chronic	19 (38%)	16 (33%)	21 (42%)
Serosa, inflammation, acute	5 (10%)	1 (2%)	4 (8%)
Mesentery	(9)	(8)	(4)
Abscess		1 (13%)	
Fibrosis			1 (25%)
Inflammation, acute	1 (11%)	3 (38%)	1 (25%)
Inflammation, chronic	1 (11%)		
Inflammation, chronic active	5 (56%)	1 (13%)	2 (50%)
Necrosis	1 (11%)	1 (13%)	1 (25%)

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

	Vehicle Control	Low Dose	High Dose
ALIMENTARY SYSTEM (Continued)			
Pancreas	(50)	(19)	(49)
Abscess		2 (11%)	1 (2%)
Atrophy	2 (4%)		2 (4%)
Fatty change	1 (2%)		
Fibrosis	1 (2%)		
Inflammation, acute	2 (4%)	1 (5%)	
Inflammation, chronic	17 (34%)	2 (11%)	20 (41%)
Inflammation, chronic active	5 (10%)		
Duct, dilatation	1 (2%)		1 (2%)
Serosa, fibrosis	2 (4%)		
Serosa, inflammation, acute	5 (10%)	3 (16%)	1 (2%)
Serosa, inflammation, chronic active	3 (6%)		3 (6%)
Salivary glands	(48)	(16)	(49)
Parotid gland, inflammation, chronic	2 (4%)		
Sublingual gland, inflammation, chronic	3 (6%)		3 (6%)
Submandibular gland, atrophy		1 (6%)	
Submandibular gland, inflammation, chronic	26 (54%)	4 (25%)	27 (55%)
Stomach, forestomach	(50)	(16)	(48)
Acanthosis	3 (6%)		4 (8%)
Hyperkeratosis	4 (8%)		4 (8%)
Hyperplasia, basal cell			1 (2%)
Inflammation, chronic	3 (6%)		
Inflammation, chronic active			1 (2%)
Inflammation, necrotizing, chronic active	1 (2%)		1 (2%)
Stomach, glandular	(49)	(16)	(48)
Inflammation, chronic	13 (27%)		13 (27%)
Inflammation, chronic active	5 (10%)		3 (6%)
Epithelium, hyperplasia, focal	1 (2%)		
Tooth	(35)		(28)
Dysplasia	1 (3%)		
Incisor, abscess	3 (9%)		
CARDIOVASCULAR SYSTEM			
Heart	(50)	(16)	(50)
Abscess	1 (2%)		
Bacterium	1 (2%)		1 (2%)
Infiltration cellular, mononuclear cell	1 (2%)		
Inflammation, acute	2 (4%)		1 (2%)
Inflammation, chronic	5 (10%)		6 (12%)
Inflammation, chronic active	1 (2%)		
Mineralization		1 (6%)	1 (2%)
Necrosis, focal	1 (2%)		
Coronary artery, perivascular, inflammation, acute	1 (2%)		
Coronary artery, perivascular, inflammation, chronic active	1 (2%)		
Epicardium, inflammation, acute		1 (6%)	
ENDOCRINE SYSTEM			
Adrenal gland	(48)	(15)	(49)
Capsule, inflammation, chronic active	6 (13%)		3 (6%)
Adrenal gland, cortex	(48)	(15)	(49)
Angiectasis	2 (4%)		1 (2%)
Congestion		1 (7%)	
Cyst	2 (4%)		1 (2%)
Hematopoietic cell proliferation	3 (6%)		1 (2%)
Inflammation, chronic active	1 (2%)		1 (2%)
Adrenal gland, medulla	(47)	(15)	(48)
Angiectasis	1 (2%)		
Hyperplasia	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
Parathyroid gland	(31)	(8)	(30)
Cyst	1 (3%)	1 (13%)	
Pituitary gland	(44)	(17)	(47)
Pars distalis, angiectasis		4 (24%)	2 (4%)
Pars distalis, congestion	1 (2%)		
Pars distalis, cyst	1 (2%)	1 (6%)	1 (2%)
Pars distalis, hyperplasia	16 (36%)	3 (18%)	22 (47%)
Thyroid gland	(48)	(14)	(50)
Inflammation, chronic	1 (2%)		3 (6%)
Ultimobranchial cyst	1 (2%)		1 (2%)
C-cell, hyperplasia	1 (2%)		
Follicle, cyst	2 (4%)		1 (2%)
Follicular cell, hyperplasia	4 (8%)		
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland		(2)	
Cyst		1 (50%)	
Ovary	(50)	(47)	(47)
Abscess	19 (38%)	4 (9%)	10 (21%)
Angiectasis		1 (2%)	1 (2%)
Cyst	7 (14%)	9 (19%)	16 (34%)
Hemorrhage	2 (4%)		
Mineralization	1 (2%)		
Necrosis, coagulative			1 (2%)
Pigmentation		6 (13%)	
Periovarian tissue, cyst	4 (8%)	5 (11%)	2 (4%)
Periovarian tissue, hemorrhage		1 (2%)	
Periovarian tissue, inflammation, acute		1 (2%)	
Periovarian tissue, inflammation, chronic	14 (28%)		5 (11%)
Periovarian tissue, inflammation, chronic active	1 (2%)	1 (2%)	1 (2%)
Periovarian tissue, necrosis		1 (2%)	
Periovarian tissue, thrombus		1 (2%)	
Serosa, inflammation, chronic active	1 (2%)		
Oviduct	(8)		
Inflammation, acute	6 (75%)		
Inflammation, chronic active	1 (13%)		
Inflammation, hemorrhagic, acute	1 (13%)		
Uterus	(50)	(49)	(48)
Abscess	3 (6%)	4 (8%)	2 (4%)
Hydrometria	1 (2%)		1 (2%)
Inflammation, acute	19 (38%)	5 (10%)	9 (19%)
Inflammation, chronic	1 (2%)		
Inflammation, chronic active	1 (2%)		4 (8%)
Necrosis, coagulative		1 (2%)	
Pigmentation		1 (2%)	
Endometrium, hyperplasia	50 (100%)	42 (86%)	41 (85%)
Muscularis, congestion	1 (2%)		
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(15)	(50)
Bacterium	1 (2%)		
Congestion		1 (7%)	4 (8%)
Hypoplasia			3 (6%)
Myelofibrosis	42 (84%)	1 (7%)	28 (56%)
Myeloid cell, hyperplasia	4 (8%)	2 (13%)	1 (2%)

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
Lymph node	(47)	(24)	(48)
Bronchial, inflammation, chronic active		1 (4%)	
Lumbar, bacterium	1 (2%)		
Lumbar, hemorrhage		1 (4%)	
Lumbar, hyperplasia, lymphoid		1 (4%)	
Lumbar, hyperplasia, plasma cell	9 (19%)	1 (4%)	2 (4%)
Lumbar, inflammation, acute			1 (2%)
Lumbar, inflammation, chronic active	4 (9%)		
Mediastinal, abscess		1 (4%)	1 (2%)
Mediastinal, congestion	1 (2%)		
Mediastinal, depletion lymphoid	2 (4%)	1 (4%)	
Mediastinal, hemorrhage	2 (4%)		
Mediastinal, hyperplasia, lymphoid	1 (2%)	1 (4%)	
Mediastinal, hyperplasia, plasma cell	6 (13%)		2 (4%)
Mediastinal, inflammation, acute	4 (9%)	2 (8%)	2 (4%)
Mediastinal, inflammation, chronic active			1 (2%)
Pancreatic, angiectasis	1 (2%)		
Pancreatic, hemorrhage	1 (2%)	1 (4%)	
Pancreatic, hyperplasia, plasma cell	2 (4%)		2 (4%)
Pancreatic, inflammation, acute	2 (4%)		
Renal, bacterium	1 (2%)		
Renal, hemorrhage	1 (2%)		
Renal, hyperplasia, lymphoid		1 (4%)	
Renal, hyperplasia, plasma cell	11 (23%)	3 (13%)	7 (15%)
Renal, inflammation, acute		1 (4%)	3 (6%)
Renal, inflammation, chronic active	2 (4%)		
Lymph node, mandibular	(34)	(12)	(30)
Depletion lymphoid	1 (3%)	1 (8%)	1 (3%)
Ectasia			1 (3%)
Hyperplasia, plasma cell	3 (9%)		
Inflammation, acute	1 (3%)		
Lymph node, mesenteric	(42)	(18)	(41)
Abscess		1 (6%)	
Angiectasis	5 (12%)	1 (6%)	1 (2%)
Congestion	1 (2%)		
Depletion lymphoid	2 (5%)	1 (6%)	
Hemorrhage	2 (5%)		
Hyperplasia, histiocyte	1 (2%)		
Hyperplasia, lymphoid	4 (10%)	1 (6%)	2 (5%)
Hyperplasia, plasma cell	2 (5%)		1 (2%)
Inflammation, acute	3 (7%)	1 (6%)	1 (2%)
Inflammation, chronic		1 (6%)	
Inflammation, chronic active	2 (5%)	1 (6%)	
Inflammation, necrotizing, acute		1 (6%)	
Necrosis		1 (6%)	
Serosa, congestion	1 (2%)		
Serosa, fibrosis	1 (2%)		
Serosa, inflammation, chronic active	1 (2%)		
Spleen	(50)	(29)	(49)
Angiectasis	1 (2%)	1 (3%)	
Congestion		1 (3%)	1 (2%)
Depletion lymphoid	4 (8%)	6 (21%)	7 (14%)
Hematopoietic cell proliferation	23 (46%)	8 (28%)	8 (16%)
Hemorrhage	1 (2%)		
Hyperplasia, lymphoid	9 (18%)	1 (3%)	8 (16%)
Inflammation, acute			1 (2%)
Necrosis, coagulative	1 (2%)		
Capsule, abscess	1 (2%)		
Capsule, fibrosis	1 (2%)		
Capsule, inflammation, acute	3 (6%)	1 (3%)	
Capsule, inflammation, chronic active		1 (3%)	

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
Thymus	(37)	(11)	(39)
Cyst		1 (9%)	
Depletion lymphoid	9 (24%)	7 (64%)	6 (15%)
Hemorrhage	3 (8%)	1 (9%)	1 (3%)
Hyperplasia, lymphoid			2 (5%)
Inflammation, acute	2 (5%)		
Necrosis		3 (27%)	1 (3%)
INTEGUMENTARY SYSTEM			
Mammary gland	(31)	(5)	(23)
Galactocele	1 (3%)		
Hyperplasia	2 (6%)		1 (4%)
Infiltration cellular, mixed cell	1 (3%)		
Inflammation, chronic	3 (10%)		
Skin	(49)	(16)	(48)
Inflammation, necrotizing, acute	2 (4%)		1 (2%)
Subcutaneous tissue, fibrosis			2 (4%)
Subcutaneous tissue, inflammation, chronic active	1 (2%)		
MUSCULOSKELETAL SYSTEM			
Skeletal muscle	(2)	(4)	(4)
Intercostal, inflammation, acute		1 (25%)	
Thoracic, inflammation, acute		1 (25%)	2 (50%)
Thoracic, inflammation, chronic active			1 (25%)
NERVOUS SYSTEM			
Brain	(50)	(16)	(50)
Bacterium	1 (2%)		
Hemorrhage	2 (4%)		1 (2%)
Infarct, multifocal	1 (2%)		
Cerebellum, inflammation, chronic			1 (2%)
Thalamus, mineralization	40 (80%)	4 (25%)	25 (50%)
Spinal cord	(1)	(1)	
Hemorrhage, focal	1 (100%)		
RESPIRATORY SYSTEM			
Lung	(50)	(21)	(50)
Bacterium			2 (4%)
Congestion	2 (4%)	2 (10%)	1 (2%)
Hemorrhage	6 (12%)		3 (6%)
Infiltration cellular, histiocytic	1 (2%)	1 (5%)	
Inflammation, chronic	1 (2%)		1 (2%)
Inflammation, chronic active			2 (4%)
Leukocytosis	3 (6%)		1 (2%)
Alveolar epithelium, hyperplasia			2 (4%)
Artery, hyperplasia	1 (2%)		
Artery, thrombus	1 (2%)		
Mediastinum, inflammation, chronic active	1 (2%)		
Peribronchiolar, inflammation, chronic	1 (2%)		1 (2%)
Perivascular, inflammation, acute	4 (8%)		1 (2%)
Perivascular, inflammation, chronic	3 (6%)	2 (10%)	3 (6%)
Perivascular, inflammation, chronic active	1 (2%)		1 (2%)
Pleura, inflammation, acute	2 (4%)	1 (5%)	1 (2%)
Pleura, inflammation, chronic	1 (2%)		1 (2%)
Pleura, inflammation, chronic active		1 (5%)	
Pleura, inflammation, hemorrhagic, chronic active	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
RESPIRATORY SYSTEM (Continued)			
Nose	(50)	(12)	(41)
Lumen, inflammation, acute	4 (8%)		2 (5%)
Mucosa, glands, dilatation			1 (2%)
Mucosa, glands, inflammation, acute	18 (36%)		19 (46%)
Mucosa, glands, inflammation, chronic active	1 (2%)		
Nasolacrimal duct, inflammation, acute		1 (8%)	
Nasolacrimal duct, inflammation, chronic		3 (25%)	
Nasolacrimal duct, inflammation, chronic active	5 (10%)		4 (10%)
Trachea	(49)	(15)	(50)
Inflammation, acute	1 (2%)		
SPECIAL SENSES SYSTEM			
Harderian gland	(2)	(1)	(1)
Hyperplasia		1 (100%)	1 (100%)
Inflammation, chronic		1 (100%)	
Inflammation, necrotizing, acute	1 (50%)		
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Abscess	1 (2%)		
Bacterium	1 (2%)	1 (2%)	1 (2%)
Glomerulosclerosis	15 (30%)	2 (4%)	2 (4%)
Hydronephrosis			1 (2%)
Inflammation, chronic	44 (88%)	39 (78%)	41 (82%)
Inflammation, chronic active	1 (2%)		
Inflammation, necrotizing, acute			1 (2%)
Metaplasia, osseous	2 (4%)	1 (2%)	2 (4%)
Necrosis, coagulative, focal	1 (2%)		
Artery, thrombus			1 (2%)
Capsule, inflammation, acute	1 (2%)		
Papilla, inflammation, necrotizing, acute		1 (2%)	
Proximal convoluted renal tubule, atrophy	1 (2%)	2 (4%)	
Proximal convoluted renal tubule, regeneration	7 (14%)	1 (2%)	9 (18%)
Urinary bladder	(50)	(16)	(48)
Inflammation, acute	1 (2%)		1 (2%)
Inflammation, chronic	38 (76%)	6 (38%)	36 (75%)
Inflammation, chronic active	1 (2%)		1 (2%)
Serosa, inflammation, acute	2 (4%)		
Serosa, inflammation, chronic active	2 (4%)		
Submucosa, fibrosis			1 (2%)
Transitional epithelium, hyperplasia			1 (2%)

APPENDIX E

SENTINEL ANIMAL PROGRAM

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APPENDIX E. 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. Under this program, the disease state of the rodents is monitored via viral serology on sera from extra (sentinel) animals in the study rooms. These animals are untreated, and these animals and the study animals are both subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Fifteen B6C3F$_1$ mice and 15 F344/N rats of each sex were selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group were killed at 6, 12, and 18 months on study. Data from animals surviving 24 months were collected from 5/50 randomly selected vehicle control animals of each sex and species. The blood from each animal was collected and clotted, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests were performed:

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	PVM (pneumonia virus of mice) Reo 3 (reovirus type 3) GDVII (Theiler's encephalomyelitis virus) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia) Sendai (6,18,24 mo)	M. Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) Sendai (12 mo)	MHV (mouse hepatitis virus)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai (6,18,24 mo)	RCV (rat coronavirus) (6,12,18 mo) Sendai (12 mo)	RCV/SDA (sialodacryoadenitis virus) (24 mo)

Results

Results are presented in Table E1.

TABLE E1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF PHENYLBUTAZONE (a)

Interval (months)	Number of Animals	Positive Serologic Reaction for
RATS		
6	8/10	Sendai
12	9/9	Sendai
18	1/8	Sendai
24	3/10	Sendai
MICE		
6	--	None positive
12	4/10	Sendai
18	--	None positive
24	--	None positive

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

APPENDIX F

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

Meal Diet: September 1981 to October 1983

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

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TABLE F1. 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 F2. 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 F3. . NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Protein (percent by weight)	23.62 ± 1.08	22.0-25.9	26
Crude fat (percent by weight)	4.90 ± 0.41	4.2-5.7	26
Crude fiber (percent by weight)	3.36 ± 0.35	2.4-3.9	26
Ash (percent by weight)	6.58 ± 0.28	5.97-7.11	26
Amino Acids (percent of total diet)			
Arginine	1.323 ± 0.830	1.21-1.39	4
Cystine	0.310 ± 0.099	0.218-0.400	4
Glycine	1.155 ± 0.069	1.06-1.21	4
Histidine	0.572 ± 0.030	0.530-0.603	4
Isoleucine	0.910 ± 0.033	0.881-0.944	4
Leucine	1.949 ± 0.065	1.85-1.99	4
Lysine	1.275 ± 0.076	1.20-1.37	4
Methionine	0.422 ± 0.187	0.306-0.699	4
Phenylalanine	0.909 ± 0.167	0.665-1.04	4
Threonine	0.844 ± 0.029	0.824-0.886	4
Tryptophan	0.187	0.171-0.211	3
Tyrosine	0.631 ± 0.094	0.566-0.769	4
Valine	1.11 ± 0.050	1.05-1.17	4
Essential Fatty Acids (percent of total diet)			
Linoleic	2.44	2.37-2.52	3
Linolenic	0.274	0.256-0.308	3
Arachisonic	0.008		1
Vitamins			
Vitamin A (IU/kg)	11,665 ± 3,519	4,200-22,000	26
Vitamin D (IU/kg)	4,650	3,000-6,300	2
α-Tocopherol (ppm)	41.53 ± 7.52	31.1-48.9	4
Thiamine (ppm)	18.5 ± 3.5	12.0-26.0	26
Riboflavin (ppm)	7.5 ± 0.96	6.1-8.2	4
Niacin (ppm)	85.0 ± 14.2	65.0-97.0	4
Pantothenic acid (ppm)	29.3 ± 4.6	23.0-34.0	4
Pyridoxine (ppm)	7.6 ± 1.5	5.6-8.8	4
Folic acid (ppm)	2.8 ± 0.88	1.8-3.7	4
Biotin (ppm)	0.27 ± 0.05	0.21-0.32	4
Vitamin B_{12} (ppb)	21.0 ± 11.9	11.0-38.0	4
Choline (ppm)	3,302.0 ± 120.0	3,200.0-3,430.0	4
Minerals			
Calcium (percent)	1.24 ± 0.10	1.10-1.43	26
Phosphorus (percent)	0.96 ± 0.05	0.84-1.10	26
Potassium (percent)	0.862 ± 0.100	0.772-0.974	3
Chloride (percent)	0.546 ± 0.100	0.442-0.635	4
Sodium (percent)	0.311 ± 0.038	0.258-0.350	4
Magnesium (percent)	0.169 ± 0.133	0.151-0.181	4
Sulfur (percent)	0.316 ± 0.070	0.270-0.420	4
Iron (ppm)	447.0 ± 57.3	409.0-523.0	4
Manganese (ppm)	90.6 ± 8.20	81.7-95.5	4
Zinc (ppm)	53.6 ± 5.27	46.1-58.6	4
Copper (ppm)	10.77 ± 3.19	8.09-15.39	4
Iodine (ppm)	2.95 ± 1.05	1.52-3.82	4
Chromium (ppm)	1.81 ± 0.28	1.44-2.09	4
Cobalt (ppm)	0.68 ± 0.14	0.49-0.80	4

(a) One or two lots of feed analyzed for nutrients reported in this table were manufactured in January and/or April 1983.

TABLE F4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.51 ± 0.13	0.28-0.74	26
Cadmium (ppm) (a)	<0.01		26
Lead (ppm)	0.73 ± 0.53	0.27-2.93	26
Mercury (ppm) (a)	<0.05		26
Selenium (ppm)	0.29 ± 0.06	0.21-0.40	26
Aflatoxins (ppb) (a)	<5.0		26
Nitrate nitrogen (ppm) (b)	9.71 ± 4.54	2.5-19.0	26
Nitrite nitrogen (ppm) (b)	2.0 ± 1.59	<0.1-6.1	26
BHA (ppm) (c)	4.95 ± 5.03	<2.0-20.0	26
BHT (ppm) (c)	2.98 ± 2.61	<1.0-13.0	26
Aerobic plate count (CFU/g) (d,e)	109,421 ± 86,381	6,200-310,000	24
Aerobic plate count (CFU/g) (f)	136,204 ± 119,767	6,200-420,000	26
Coliform (MPN/g) (g)	898.0 ± 997.2	<3.0->2,400	26
E. coli (MPN/g)	6.58 ± 6.91	<3.0->23.0	26
Total nitrosamines (ppb) (h)	4.20 ± 3.27	0.9-12.9	26
N-Nitrosodimethylamine (ppb) (h)	3.51 ± 3.05	0.9-12.0	26
N-Nitrosopyrrolidine (ppb) (i)	1.26 ± 0.46	<0.9-2.2	20
Pesticides (ppm)			
α-BHC (a, j)	<0.01		26
β-BHC (a)	<0.02		26
γ-BHC (a)	<0.01		26
δ-BHC (a)	<0.01		26
Heptachlor (a)	<0.01		26
Aldrin (a)	<0.01		26
Heptachlor epoxide (a)	<0.01		26
DDE (a)	<0.01		26
DDD (a)	<0.01		26
DDT (a)	<0.01		26
HCB (a)	<0.01		26
Mirex (a)	<0.01		26
Methoxychlor (k)	<0.05	0.06 (6/24/82)	26
Dieldrin (k)	<0.01	0.02 (7/27/82)	26
Endrin (a)	<0.01		26
Telodrin (a)	<0.01		26
Chlordane (a)	<0.05		26
Toxaphene (a)	<0.1		26
Estimated PCBs (a)	<0.2		26
Ronnel (a)	<0.01		26
Ethion (a)	<0.02		26
Trithion (a)	<0.05		26
Diazinon (a)	<0.1		26
Methyl parathion (a)	<0.02		26
Ethyl parathion (a)	<0.02		26
Malathion (l)	0.11 ± 0.10	<0.05-0.48	26
Endosulfan I (a,m)	<0.01		23
Endosulfan II (a,m)	<0.01		23
Endosulfan sulfate (a,m)	<0.03		23

TABLE F4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) All values were less than the detection limit, given in the table as the mean.
(b) Source of contamination: alfalfa, grains, and fish meal
(c) Source of contamination: soy oil and fish meal
(d) CFU = colony-forming unit
(e) Mean, standard deviation, and range exclude one very high value of 420,000 CFU/g obtained for lots produced on March 23, 1983, and July 12, 1983.
(f) Mean, standard deviation, and range include the extremely high value given in footnote (e).
(g) MPN = most probable number
(h) All values were corrected for percent recovery.
(i) Not detected in lots produced on June 24, 1982, and from June 22, 1983, through October 19, 1983.
(j) BHC = hexachlorocyclohexane or benzene hexachloride
(k) One observation was above the detection limit. The value and the date it was obtained are listed under the range.
(l) Twelve lots contained more than 0.05 ppm.
(m) Three lots, from September 25, 1981, through November 27, 1981, were not analyzed for endosulfan I, endosulfan II, or endosulfan sulfate.

APPENDIX G

CHEMICAL CHARACTERIZATION, ANALYSIS, AND DOSE PREPARATION OF PHENYLBUTAZONE FOR THE TOXICOLOGY STUDIES

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APPENDIX G. CHEMICAL CHARACTERIZATION

Procurement and Characterization of Phenylbutazone

Phenylbutazone (USP-grade, medicine NOIBN) was obtained in one lot (lot no. 62642) from the Ciba Geigy Corporation (Summit, NJ). Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, MO). MRI reports on the analyses performed in support of the phenylbutazone studies are on file at the National Institute of Environmental Health Sciences.

Lot no. 62642 was identified as phenylbutazone by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with those expected for the structure and with literature spectra (Figures G1 and G2) (Sadtler Standard Spectra; Handbook of Analytical Toxicology, 1969). The ultraviolet/visible spectrum was consistent with that of a USP standard.

The purity of lot no. 62642 was determined by elemental analysis, Karl Fischer water analysis, a USP titration method using tetrabutylammonium hydroxide as the titrant, USP chloride and sulfate assays, thin-layer chromatography, and high-performance liquid chromatography. Thin-layer chromatography was performed on silica gel plates with two solvent systems: toluene:methanol (90:10, v/v) (system 1) and chloroform:diethyl ether (95:5 v/v) (system 2). High-performance liquid chromatography was performed with ultraviolet detection at 254 nm on a Waters μBondapak C_{18} column, a Whatman CO:PELL ODS guard column, and a solvent system of aqueous 1% (v/v) acetic acid:acetonitrile with 1% (v/v) acetic acid (65:35).

The results of elemental analysis for hydrogen and nitrogen were in agreement with the theoretical values, whereas that for carbon was slightly high. Karl Fischer analysis indicated the presence of 0.062% water. Neither chloride nor sulfate was detected. Titration indicated a purity of 99.94%. Three trace impurities were detected by thin-layer chromatographic system 1; system 2 indicated a minor and a trace impurity. High-performance liquid chromatography detected three impurities, all with relative areas less than 0.1% of the major peak area and totaling 0.16% that of the major peak. Cumulative data indicated that lot no. 62642 was greater than 99% pure.

Stability studies performed by high-performance liquid chromatography with the same system as before, but with a solvent ratio of 35:65 and with hexanophenone as an internal standard, indicated that phenylbutazone is stable as a bulk chemical for 2 weeks at temperatures up to 60° C. During the 2-year studies, the stability of the bulk chemical was confirmed at the study laboratory by high-performance liquid chromatography and infrared spectroscopy. No deterioration of the study material was seen over the course of the studies.

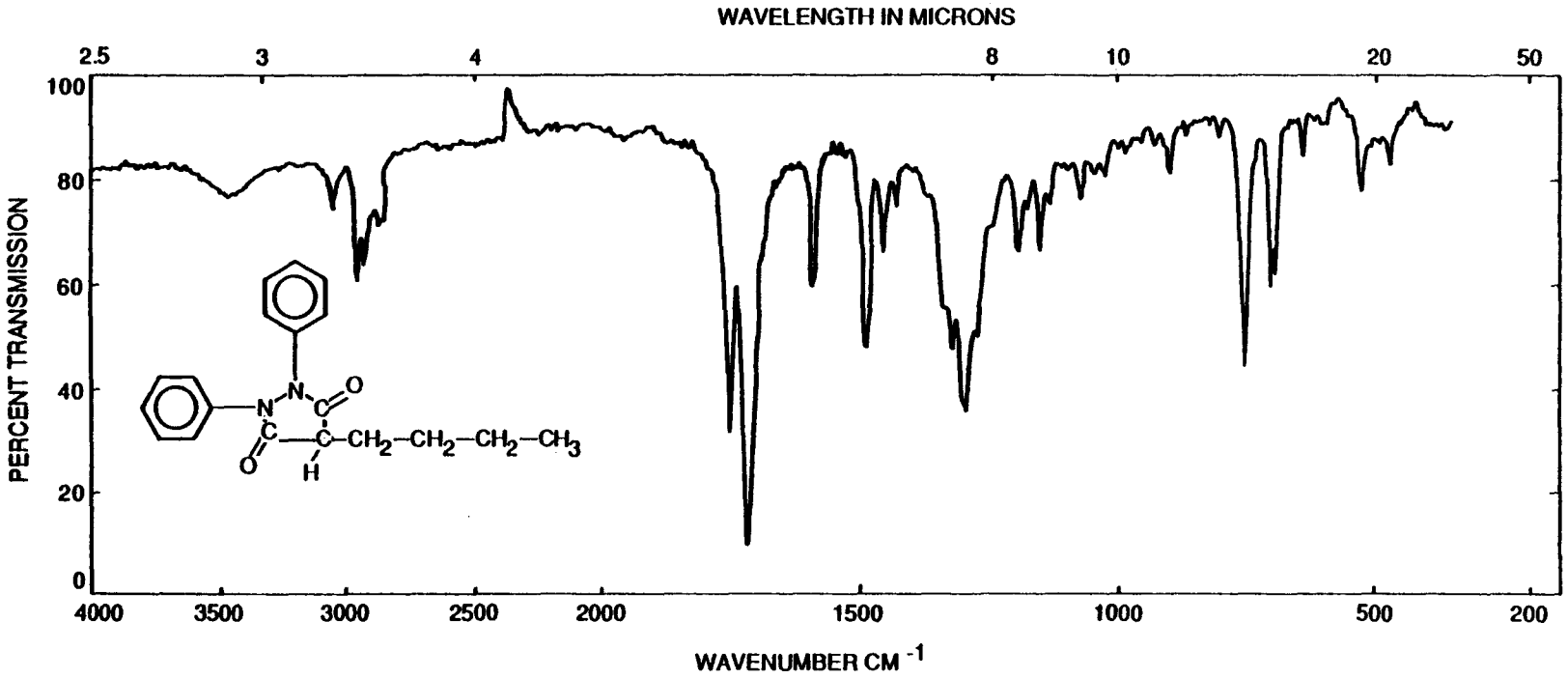

FIGURE G1. INFRARED ABSORPTION SPECTRUM OF PHENYLBUTAZONE (LOT NO. 62642)

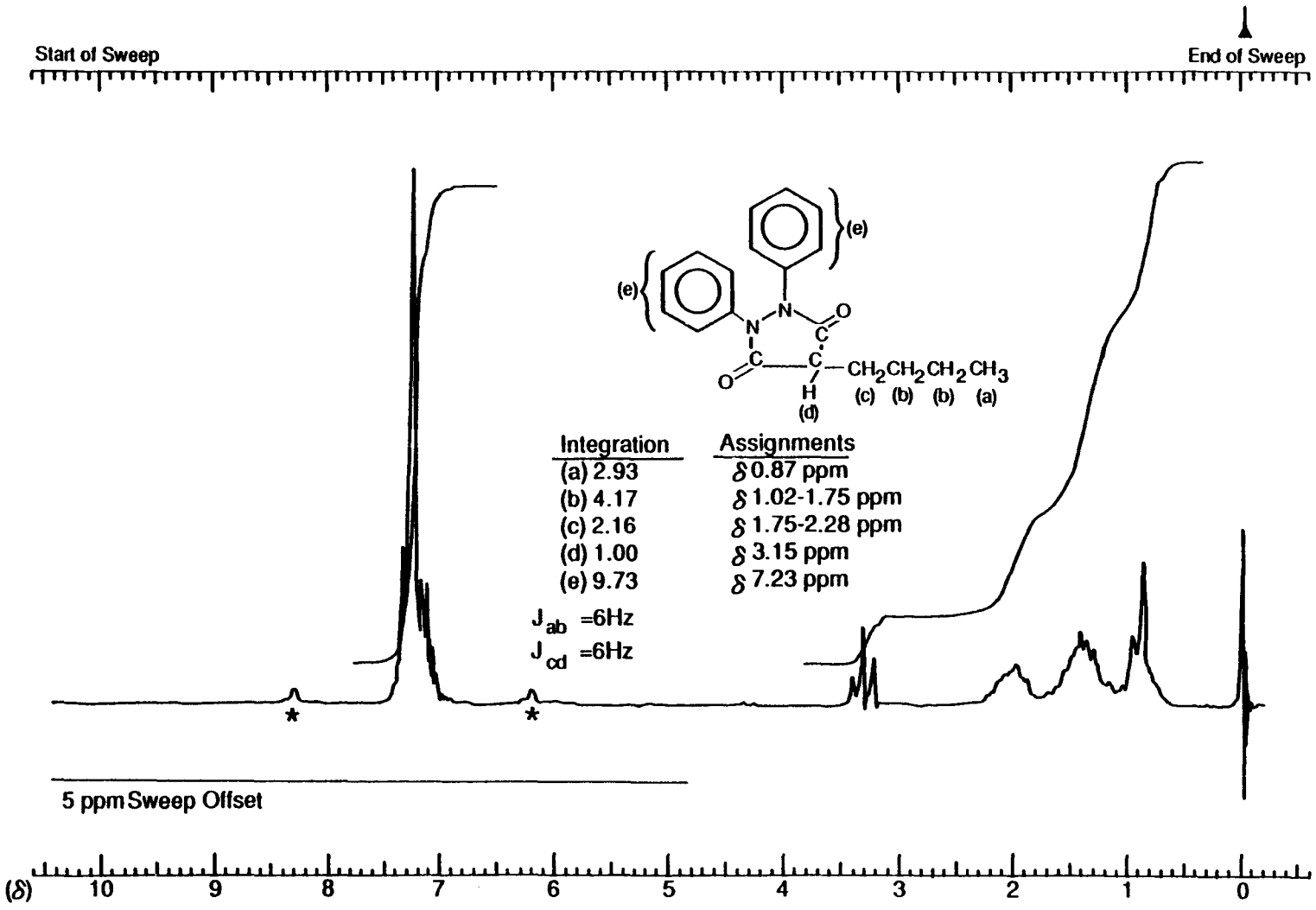

FIGURE G2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF PHENYLBUTAZONE (LOT NO. 62642)

Preparation and Characterization of Dose Mixtures

The stability of 5,000 ppm phenylbutazone in feed was determined by high-performance liquid chromatography with a μBondapak C_{18} column and ultraviolet detection at 254 nm after extraction with a methanol/acetic acid (99:1) solution. The chemical in feed was found to be unstable under storage conditions. After storage in the dark for 2 weeks, losses of about 6%, 8%, 20%, and 77% were observed at −20°, 5°, 25°, and 45° C, respectively. Based on these results, it was decided to use corn oil gavage rather than feed as the route of chemical administration.

The appropriate amounts of phenylbutazone and corn oil were mixed to give the desired concentrations (Table G1). The stability of phenylbutazone in corn oil (50 mg/ml) was determined by high-performance liquid chromatography with a μBondapak C_{18} column and ultraviolet detection at 254 nm after extraction with acetonitrile and the addition of hexanophenone as an internal standard. The chemical in corn oil was found to be stable for at least 14 days when stored in the dark at room temperature or at 5° C. During the studies, dose mixtures were stored for no longer than 2 weeks at 0° ± 5° C.

Because phenylbutazone is relatively insoluble in corn oil, the effectiveness of the gavage preparation procedure in producing a uniform suspension was determined. The chemical was mixed with corn oil and stirred with a magnetic stirrer; while the mixture was stirred, aliquots were removed and analyzed for phenylbutazone content. The mean concentration of the chemical was 99.9% of the target concentration, and the average deviation in concentration was ±0.6%, indicating a very satisfactory degree of uniformity.

Periodic analysis of formulated phenylbutazone/corn oil dose mixtures was conducted at the study laboratory and the analytical chemistry laboratory. At the study laboratory, the dose mixtures were extracted with methanol, the extractants were centrifuged, and the absorbance was read at 268 nm on a Hitachi spectrophotometer. After receipt of the revised MRI report of October 3, 1980, the absorbance was read at 240 nm. The analytical chemistry laboratory extracted the phenylbutazone with acetonitrile. Dose mixtures were analyzed two times during the 13-week studies. Three of the nine dose mixtures in the second group were more than 10% different from the target concentrations; none was more than 15% different (Table G2).

During the 2-year studies, the dose mixtures were analyzed at approximately 8-week intervals. For the phenylbutazone studies, the mixtures were formulated within ±10% of the target concentrations approximately 98% (55/56) of the time throughout the studies (Table G3). The one mixture that was found to be out of specifications was 112% of the target concentration. Results of periodic referee analysis performed by the analytical chemistry laboratory indicated generally good agreement with the results from the study laboratory (Table G4).

TABLE G1. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF PHENYLBUTAZONE

Single-Administration Studies	Nineteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation			
A weighed quantity of phenylbutazone was added with stirring to the appropriate amount of corn oil. The mixture was shaken until visually uniform, mixed in a tissue homogenizer, and placed in serum vials containing stir bars	Same as single-administration studies	The appropriate amount of corn oil was added to a weighed amount of phenylbutazone; the mixture was homogenized for 30 sec with a Brinkmann Polytron® at a control setting of 5 and placed in amber or foil-covered vials	Same as 13-wk studies
Maximum Storage Time			
Not stored	2 wk	2 wk	2 wk
Storage Conditions			
N/A	0° ± 5° C in amber or foil-covered serum vials	Same as 19-d studies	Same as 19-d studies

TABLE G2. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF PHENYLBUTAZONE

Date Mixed	Concentration of Phenylbutazone in Corn Oil (mg/ml) (a) Target	Determined	Determined as a Percent of Target
07/14/80	4	3.84	96.0
	5	5.16	103.2
	8	7.89	98.6
	10	9.12	91.2
	15	14.42	96.1
	20	18.30	91.5
	30	28.8	96.0
	40	42.1	105.3
	60	58.4	97.3
09/08/80	4	4.10	102.5
	5	5.71	(b) 114.2
	8	9.08	(b) 113.5
	10	10.74	107.4
	15	15.76	105.1
	20	22.2	(c) 111.0
	30	31.3	104.3
	40	43.3	108.3
	60	63.6	106.0

(a) Results of duplicate analysis
(b) Out of specifications; was remixed.
(c) Out of specifications

TABLE G3. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF PHENYLBUTAZONE

Date Mixed	Concentration of Phenylbutazone in Corn Oil for Target Concentration (mg/ml) (a)			
	10	15	20	30
08/17/81		15.5		(b) 33.5
08/24/81				(c) 30.4
09/02/81	10.3		20.3	
09/14/81	10.5	14.9	20.3	31.0
10/26/81		15.4		29.2
11/02/81	10.2		20.4	
01/18/82	10.3	15.0	20.0	29.3
03/15/82	9.9	13.9	19.8	29.6
04/26/82	9.8	15.5	19.7	31.4
07/12/82	9.9	15.5	19.8	29.5
07/26/82	10.0	14.4	19.2	28.7
10/25/82	9.9	14.7	20.0	29.5
11/15/82	10.3	14.0	19.8	29.8
01/24/83	9.9	15.1	20.2	29.6
03/21/83	9.8	13.7	19.9	28.1
06/06/83	10.2	14.8	19.9	30.0
07/11/83	10.0	14.5	20.0	30.0
Mean (mg/ml)	10.1	14.8	19.9	29.9
Standard deviation	0.22	0.61	0.31	1.31
Coefficient of variation (percent)	2.2	4.1	1.6	4.4
Range (mg/ml)	9.8-10.5	13.7-15.5	19.2-20.4	28.1-33.5
Number of samples	14	14	14	14

(a) Results of duplicate analysis
(b) Out of specifications; not used in the studies.
(c) Remix; not included in the mean.

TABLE G4. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF PHENYLBUTAZONE

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (mg/ml)	
		Study Laboratory (a)	Referee Laboratory (b)
08/24/81	30.0	30.4	29.7
(c) 08/24/81	30.0	30.1	29.5
01/18/82	20.0	20.0	21.2
(c) 01/18/82	20.0	20.0	21.2
07/12/82	10.0	9.9	9.8
01/24/83	15.0	15.1	15.2
07/11/83	20.0	20.0	19.9

(a) Results of duplicate analysis
(b) Results of triplicate analysis
(c) Samples from animal room

APPENDIX H

GENETIC TOXICOLOGY OF PHENYLBUTAZONE

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METHODS

Salmonella Protocol: Testing was performed as reported by Ames et al. (1975) with modifications listed below and described in greater detail by Haworth et al. (1983) and Mortelmans et al. (1986). Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, TX). The study chemical was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, and 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 before the addition of soft agar supplemented with L-histidine and D-biotin and subsequent plating on minimal glucose agar plates. Incubation was continued for an additional 48 hours.

Chemicals were tested in four strains; all trials were repeated. Each test consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of the study chemical. The high dose was limited by toxicity or solubility but did not exceed 10 mg/plate.

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

Mouse Lymphoma Protocol: The experimental protocol is presented in detail by Myhr et al. (1985) and follows the basic format of Clive et al. (1979). All study chemicals were supplied as coded aliquots from Radian Corporation (Austin, TX). The highest dose of the study compound was determined by solubility or toxicity and did not exceed 800 µg/ml. Mouse L5178Y/TK lymphoma cells were maintained at 37° C as suspension cultures in Fischer's medium supplemented with 2 mM L-glutamine, 110 µg/ml sodium pyruvate, 0.05% pluronic F68, antibiotics, and heat-inactivated horse serum; normal cycling time was about 10 hours. To reduce the number of spontaneously occurring trifluorothymidine (Tft)-resistant cells, subcultures were exposed once to medium containing thymidine, hypoxanthine, methotrexate, and glycine for 1 day, to thymidine, hypoxanthine, and glycine for 1 day, and to normal medium for 3-5 days. For cloning, horse serum content was increased and Noble agar was added. Freshly prepared S9 metabolic activation factors were obtained from the liver of either Aroclor 1254-induced or noninduced male F344 rats.

All doses within an experiment, including concurrent positive and solvent controls, were replicated. Treated cultures contained 6×10^6 cells in 10 ml of medium. This volume included the S9 fraction in those experiments performed with metabolic activation. Incubation with the study chemical continued for 4 hours, after which time the medium plus chemical was removed and the cells were resuspended in 20 ml of fresh medium and incubated for an additional 2 days to express the mutant phenotype. Cell density was monitored so that log phase growth was maintained. After the 48-hour expression period, 3×10^6 cells were plated in medium and soft agar supplemented with Tft for selection of Tft-resistant cells (TK +/+), and 600 cells were plated in nonselective medium and soft agar to determine cloning efficiency. Plates were incubated at 37° C under 5% carbon dioxide for 10-12 days. All data were evaluated statistically for both trend and peak response. Both responses had to be significant ($P<0.05$) for a chemical to be considered capable of inducing Tft resistance; a single significant response led to an "equivocal" conclusion, and the absence of both a trend and a peak response resulted in a "negative" call.

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented in Myhr et al. (1985). This assay was initially performed without S9; if a clearly positive response was not obtained, the experiment was repeated with induced S9.

Chinese Hamster Ovary Cytogenetics Assays: Testing was performed as reported by Galloway et al. (1987) and is described briefly below. Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, TX). 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 (BrdU)-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of the study chemical; the high dose was limited by toxicity or solubility but did not exceed 5 mg/ml.

In the SCE test without S9, CHO cells were incubated for 26 hours with the study chemical in McCoy's 5A medium supplemented with 10% fetal bovine serum, L-glutamine (2 mM), and antibiotics. BrdU was added 2 hours after culture initiation. After 26 hours, the medium containing the study 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 study chemical; incubation proceeded for an additional 26 hours, with colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9.

In the chromosomal aberration test without S9, cells were incubated in McCoy's 5A medium with the study chemical for 8 hours; colcemid was added, and incubation was continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the chromosomal aberration 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 were 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.

For the SCE test, if significant chemical-induced cell cycle delay was seen, incubation time was lengthened to ensure a sufficient number of scorable cells. The harvest time for the chromosomal aberration test was based on the cell cycle information obtained in the SCE test; if cell cycle delay was anticipated, the incubation period was extended approximately 5 hours.

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, 50 second-division metaphase cells were usually scored for frequency of SCEs per cell from each dose; 100 first-division metaphase cells were scored at each dose for the chromosomal aberration 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. An SCE 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 SCEs, both the dose-response curve and individual dose points were statistically analyzed. A statistically significant ($P<0.003$) trend test or a significantly increased dose point ($P<0.05$) was sufficient to indicate a chemical effect.

RESULTS

Phenylbutazone was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested in a preincubation protocol with doses up to 10 mg/plate in the presence or absence of Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 (Mortelmans et al., 1986; Table H1). Phenylbutazone gave a positive response in the mouse lymphoma assay for induction of Tft resistance in L5178Y/TK cells in the presence and absence of Aroclor 1254-induced male F344 rat liver S9 (Table H2). Doses tested in this assay ranged from 200 to 800 μg/ml, and significantly increased mutant counts were observed at the higher doses tested where severely reduced relative total growth was a complication. The sharp toxicity curve observed in this assay made it difficult to assess the mutagenic activity of phenylbutazone in the absence of extreme toxicity because the mutagenic response occurred within this same narrow range of doses. In cytogenetic tests with cultured CHO cells, phenylbutazone induced chromosomal aberrations with, but not without, Aroclor 1254-induced male Sprague Dawley rat liver S9 at doses of 1,600 and 5,000 μg/ml (Table H4); no SCEs were induced in CHO cells treated with similar concentrations of phenylbutazone (Galloway et al., 1987; Table H3).

TABLE H1. MUTAGENICITY OF PHENYLBUTAZONE IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/Plate (b) −S9 Trial 1	−S9 Trial 2	+S9 (hamster) Trial 1	+S9 (hamster) Trial 2	+S9 (rat) Trial 1	+S9 (rat) Trial 2
TA100	0	126 ± 9.3	110 ± 8.1	223 ± 15.6	130 ± 3.0	203 ± 10.4	124 ± 2.7
	33	--	102 ± 5.0	--	--	--	--
	100	98 ± 2.7	88 ± 2.3	228 ± 7.7	125 ± 5.8	175 ± 6.2	173 ± 11.0
	333	85 ± 1.5	80 ± 3.2	201 ± 13.9	128 ± 11.5	194 ± 11.3	161 ± 8.1
	1,000	93 ± 2.3	76 ± 6.9	194 ± 9.9	142 ± 3.8	173 ± 6.2	145 ± 8.2
	3,333	Toxic	Toxic	144 ± 10.2	116 ± 7.4	116 ± 5.1	128 ± 17.8
	10,000	Toxic	--	153 ± 12.2	98 ± 9.3	152 ± 7.5	102 ± 8.7
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		673 ± 44.4	226 ± 13.2	1,799 ± 82.6	1,729 ± 154.1	1,973 ± 153.8	805 ± 34.6
TA1535	0	7 ± 0.7	7 ± 0.9	10 ± 0.9	11 ± 2.4	9 ± 0.6	14 ± 2.3
	100	7 ± 0.9	11 ± 2.3	9 ± 0.3	12 ± 1.2	7 ± 0.0	16 ± 2.6
	333	6 ± 0.3	9 ± 1.8	12 ± 0.3	12 ± 1.2	5 ± 2.0	11 ± 1.5
	1,000	7 ± 0.9	9 ± 2.3	8 ± 0.3	10 ± 0.7	9 ± 1.2	14 ± 2.6
	3,333	4 ± 0.6	7 ± 1.5	9 ± 0.6	14 ± 2.6	13 ± 0.6	15 ± 2.4
	10,000	5 ± 0.9	5 ± 0.3	11 ± 1.2	9 ± 1.9	10 ± 1.5	13 ± 1.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		207 ± 8.7	238 ± 3.7	87 ± 13.1	72 ± 3.2	57 ± 3.0	46 ± 8.2
TA1537	0	6 ± 0.6	6 ± 0.3	5 ± 0.6	9 ± 2.3	7 ± 0.9	11 ± 2.3
	100	6 ± 0.3	4 ± 1.2	7 ± 0.7	10 ± 1.5	6 ± 0.6	9 ± 0.6
	333	3 ± 0.6	5 ± 0.9	8 ± 0.7	12 ± 0.9	8 ± 1.2	10 ± 1.2
	1,000	4 ± 0.0	4 ± 0.3	10 ± 0.6	14 ± 2.0	7 ± 0.9	8 ± 1.3
	3,333	2 ± 0.6	2 ± 0.3	6 ± 0.7	9 ± 1.2	8 ± 0.3	11 ± 0.9
	10,000	6 ± 0.7	5 ± 2.1	8 ± 1.2	11 ± 2.0	7 ± 1.2	7 ± 1.9
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		232 ± 64.7	46 ± 2.5	140 ± 5.8	77 ± 17.0	83 ± 1.3	52 ± 9.0
TA98	0	12 ± 2.0	13 ± 1.0	26 ± 2.7	22 ± 3.1	26 ± 3.8	24 ± 1.2
	100	22 ± 3.3	17 ± 3.6	29 ± 3.8	19 ± 3.5	28 ± 0.6	25 ± 0.6
	333	18 ± 1.3	20 ± 0.9	29 ± 1.0	24 ± 2.6	27 ± 1.5	22 ± 1.8
	1,000	17 ± 2.1	17 ± 1.2	18 ± 1.8	16 ± 3.2	30 ± 4.7	22 ± 2.9
	3,333	19 ± 0.9	17 ± 2.7	20 ± 3.3	18 ± 0.6	22 ± 1.8	20 ± 0.9
	10,000	24 ± 0.9	10 ± 0.3	26 ± 1.0	15 ± 3.5	24 ± 2.1	15 ± 3.7
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		268 ± 14	200 ± 8.7	2,408 ± 68.6	1,042 ± 65.2	682 ± 50.4	576 ± 35.3

(a) Study performed at Case Western Reserve University. The detailed protocol is presented by Haworth et al. (1983); data are presented in Mortelmans et al. (1986). Cells and study compound or solvent (dimethyl sulfoxide) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.

(b) Revertants are presented as mean ± standard error from three plates.

(c) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-o-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA1537.

TABLE H2. INDUCTION OF TRIFLUOROTHYMIDINE RESISTANCE BY PHENYLBUTAZONE IN MOUSE L5178Y LYMPHOMA CELLS (a,b)

Compound	Concentration (µg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Tft-Resistant Cells	Mutant Fraction (c)
-S9					
Trial 1					
Acetone		112.3 ± 1.9	100.0 ± 1.2	120.3 ± 22.0	36.0 ± 6.4
Phenylbutazone	200	104.3 ± 8.0	116.7 ± 27.9	88.3 ± 4.1	28.7 ± 3.7
	300	91.0 ± 2.0	77.7 ± 1.5	99.7 ± 3.8	36.3 ± 0.7
	400	93.0 ± 3.0	68.0 ± 1.5	92.3 ± 5.5	33.7 ± 3.2
	(d) 500	94.7 ± 10.5	29.0 ± 4.9	233.7 ± 23.8	(e) 85.7 ± 15.1
	600	85.0 ± 9.7	25.3 ± 17.3	363.3 ± 117.4	(e) 154.7 ± 56.2
	800	Lethal	--	--	--
Methyl methanesulfonate	5	89.0 ± 2.3	46.3 ± 1.9	628.0 ± 80.8	(e) 234.3 ± 28.1
Trial 2					
Acetone (f)		101.5 ± 3.6	100.0 ± 6.5	96.8 ± 17.9	32.0 ± 6.1
Phenylbutazone	200	93.0 ± 4.0	92.7 ± 4.7	82.7 ± 14.9	29.7 ± 5.5
	300	96.3 ± 8.3	79.7 ± 6.9	90.3 ± 5.5	31.7 ± 3.8
	400	101.0 ± 8.7	71.0 ± 2.5	112.0 ± 12.2	37.3 ± 3.5
	(d) 500	97.7 ± 4.1	60.0 ± 9.3	110.0 ± 5.0	37.3 ± 2.2
	600	94.7 ± 9.5	74.3 ± 15.1	131.7 ± 24.2	47.7 ± 9.8
	(g) 700	61.0 ± 17.0	13.5 ± 10.5	188.5 ± 73.5	(e) 123.5 ± 74.5
Methyl methanesulfonate	5	69.3 ± 2.7	50.3 ± 3.7	503.7 ± 43.3	(e) 243.0 ± 20.5
+S9 (h)					
Trial 1					
Acetone (f)		75.5 ± 2.7	100.3 ± 7.8	87.0 ± 4.9	38.5 ± 1.7
Phenylbutazone	200	75.3 ± 3.4	97.3 ± 6.0	85.3 ± 1.2	38.0 ± 2.1
	300	88.3 ± 11.4	102.3 ± 9.4	126.3 ± 24.4	46.7 ± 3.2
	400	87.0 ± 3.1	72.0 ± 17.1	255.7 ± 65.7	(e) 98.0 ± 23.7
	(g) 500	77.0 ± 29.0	24.0 ± 18.0	610.5 ± 64.5	(e) 319.0 ± 147.0
	600	Lethal	--	--	--
Methylcholanthrene	2.5	94.0 ± 4.7	65.3 ± 17.0	570.3 ± 57.5	(e) 202.0 ± 16.0
Trial 2					
Acetone (f)		102.3 ± 5.0	100.0 ± 5.6	90.0 ± 4.9	30.0 ± 2.9
Phenylbutazone	100	84.7 ± 7.5	62.0 ± 4.0	86.3 ± 3.9	34.7 ± 3.5
	200	87.7 ± 4.7	73.3 ± 3.0	97.7 ± 15.9	37.7 ± 7.5
	300	90.7 ± 7.1	81.0 ± 2.6	101.3 ± 12.8	37.3 ± 3.2
	400	101.3 ± 9.0	67.0 ± 7.9	98.3 ± 12.2	33.3 ± 5.7
	500	85.3 ± 6.0	34.3 ± 9.8	261.0 ± 57.0	(e) 105.3 ± 26.6
	(g) 600	61.5 ± 21.5	17.0 ± 13.0	508.5 ± 205.5	(e) 357.5 ± 235.5
Methylcholanthrene	2.5	68.0 ± 7.5	32.7 ± 10.7	592.3 ± 8.2	(e) 295.3 ± 27.6

TABLE H2. INDUCTION OF TRIFLUOROTHYMIDINE RESISTANCE BY PHENYLBUTAZONE IN MOUSE L5178Y LYMPHOMA CELLS (Continued)

(a) Study performed at Litton Bionetics, Inc. The experimental protocol is presented in detail by Myhr et al. (1985) and follows the basic format of Clive et al. (1979). The highest dose of study compound is determined by solubility or toxicity and may not exceed 5 mg/ml. All doses are tested in triplicate, unless otherwise specified; the average for the tests is presented in the table. Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine (Tft) for selection of Tft-resistant cells, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency.
(b) Mean ± standard error from replicate trials of approximately 1×10^6 cells each. All data are evaluated statistically for both trend and peak response ($P<0.05$ for at least one of the three highest dose sets). Both responses must be significantly ($P<0.05$) positive for a chemical to be considered capable of inducing Tft resistance. If only one of these responses is significant, the call is "equivocal"; the absence of both trend and peak response results in a "negative" call.
(c) Mutant fraction (frequency) is a ratio of the Tft-resistant cells to the cloning efficiency, divided by 3 (to arrive at MF per 1×10^6 cells treated); MF = mutant fraction.
(d) Acidic pH shift at this and higher concentrations
(e) Significant positive response; occurs when the relative mutant fraction (average MF of treated culture/average MF of solvent control) is greater than or equal to 1.6.
(f) Data presented are the results of four tests.
(g) Data presented are the results of two tests; the dose in one test was lethal.
(h) Tests conducted with metabolic activation were performed as described in (a) except that S9, prepared from the liver of Aroclor 1254-induced F344 rats, was added at the same time as the study chemical and/or solvent (acetone).

TABLE H3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY PHENYLBUTAZONE (a)

Compound	Dose (µg/ml)	Total Cells	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
−S9 (c)--Summary: Negative								
Dimethyl sulfoxide		50	1,049	428	0.41	8.6	26.0	
Phenylbutazone	50	50	1,047	408	0.39	8.2	26.0	95.3
	160	50	1,044	440	0.42	8.8	26.0	102.3
	500	50	1,045	412	0.39	8.2	26.0	95.3
Mitomycin C	0.005	25	525	619	1.18	24.8	26.0	288.4
+S9 (d)--Summary: Negative								
Dimethyl sulfoxide		50	1,049	461	0.44	9.2	26.0	
Phenylbutazone	160	50	1,048	423	0.40	8.5	26.0	92.4
	500	50	1,047	452	0.43	9.0	26.0	97.8
	1,600	50	1,042	450	0.43	9.0	26.0	97.8
	5,000	50	1,051	475	0.45	9.5	28.0	103.3
Cyclophosphamide	1	50	1,047	826	0.79	16.5	26.0	179.3

(a) Study performed at Columbia University. 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 study compound or solvent (dimethyl sulfoxide) 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) SCEs/cell of culture exposed to study chemical relative to those of culture exposed to solvent
(c) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours.
(d) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. 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 liver of Aroclor 1254-induced male Sprague Dawley rats.

TABLE H4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY PHENYLBUTAZONE (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
Harvest time: 14 hours					Harvest time: 14 hours				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	2	0.02	2.0		100	5	0.05	5.0
Phenylbutazone					Phenylbutazone				
160	100	5	0.05	5.0	500	100	7	0.07	6.0
500	100	6	0.06	6.0	1,600	100	29	0.29	22.0
1,600	100	7	0.07	6.0	5,000	100	29	0.29	23.0
Mitomycin C					Cyclophosphamide				
0.15	50	15	0.30	22.0	15	50	21	0.42	24.0
Summary: Negative					Summary: Positive				

(a) Study performed at Columbia University; 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 study compound or solvent (dimethyl sulfoxide) as indicated 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 study compound 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 study compound or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid was added for the last 2-3 hours of incubation before harvest. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

APPENDIX I

AUDIT SUMMARY

APPENDIX I. AUDIT SUMMARY

The pathology specimens, experimental data, study documents, and draft of NTP Technical Report No. 367 for the 2-year studies of phenylbutazone in rats and mice were audited for the National Institute of Environmental Health Sciences (NIEHS) at the National Toxicology Program (NTP) Archives by quality assurance, resource-support contractors. The audit included review of:

(1) All records concerning animal receipt, quarantine, randomization, and disposition prior to study start.
(2) All inlife records including protocol, correspondence, animal husbandry, room and exposure chamber environmental conditions, dosing, external masses, mortality, animal identification, and serology.
(3) Body weight and clinical observation data; all data were scanned before individual data for a random 10% sample of animals in each study group were reviewed in detail.
(4) All chemistry records.
(5) All postmortem records for individual animals concerning date of death, disposition code, condition code, tissue accountability, correlation of masses or clinical signs recorded at or near the last inlife observation with gross observations and microscopic diagnoses, consistency of data entry on necropsy record forms, and correlation between gross observations and microscopic diagnoses.
(6) All wet tissue bags for inventory and residual wet tissues from a random 20% sample of animals in each study group, plus other relevant cases, to evaluate the integrity of individual animal identity and the thoroughness of necropsy and trimming procedure performance.
(7) Blocks and slides of tissues from a random 20% sample of animals from each study group, plus animals with less than complete or correct identification, to examine for proper inventory, matching of tissue sections, and preservation.
(8) All microscopic diagnoses for a random 20% of animals, plus 100% of the changes in diagnoses made to preliminary pathology tables, to verify their incorporation into the final pathology tables.
(9) The extent of correlation between the data, factual information, and procedures for the 2-year studies as presented in the draft Technical Report and the study records available at the NTP Archives.

Procedures and events for the exposure phase of the studies were documented adequately by the archival records, with the exception that some or all of the records for disposition of surplus animals, room air change rate, room light cycle, cleaning agents used, temperature and humidity (for August and September 1981), and corn oil analyses performed for 5 months were not available at the Archives. Review of the records indicated that protocol procedures for animal care were followed adequately. Records that documented the preparation, analysis, storage, and administration of doses to animals were complete and accurate. Recalculation of approximately 20% of the group mean body weight values in the Technical Report showed that the data for 31/36 rats and 36/36 mice were correct; differences ranged from 2% to 12% The correlation between observations of external masses recorded both during the last few months of life and at necropsy was good (all correlated except for four in rats and one in mice). The date of death recorded at necropsy for each unscheduled-death animal (153 rats and 116 mice) had matching entries in the inlife animal-removal records, except for those of 4 mice, 2 of which were off by exactly 1 year and have a small effect on the survival-adjusted statistics given in the Technical Report for low and high dose female mice. The reason for removal recorded during life differed from the disposition code recorded at necropsy for eight rats and one mouse; in addition, three high dose female rats that died after being dehydrated during the second month of exposure were assigned the disposition code for natural death in both types of record.

Individual animal identifiers (ear punches) were present and correct in the residual tissue bags for 76/80 rats and 94/114 mice examined. Review of the entire data trail for the 4 rats and 20 mice with less than complete and correct identifiers indicated that the integrity of the individual-animal

identity for all but 2 mice had been maintained, but their ears either had not been saved, had been altered during the studies, or had been marked inconsistently at the start of the studies without documentation. Two low dose male mice apparently had been switched at necropsy, but all tissues and data had been processed completely and consistently. A total of 6 untrimmed potential lesions (2 involved the stomach) were found in the wet tissues of 80 rats examined, and 5 (2 involved the liver) were found in those of 114 mice examined. Intestinal segments were incompletely opened for 22/80 rats and 18/114 mice, the cecum was unopened in 48/80 rats and 54/114 mice, and the stomach was unopened in 18/18 low dose mice examined. However, there were no apparent untrimmed potential lesions evident by external examination of residual tissues for the gastrointestinal tract. Each gross observation made at necropsy had a corresponding microscopic diagnosis, except for five in rats (two involved the kidney) and five in mice (two involved the liver). Tissue sections on blocks and slides matched each other properly. All post-Pathology Working Group changes in diagnoses had been incorporated into the final pathology tables. P values for the analysis of tumor incidence given in the Technical Report were the same as those in the final pathology tables in the study records.

Full details about these and other audit findings are presented in audit reports that are on file at the NIEHS. This summary describes the extent to which the data and factual information presented in the Technical Report are supported by records at the NTP Archives.

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